Optimising management with combotherapy

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Combotherapy

- Is it a double buggy?

- Or a tandem cycle?

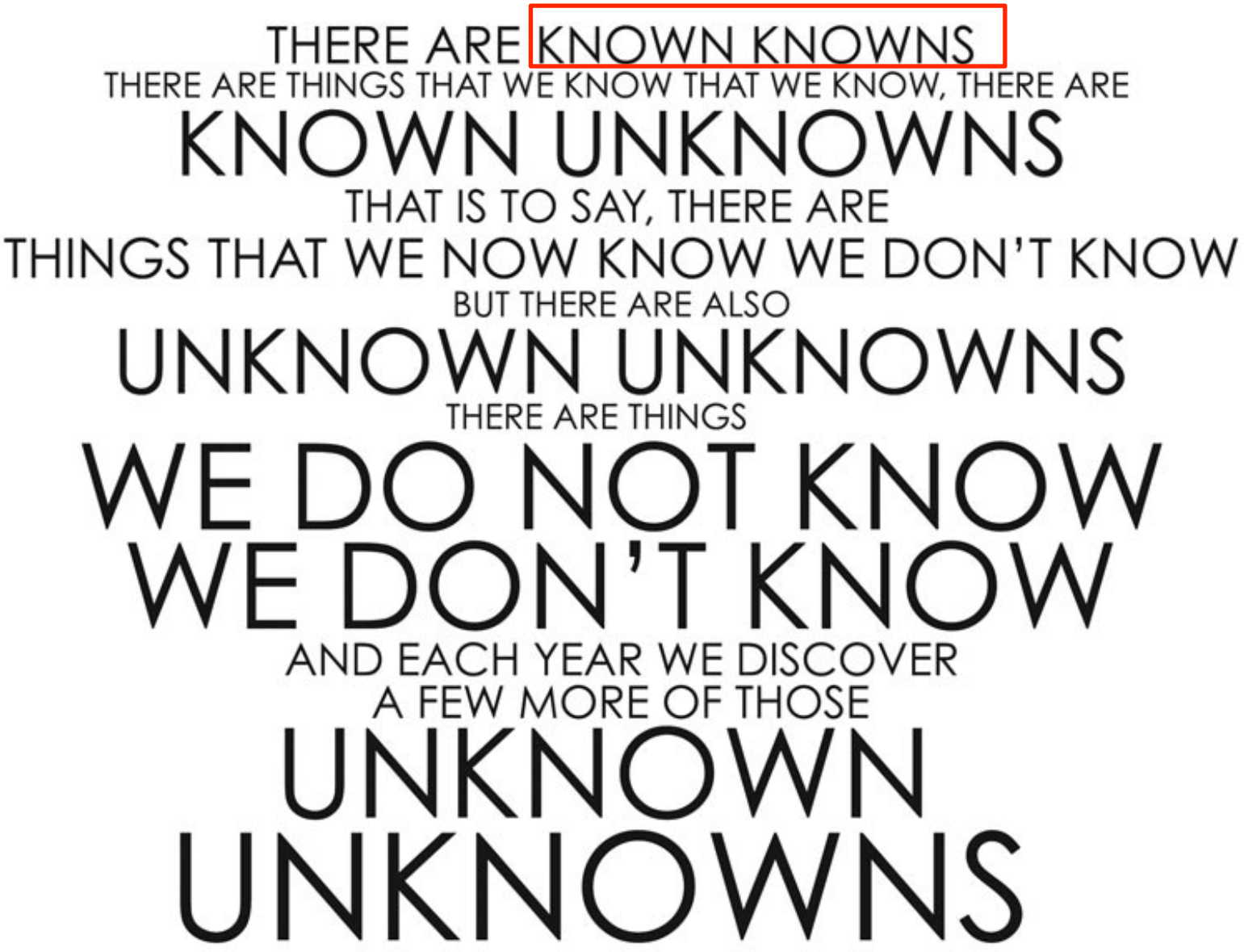
- Or even a pushmepullu?

Combotherapy

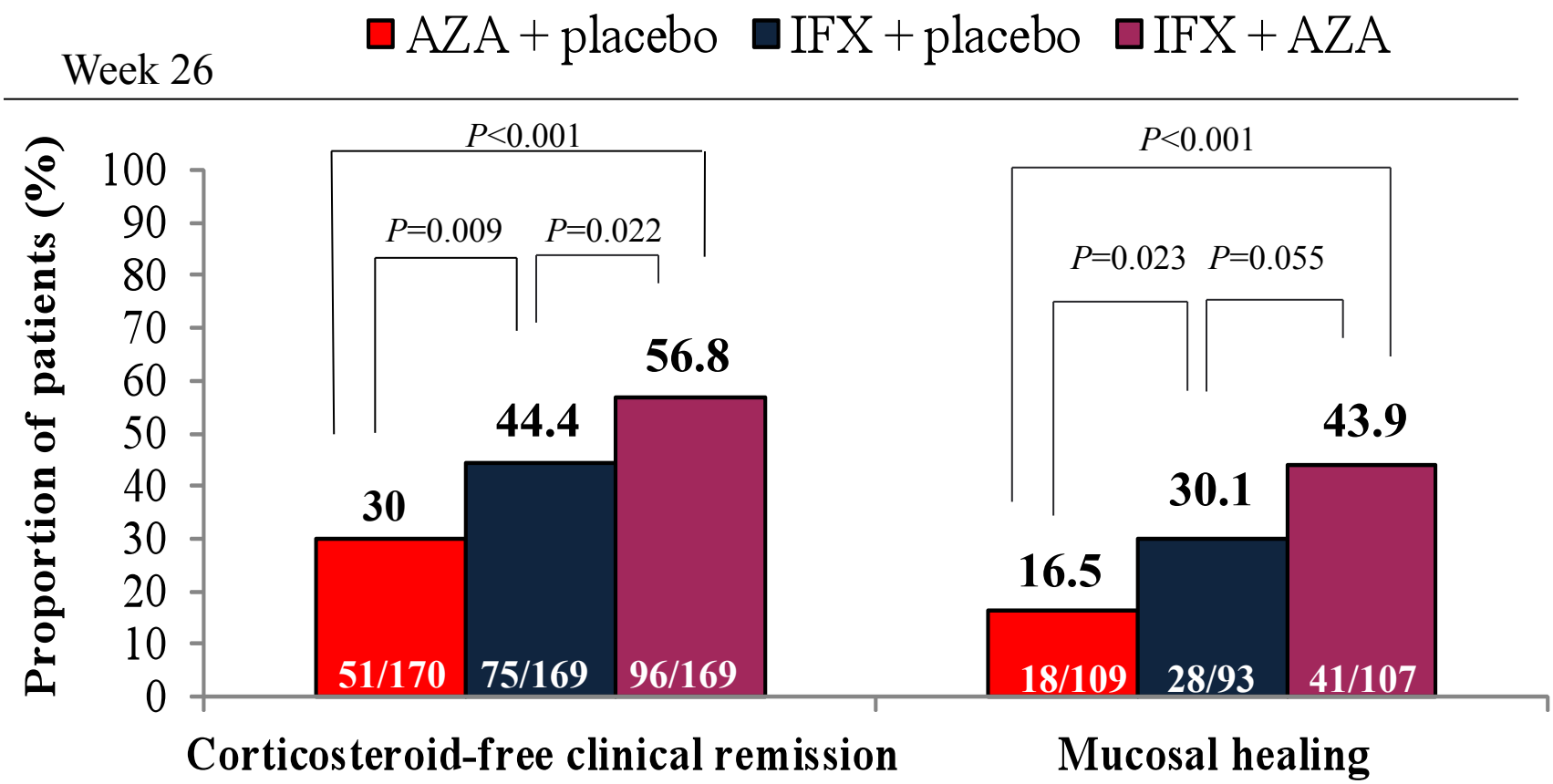
- **Like any marriage, some are made in heaven**

and some…

Donald Rumsfeld



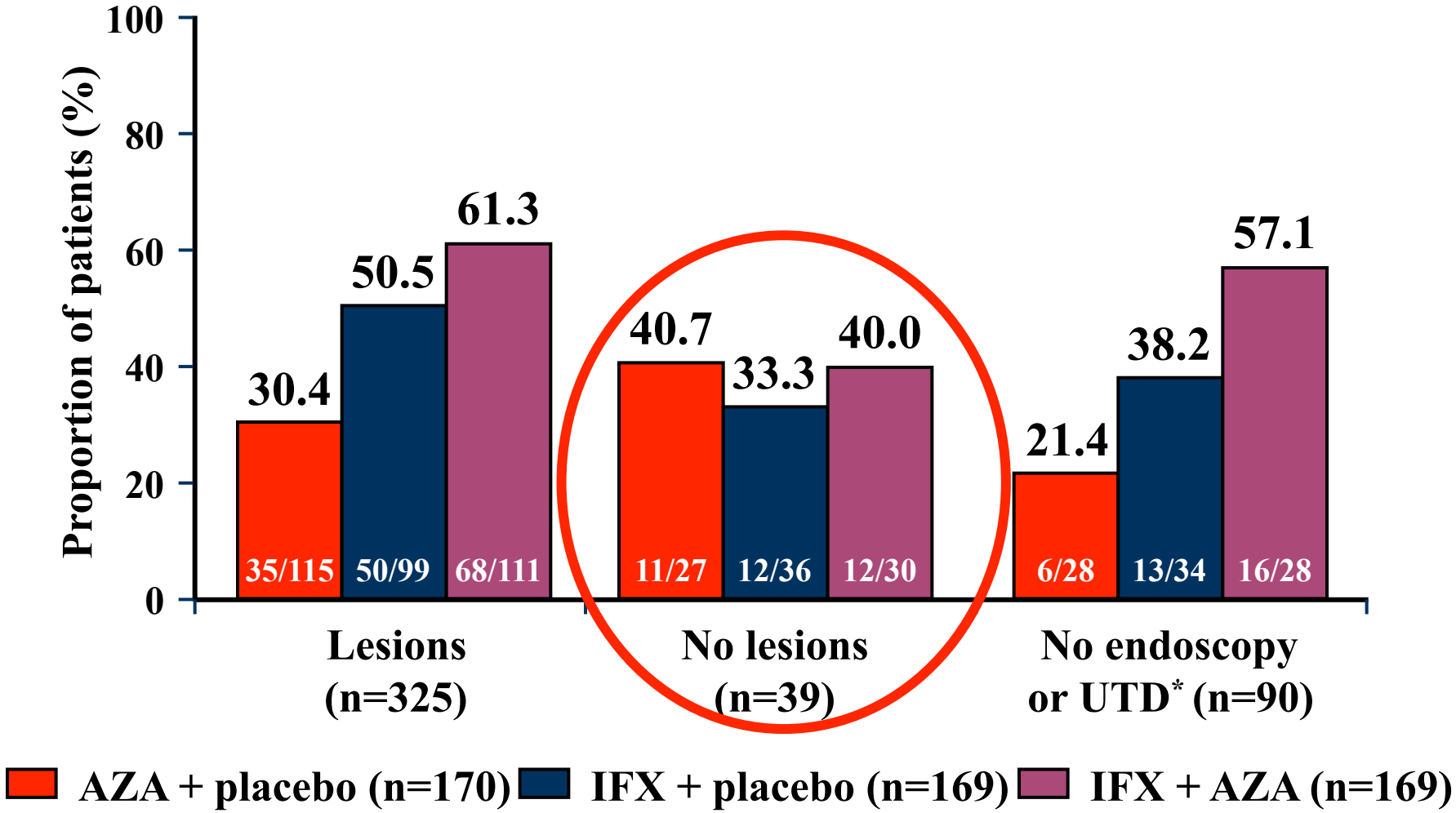
SONIC: AZA vs IFX vs AZA+IFX for early CD



Crohn's disease naïve to azathioprine and anti-TNF

Colombel JF et al. *N Engl J Med* 2010;**362:**1383-95

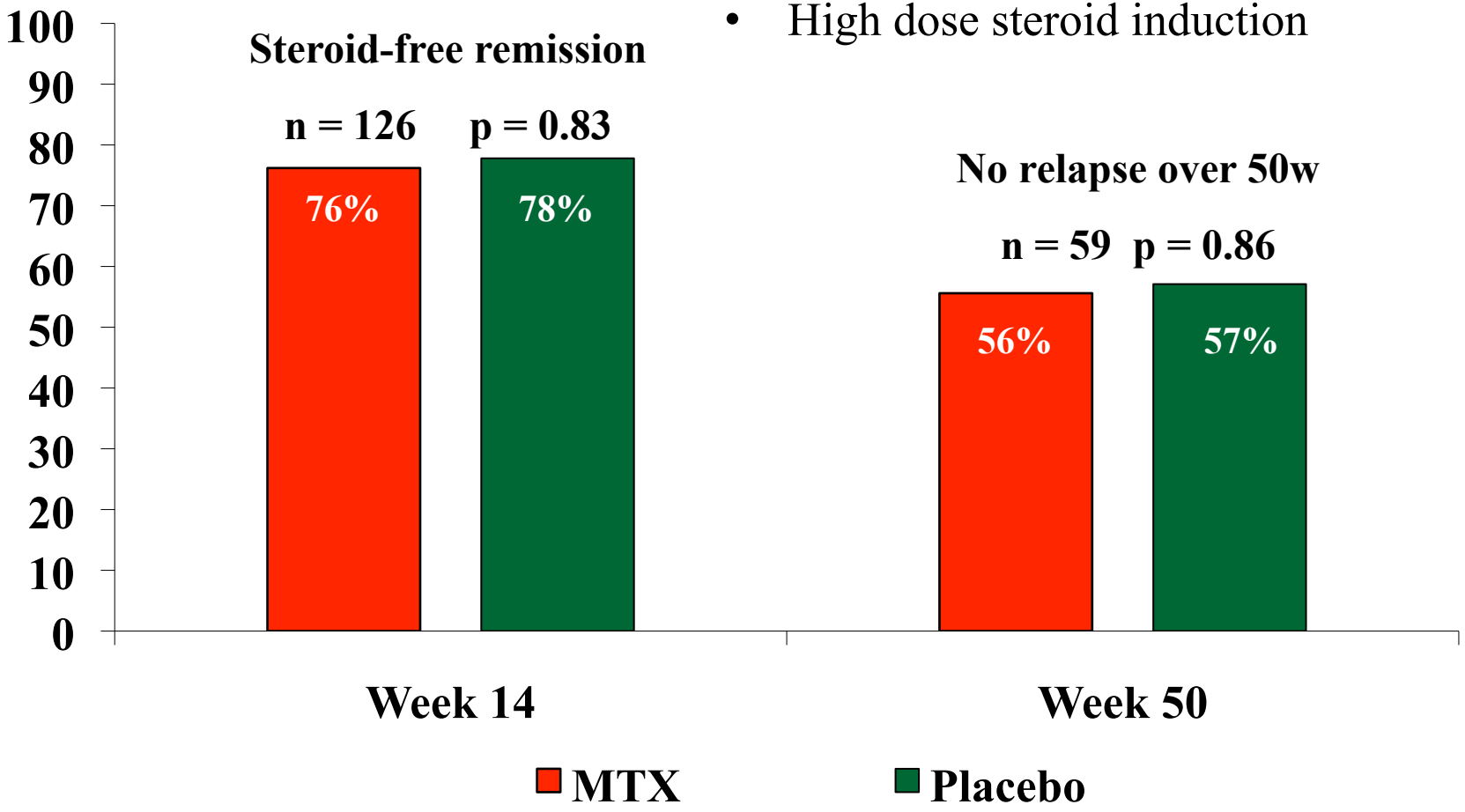
Absence of active disease: steroid-free remission at wk 26 by baseline endoscopy (SONIC)



Colombel JF *et al. N Engl J Med* 2010;**362:**1383–95

COMMIT: IFX +/- MTX: treatment success

- Highest induction rates ever
- No minimum CDAI (30% ≤150)
- 1º = SF-remission (CDAI ≤150)@w14
- High dose steroid induction



Comparative effectiveness combo vs mono RCTs in CD

Systematic review: monotherapy with antitumour necrosis factor α agents versus combination therapy with an immunosuppressive for IBD

Gut ePub 26 June 2014

Parambir S Dulai,[1] Corey A Siegel,[1] Jean-Frederic Colombel,[2] William J Sandborn,[3] Laurent Peyrin-Biroulet[4]

SONIC vs COMMIT for Crohn's disease comparing mono- vs combo-

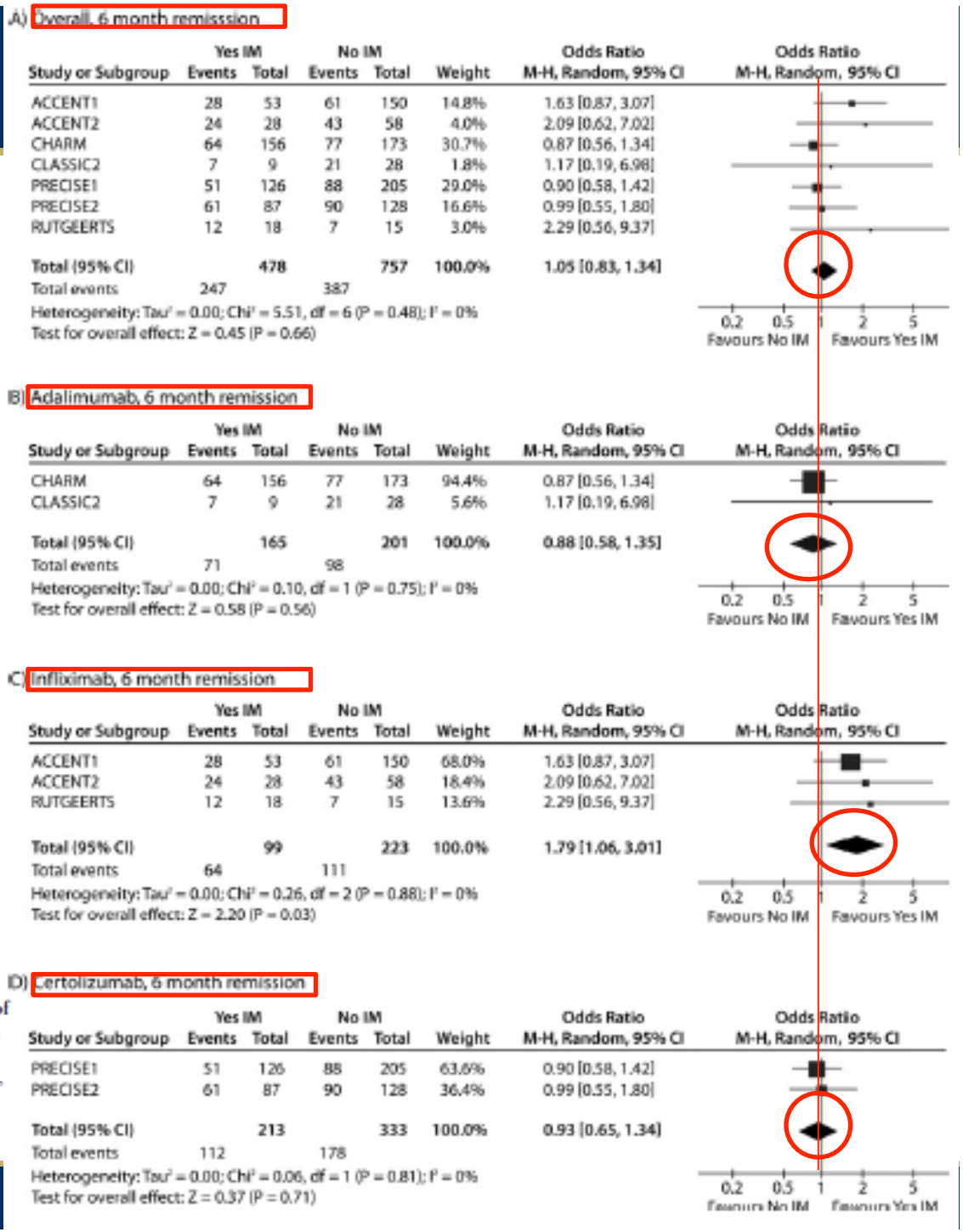
	Crohn's disease			
	SONIC[14]		COMMIT[15]	
	IFX mono	IFX combo	IFX mono	IFX combo
Patient characteristics				
Participants, n	169	169	63	63
Treatment regimen	IFX+PBO	IFX+AZA	IFX+PBO	IFX+MTX
Male, %	50	52	59	54
Mean age, years	35	34	39	40
Disease characteristics				
Mean duration, years	2.2	2.2	9.6	10.9
Extensive*, %	39	44	56	60
Prior surgery, %	28	26	46	57
Prior IS therapy, %	0	0	25	24
Baseline steroids, %	31	28	100	100
Clinical disease activity score†, mean	285	290	208	208
Clinically active disease at baseline‡, %	100	100	73	68
Endoscopic lesions at baseline, %	57	66	n/a	n/a
CRP, mean	1.1	1.0	6.0	3.0§
Outcomes				
Primary CFREM¶, %	44	57§	78	76
Week 50 CFREM, %	35	46§	57	56
Mucosal healing, %	30	44*	n/a	n/a
Antidrug antibody, %	14.6	0.9	20.4	4.0
IFX concentration, mean μg/mL	1.6	3.5§	3.8	6.4
Serious infection, %	4.9	3.9	n/a	n/a

Meta-analysis 2013

- **Impact of combo in RCTs**
  - Overall ‘no’
  - IFX ‘yes’ for combo
  - ADA/CZP ‘no’
  - Abstract only Jones et al *Gastroenterology* 2013:**144:** S179

Impact of Concomitant Immunomodulator Treatment on Efficacy and Safety of Anti-TNF Therapy in Crohn's Disease: A Meta-Analysis of Placebo Controlled Trials With Individual Patient-Level Data

Jennifer Jones, Gilaad G. Kaplan, Laurent Peyrin-Biroulet, Leonard Baidoo, Shane Devlin, Gil Y. Melmed, Divine Tanyingoh, Laura H. Raffals, Peter M. Irving, Patricia L. Kozuch, Miles Sparrow, Fernando S. Velayos, Brian Bressler, Adam S. Cheifetz, Jean-Frederic Colombel, Corey A. Siegel



Comparative effectiveness combo vs mono RCTs in UC

Systematic review: monotherapy with antitumour necrosis factor α agents versus combination therapy with an immunosuppressive for IBD

Parambir S Dulai,[1] Corey A Siegel,[1] Jean-Frederic Colombel,[2] William J Sandborn,[3] Laurent Peyrin-Biroulet[4]

Gut ePub 26 June 2014

Effectiveness in UC-SUCCESS

comparing mono- vs combo-

	UC-SUCCESS[16]	
	IFX mono	IFX combo
Patient characteristics		
Participants, n	78	80
Treatment regimen	IFX+PBO	IFX+AZA
Male, %	54	60
Mean age, years	39	38
Disease characteristics		
Mean duration, years	6.3	5.2
Extensive*, %	19	34
Prior surgery, %	n/a	n/a
Prior IS therapy, %	10	10
Baseline steroids, %	40	48
Clinical disease activity score†, mean	6.0	6.3
Clinically active disease at baseline‡, %	100	100
Endoscopic lesions at baseline, %	99	100
CRP, mean	n/a	n/a
Outcomes		
Primary CFREM¶, %	22	40§
Week 50 CFREM, %	n/a	n/a
Mucosal healing, %	55	63**
Antidrug antibody, %	19	3
IFX concentration, mean μg/mL	n/a	n/a
Serious infection, %	0.01	0

Other trials, clinical remission combo vs mono in CD

Systematic review: monotherapy with antitumour necrosis factor α agents versus combination therapy with an immunosuppressive for IBD

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Parambir S Dulai,[1] Corey A Siegel,[1] Jean-Frederic Colombel,[2] William J Sandborn,[3] Laurent Peyrin-Biroulet[4]

Clinical remission for Crohn's disease with mono- vs combo- cohorts

ACCENT: IFX
PRECISE: CZP
CLASSIC: ADA

	Clinical remission	
ACCENT I	Mono (%)	Combo (%)
IFX		
Induction+Placebo	10	21
Induction+Maintenance	32	37
ACCENT II*		
IFX	38	32
PRECISE 2†		
CTZ		
Induction+Placebo	39	33
Induction+Maintenance	64	61
CLASSIC II		
ADA	45	48

Other trials, clinical remission combo vs mono in UC

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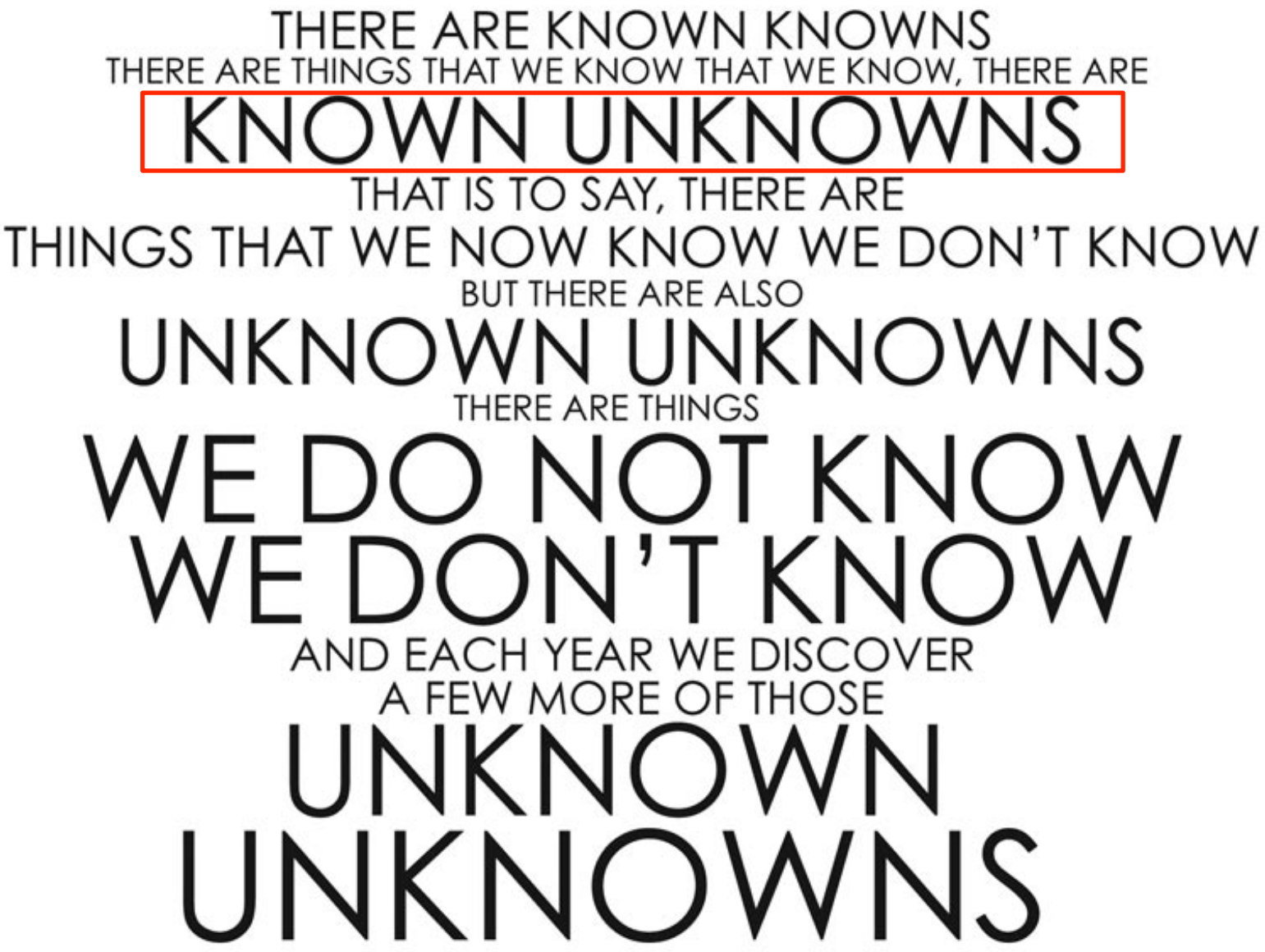
Clinical remission for UC
with mono- vs combo-cohorts

ACT 1/2: IFX
PURSUIT: GOL
ULTRA: ADA unavailable

	Clinical remission	
Agent	Mono (%)	Combo (%)
ACT 1		
IFX	36	34
ACT 2		
IFX	27	36
PURSUIT*		
Golimumab		
Induction+Placebo	34	26
Induction+Maintenance	50	50

Donald Rumsfeld



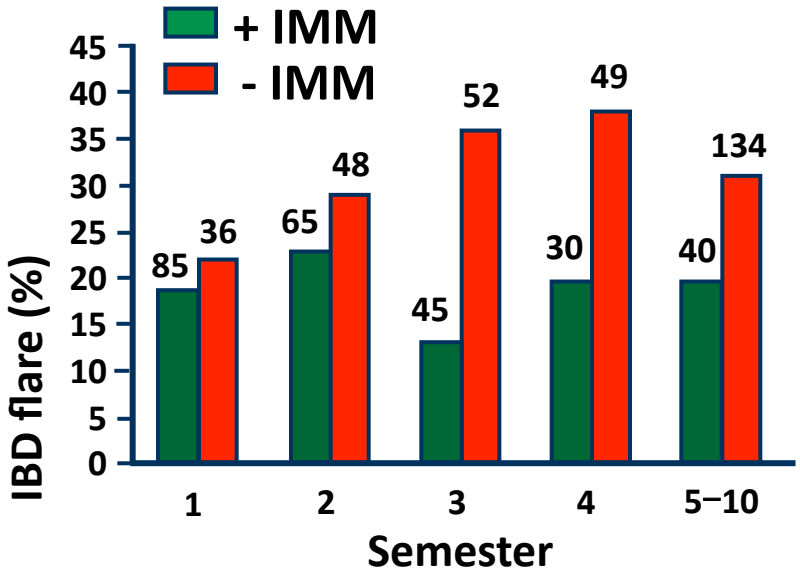
Known unknowns

- **Should you allow IMDs to take effect** before starting biologicals?
- If you do start mono- and lose response, does combo- then help?
- **Is the risk of infection really increased** by combotherapy?
- **What is the real risk of malignancy** on mono- vs combotherapy?
- **Can you safely re-start** combo- after serious infection or malignancy?
- **Do risks resolve** when combotherapy stops?
- **Is it best to stop combo- after 1-2 years**, or best to continue?
- **Can you stop** biologics and maintain with IMDs in some patients?
- What about combo- with **biosimilars, golimumab, or vedo?**

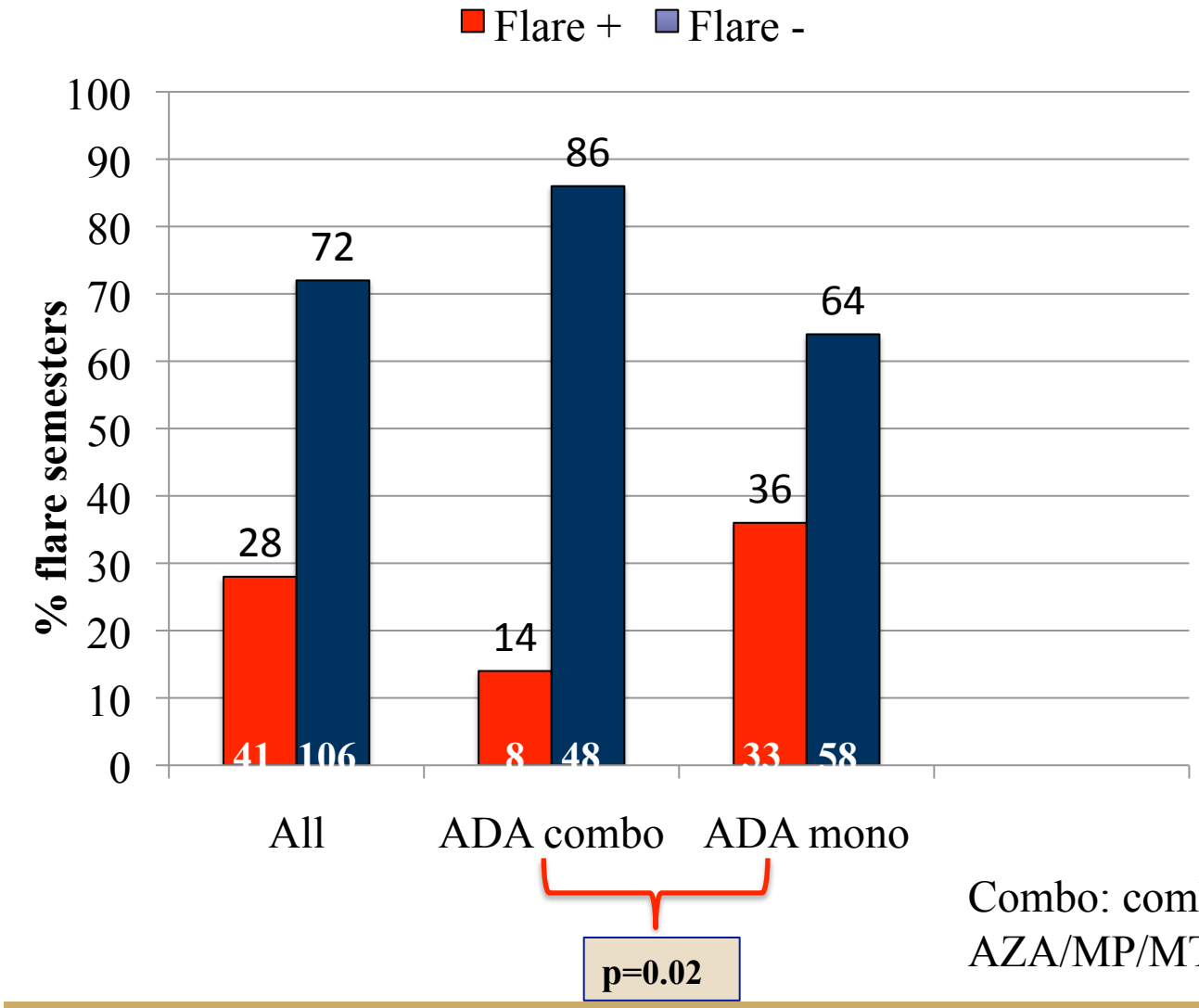
Combo in real life: IFX

- 121 patients on IFX for at least 1 year with at least 6 months' combo with IMD
- Outcomes assessed in 6 month semesters (excluding first 6 months)
- *No* difference if azathioprine-naïve or refractory *at start* of IFX
- 62 patients had colonoscopy during study
  - Mucosal healing (no ulcers): combo 75% vs mono 50% (OR 0.33, CI 0.12−0.93; *p*=0.03)

	+/- IMD		*p*-value
	Yes (n=265)	No (n=319)	
IBD flare (%)	51 (19%)	102 (32%)	0.003
Switch to ADA (%)	3 (1.1)	17 (5.3)	0.003
CRP (mean±SE)	8.7±1.1	10.9±0.8	0.001
IFX g/kg/semester (mean±SE)	16.0±0.3	17.2±0.3	<0.001



Effect of early combo for ADA



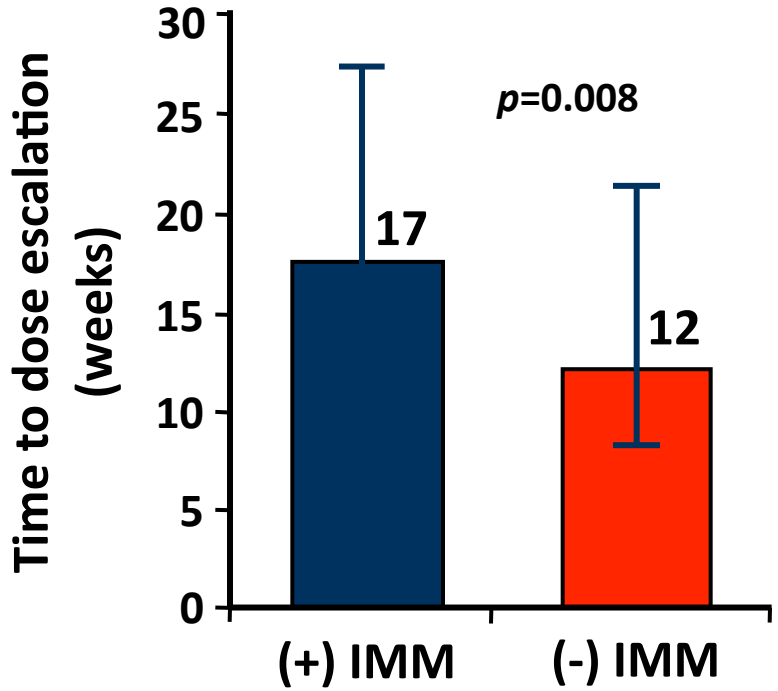
Flares in patients on combo with ADA in first semester, or not

45 patients, 147 semesters

Combo: combination therapy (ADA with AZA/MP/MTX

Mono- vs combo for ADA?

- Concomitant ADA and IMD at baseline did not affect treatment outcome, *p*=0.45
- However, time to dose escalation was longer with ADA combo

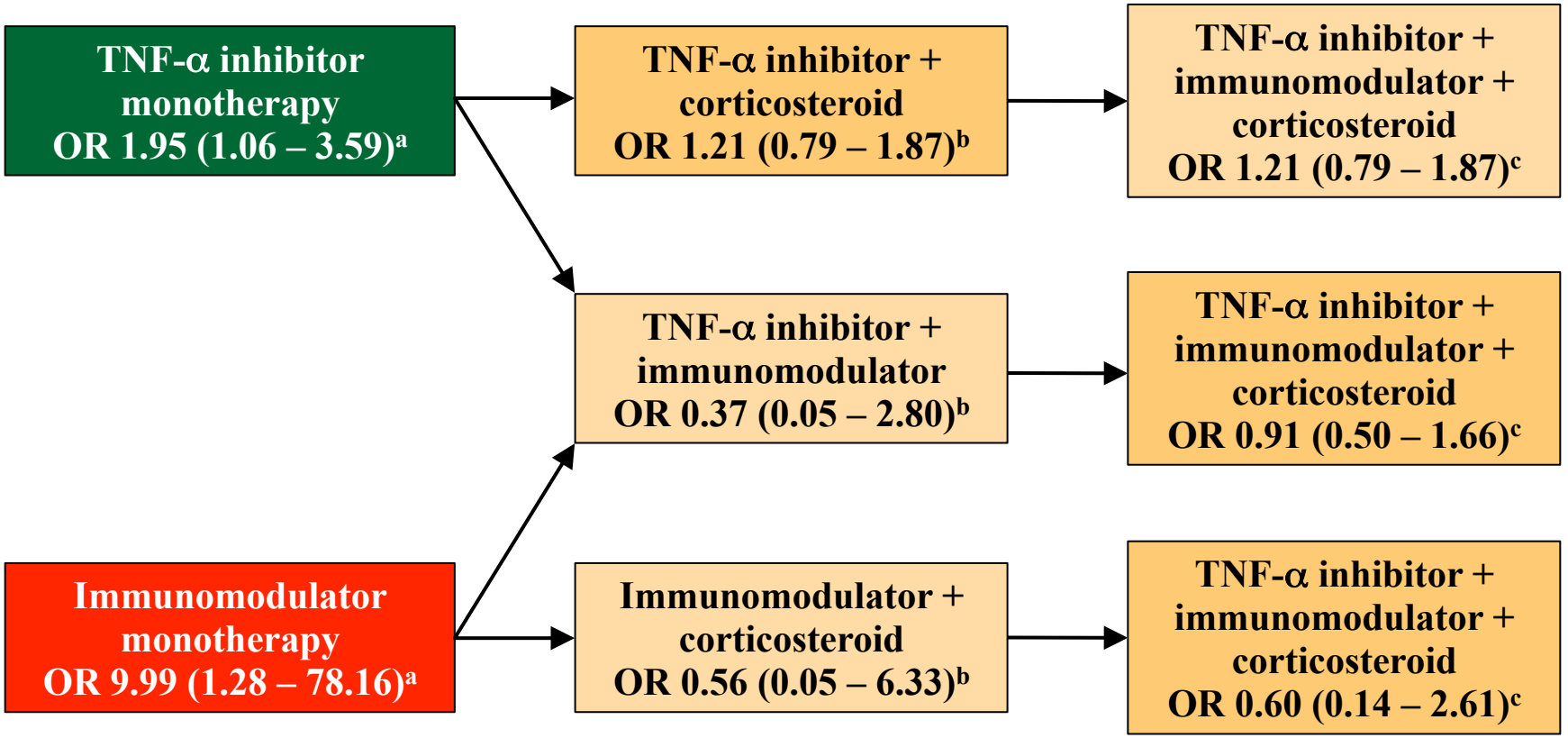


Bars represent 95% confidence intervals

Karmiris K e*t al. Gastroenterol* 2009;**137:**1628–40

Serious infections, anti-TNF & IMDs: mono- vs combo

Incremental odds of serious infections with pharmacotherapy in IBD



[a]Compared to control drugs; [b]Compared to preceding monotherapy; [c]Compared to preceding dual combination therapy

Serious Infections, anti-TNF & IMDs: Mono- vs Combo

Risk of infections with drug therapies in IBD in FDA adverse event reporting system (Jan 2003 – June 2011)

	Infections[a]		Control Reactions[a]	OR	Lower CI	Upper CI	*P* Value[b]
TNF-a blocker monotherapy	All infections Serious infections[c]	3724 1596	253 112	2.17 1.95	1.32 1.06	3.57 3.59	0.003 0.046
Immunomodulators monotherapy	All infections Serious infections	97 73	2 1	7.14 9.99	1.62 1.25	31.41 78.16	0.002 0.009
TNF-a blockers + corticosteroids	All infections Serious infections	717 466	55 27	1.92 2.36	1.10 1.18	3.34 4.75	0.03 0.019
TNF-a blockers + immunomodulators	All infections Serious infections	992 625	47 23	3.11 3.72	1.77 1.82	5.46 7.59	<0.001 <0.001
Immunomodulators + corticosteroids	All infections Serious infections	101 82	3 2	4.96 5.61	1.43 1.23	17.23 25.60	0.006 0.014
TNF-a blockers + immunomodulators + corticosteroids	All infections Serious infections	667 517	27 21	3.64 3.37	1.96 1.63	6.74 6.96	<0.001 0.002
Control drugs	All infections Serious infections	129 95	19 13				

[a]Number of reports; [b]Fisher's exact test; [c]Infections resulting in hospitalizations and/or death

Either serious infections or malignancy: combo vs mono

DESIGN

- Meta-analysis: Medline, Embase and Web of Science (1980 – 2008)
- 11 RCTs with identified pts with luminal and/or fistulizing CD

OBJECTIVE

- Compared safety and efficacy of combo- vs anti-TNF mono in RCT
- Serious adverse events (SAE) = serious infection, malignancy, or death

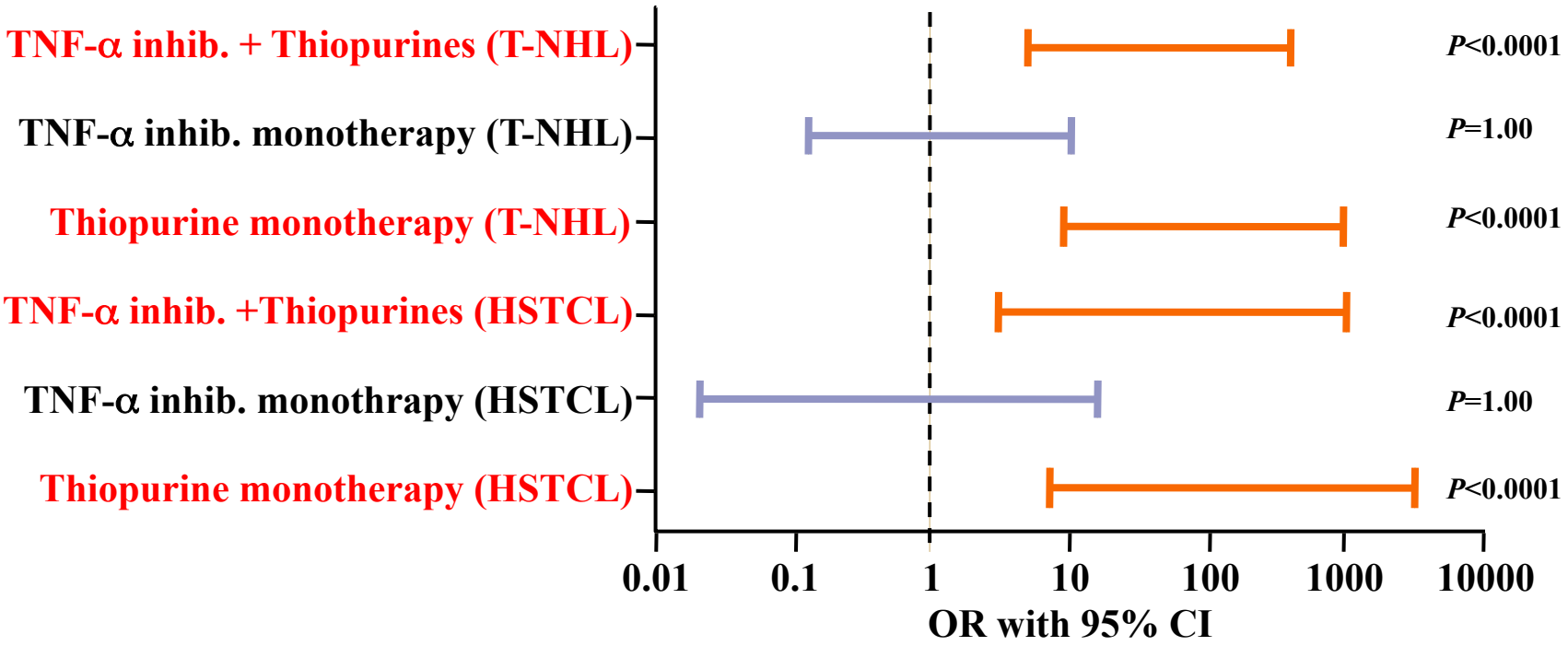
OUTCOMES

- Overall, combo was NOT associated with increased SAE vs anti-TNF mono
- **OR 1.11 (95%CI 0.56–2.20)**
- Included anti-TNF agents:
  - adalimumab
  - infliximab
  - Certolizumab pegol

Jones J, et al. *Gastroenterology.* 2013;**144:**S-179

T-Cell Non-Hodgkin's Lymphoma: REFURBISH

Odds ratios (with 95% CI) of T-cell non-Hodgkin's lymphoma (T-NHL) or Hepatosplenic T-cell lymphoma for TNF-α inhibitors alone, thiopurines alone, or in combination with each other vs other therapies for patients with IBD



Deepak P, et al. *Am J Gastroenterol*. 2013;108:99-105.

Risk synopsis

- **Thiopurines are the main culprit**
- **Thiopurine monotherapy increases the risk of**
  - Serious infections by ten-fold (OR 9.99, 95 %CI 1.25 – 78.16)
  - Lymphoma by around 3-fold
- **Anti-TNF monotherapy increases the risk of**
  - Serious infections doubles (OR 1.95; 95% CI 1.06-3.59)
  - Lymphoma NOT significantly
- **Combotherapy appears NOT to increase the overall risk**
  - OR 1.11 (95%CI 0.56–2.20)
  - But serious infections treble+ (OR 3.72; 95% CI 1.82-7.59)
  - Lymphoma similar to thiopurine monotherapy

Known unknowns

- Should you allow IMDs to take effect before starting biologicals?
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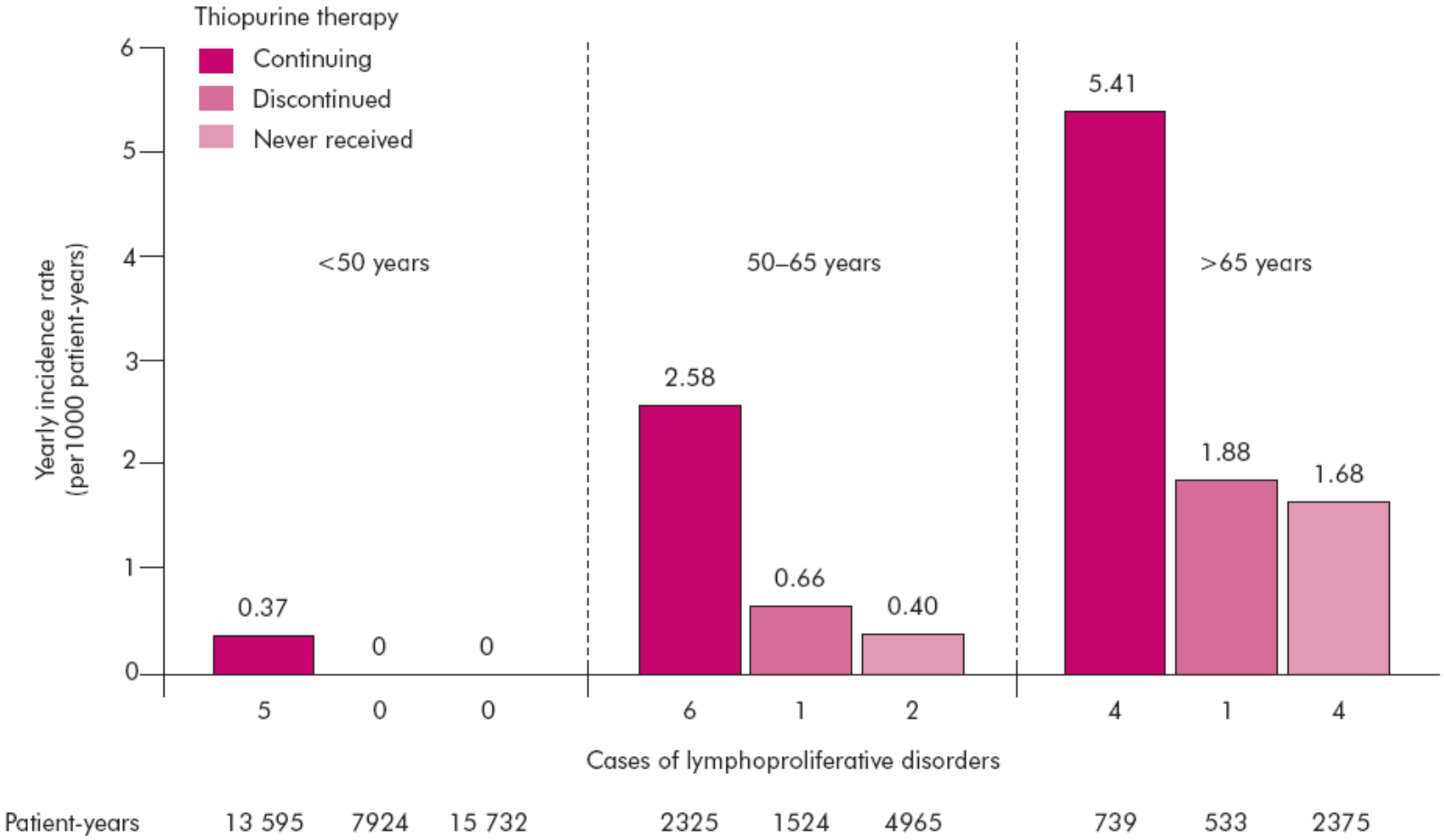
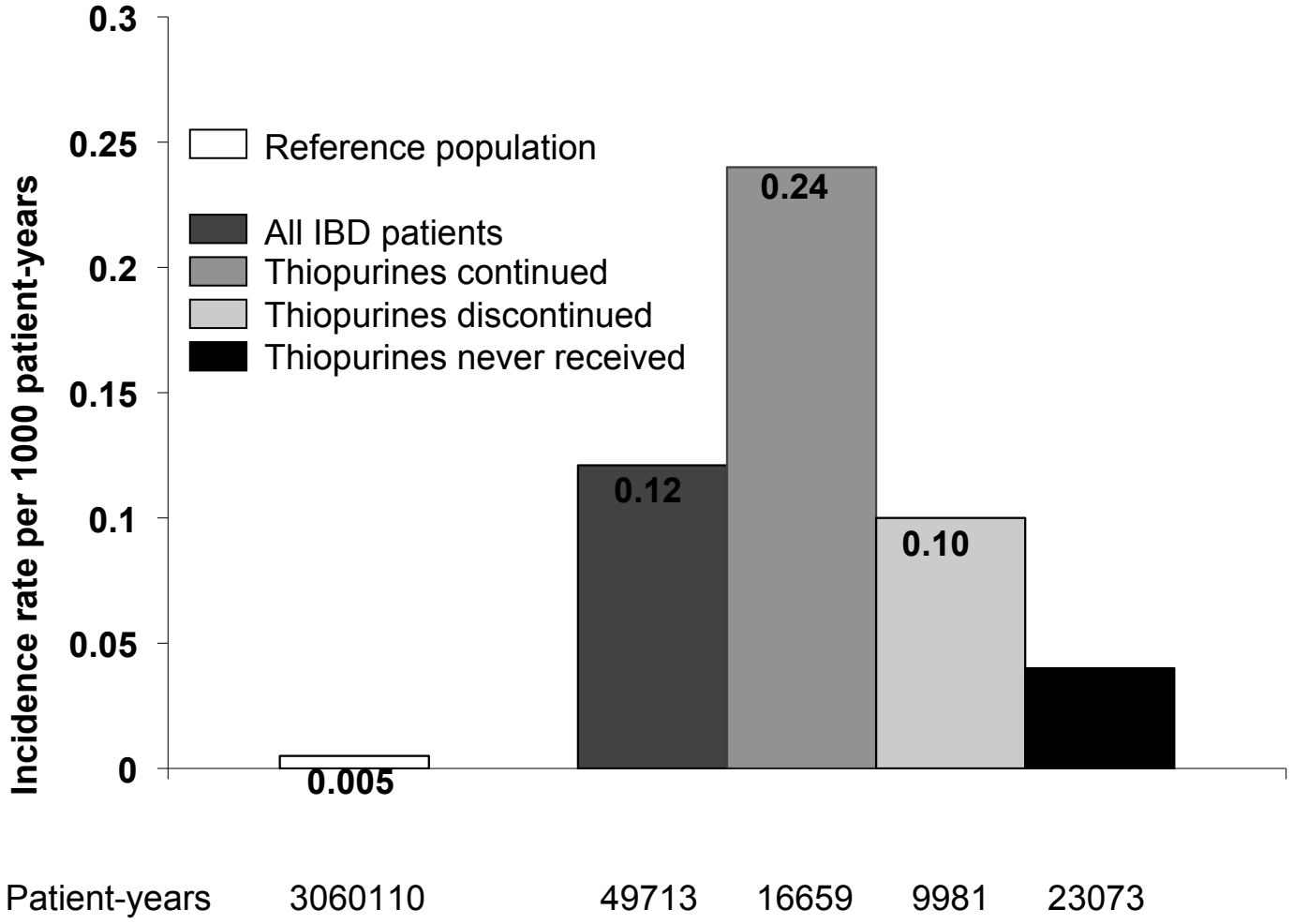
- What is the real risk of malignancy on mono- vs combotherapy?
- Can you safely re-start combo- after serious infection or malignancy?
- Do risks resolve when combotherapy stops?
- Is it best to stop combo- after 1-2 years, or best to continue?
- Can you stop biologics and maintain with IMDs in some patients?
- What about combo- with golimumab, biosimilars, or vedo?

Exposure to thiopurines and lymphomas in IBD



Beaugerie L et al., Lancet 2009;374:1617-25

Primary intestinal lymphomas and thiopurines



Sokol et al. *Inflamm Bowel Dis* 2012

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Withdrawal of immunosuppression in CD with scheduled IFX maintenance

OUTCOMES

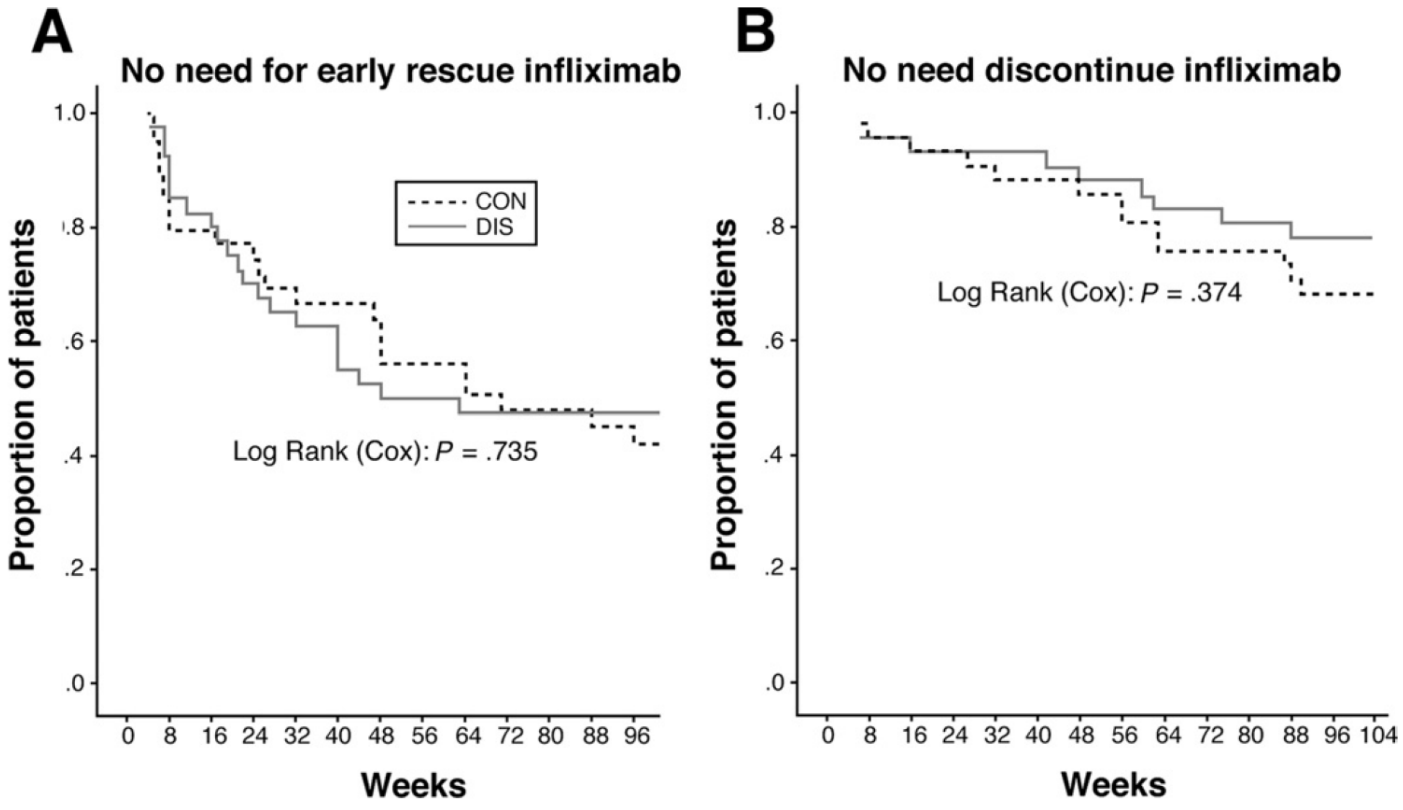


Figure 2. Life table analysis (Kaplan–Meier) of the patient outcomes. (*A*) Analysis in both groups of the need for early rescue IFX or stopping IFX therapy (primary end point). (*B*) Analysis in both groups of the need to stop further IFX therapy. *P* values are listed for the log-rank test only.

Van Assche G, et al. *Gastroenterology* 2008;**134:**1861-1868.

Maintenance of remission in CD on IMD after IFX stopped (STORI)

OUTCOMES

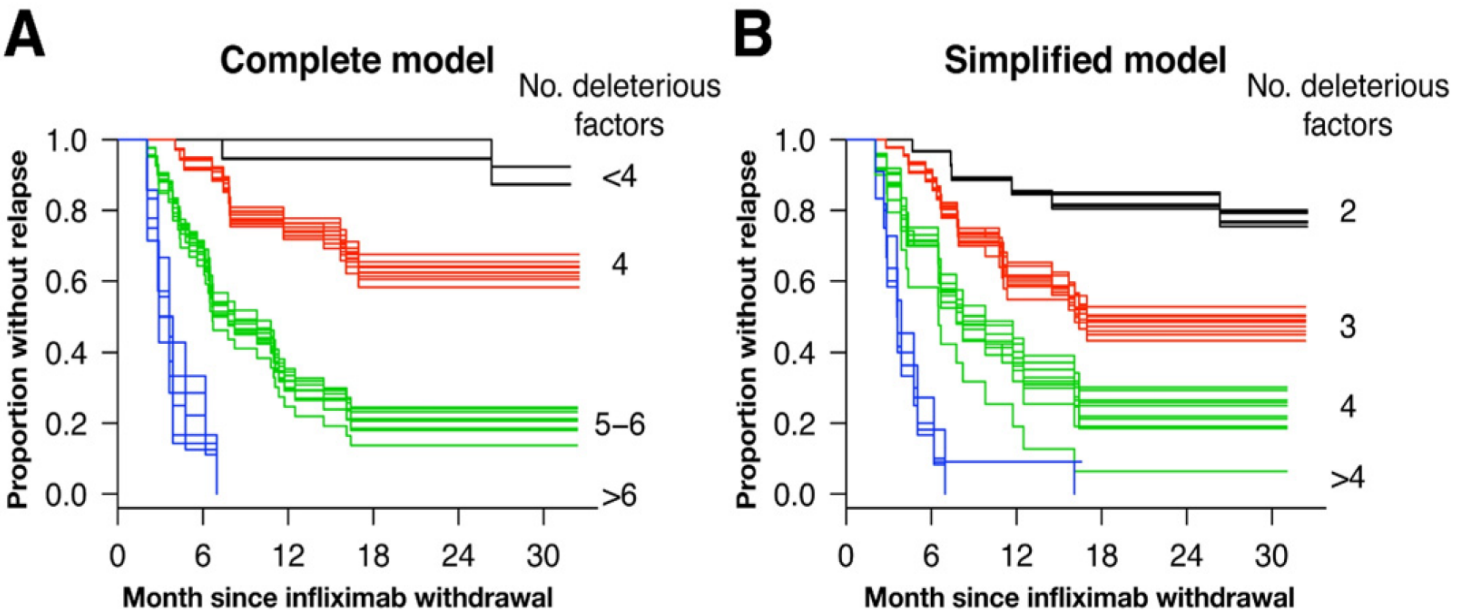
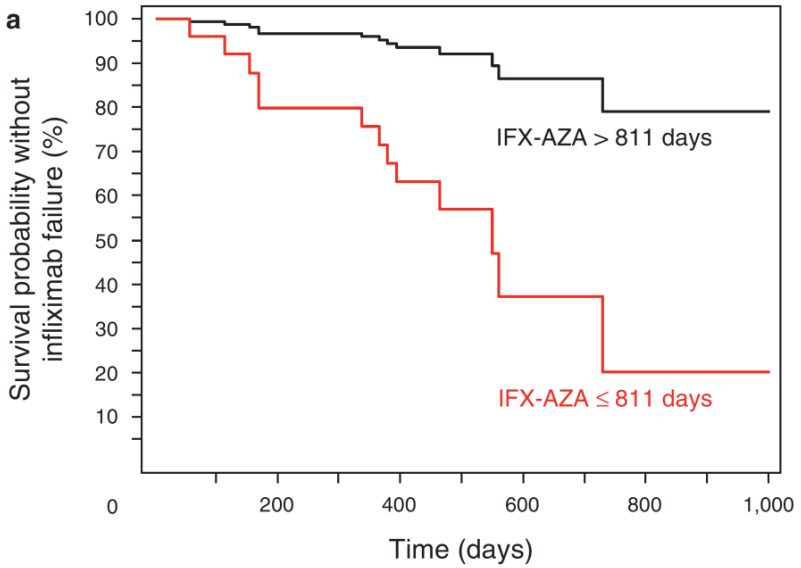


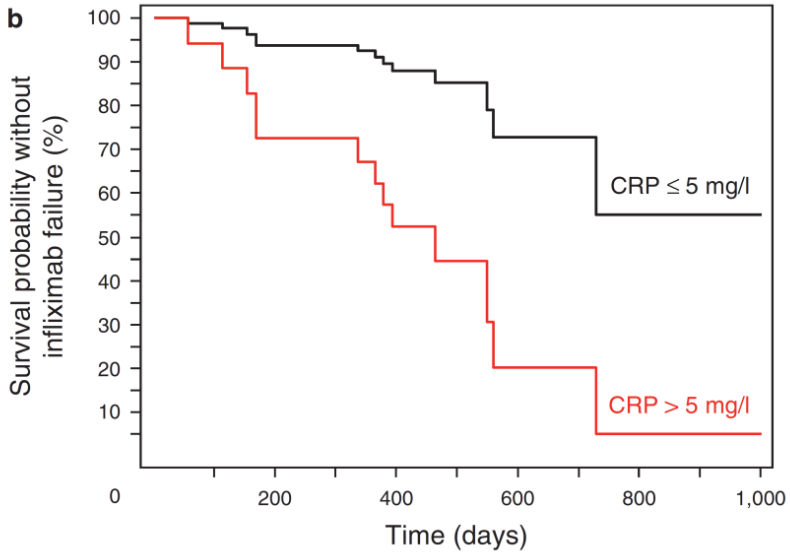
Figure 3. Kaplan–Meier time-to-relapse curves according to multivariable models and scores generated through the Cox model using the multiple imputation method. (*A*) According to a complete model: with this model (Table 2), the subgroup of patients presenting 3 deleterious prognostic factors or less corresponded to zero to one relapse over 1 year among 22 to 25 patients, depending on imputations. (*B*) According to a simplified model without infliximab trough levels and endoscopic data: with this model (Table 2), the subgroup presenting 2 deleterious prognostic factors or less corresponded to 4 relapses over 1 year among 32 to 35 patients, depending on imputations.

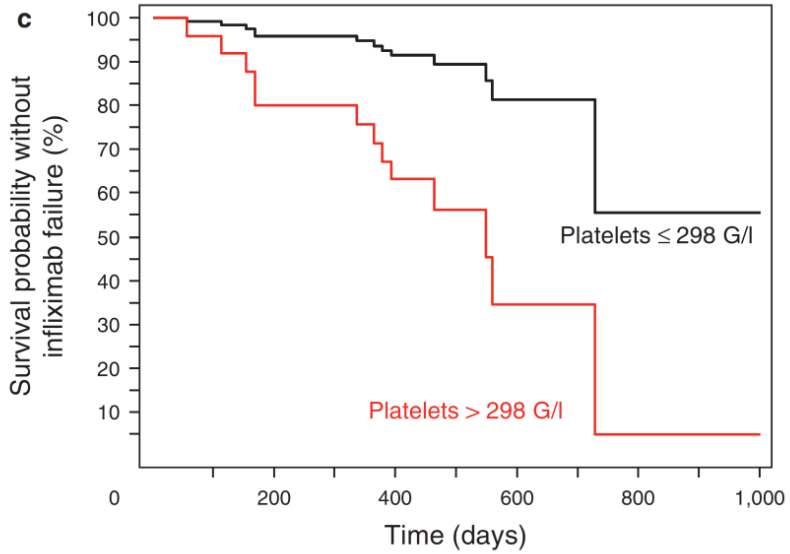
Predictors of IFX failure after AZA withdrawal in CD on comboherapy

OUTCOMES

- Survival analysis using Cox proportional-hazards regression with respect to the 3 independent predictive factors for infliximab failure: (A) “infliximab-azathioprine exposure duration until azathioprine withdrawal (days) ≤811”; (B) “C-reactive protein (mg/L) >5; and







Oussalah A, et al. *Am J Gastroenterol* 2010;**105**:1142-1149

Predictors of relapse in CD in remission after 1 yr of biological therapy (RASH study)

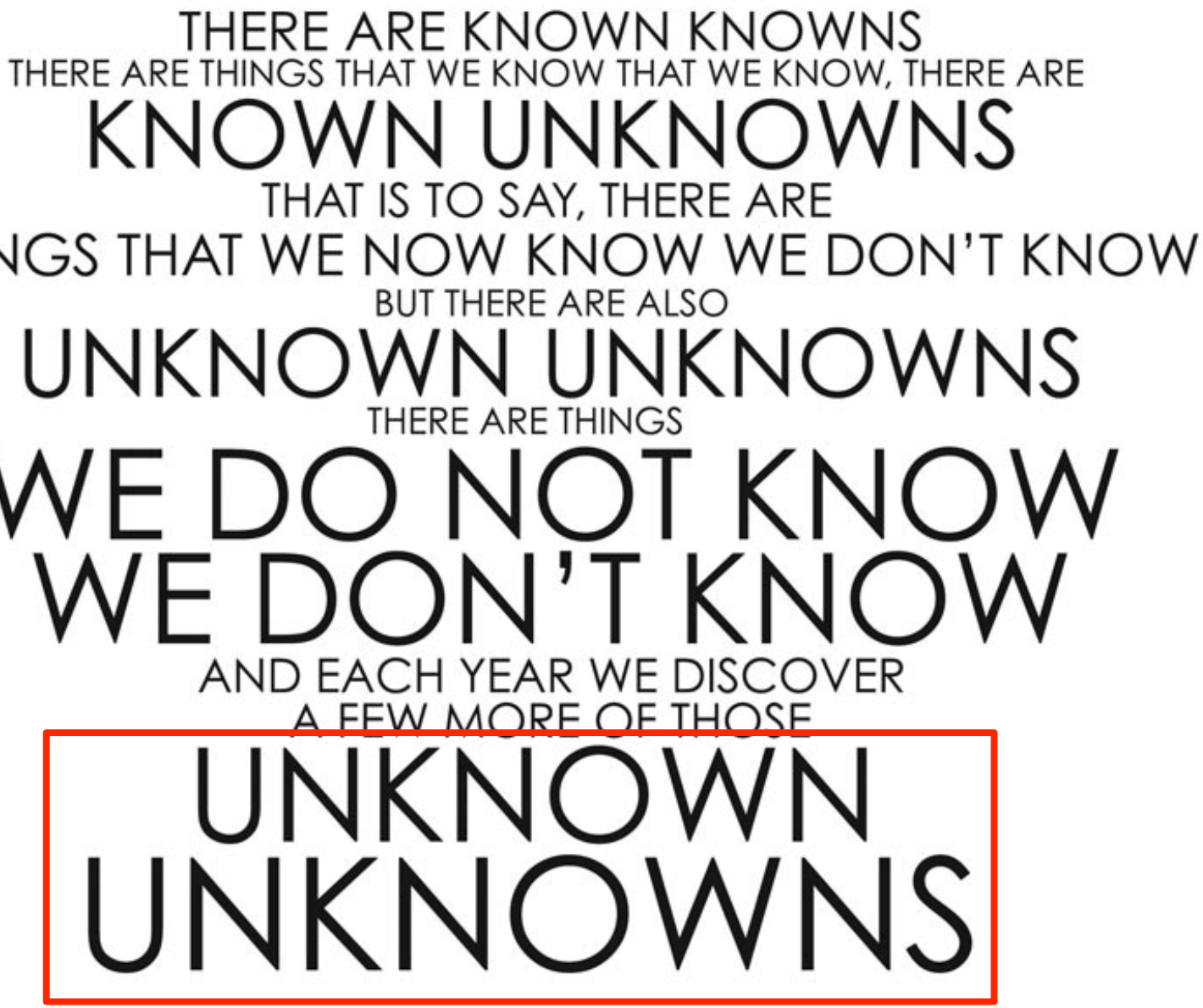
OUTCOMES

- Multivariate logistic regression: predictive factors for restarting biological therapy in Crohn's disease

Factor	*P*-value	OR	95% CI
Dose intensification	0.024	12.96	1.39–120.5
Previous biological therapy	0.011	4.23	1.39–12.84
Smoking	0.053	2.74	0.99–7.59
Elevated CRP at start of 1-year biological therapy	0.08	2.38	0.92–6.19
Corticosteroid use at start of 1-year biological therapy	0.06	1.67	0.97–2.83
Female gender	0.15	0.49	0.19–1.28

Molnár T, et al. *Aliment Pharmacol Ther* 2013;**37**:225-233

Donald Rumsfeld



Conclusions

- **Always use combo- with IFX**
- **Combo- at the start of ADA may be of benefit**
- **Combo- doesn't increase the overall risk of infection or malignancy compared to mon**
- **But either biological or IMD mono- increases the risk to start with –** in more seriously affected patients
- **Biosimilars must be assumed to need combo-**
- **In the meantime…..**

Inflammatory Bowel Diseases 2015

- **CCIB Barcelona, Spain**
- **EACCME approved**
- **Register online at www.ecco-ibd.eu**

- **Back up slides**

T-Cell Non-Hodgkin's Lymphoma: REFURBISH

DESIGN

- Retrospective analysis; all lymphoma cases FDA AE Reporting System; all approved indications and for thiopurines for IBD pts
- Medline search - additional reports
- Subtypes of T-cell NHL reported with anti-TNF-α agents compared to SEER data
- Risk with anti-TNF-α agents, thiopurines, or concomitant use; calculated using 5-ASA as a control drug

OBJECTIVE

- Evaluate risk T-cell NHL with anti-TNF-α agents in comparison to thiopurines in IBD

Table 1. Demographics of patients reported[a] with T-cell non-Hodgkin's lymphomas due to TNF-alpha inhibitor exposure

	TNF-α inhibitor alone	TNF-alpha inhibitor with immunomodulator[b]
Number of cases	32	68
Primary Indication for usage of TNF-alpha inhibitor	15 (RA), 6(AS), 5(CD), 4(Ps), 2 (UC)	31 (CD), 23 (RA), 7 (Ps), 7 (UC)
Mean age (Range) (yrs)	55.27 (20–83)	46.03 (12–86)
Median age (yrs)	56.5	46
Gender	Male: 23 (71.88%) Female: 9 (28.12%)	Male: 43 (63.24%) Female: 24 (35.29%) Unknown: 1 (1.47%)
Outcome	Alive: 13 (40.62%) Death: 7 (21.88%) Unknown: 12 (37.5%)	Alive: 24 (35.29%) Death: 34 (50.0%) Unknown: 10 (14.71%)

AS, ankylosing spondylitis; CD, Crohn's disease; Ps, Psoriasis; RA, rheumatoid arthritis; TNF-α, tumor necrosis factor alpha; yrs, years.

[a]Reported to the Food and Drug Administration Adverse Event Reporting System and/or published literature on PUBMED.

Deepak P, et al. *Am J Gastroenterol* 2013;**108:**99-105

T-Cell Non-Hodgkin's Lymphoma: (REFURBISH)

Table 2. Histological distribution of T-cell non-Hodgkin's lymphomas reported[a] due to exposure to TNF-α inhibitors

Histology of T-cell[b] NHL	TNF-α inhibitor alone	TNF-α inhibitor in combination with immunomodulators[c]
T-cell precursor NHL	1 (AS)	2 (CD)
Mycosis fungoides/Sezary syndrome NHL[d]	6 (RA), 3 (AS), 1(Ps)	5 (RA), 2 (CD), 3 (Ps)
Primary cutaneous anaplastic large cell	—	1 (CD)
Peripheral T-cell lymphoma, NOS	1 (RA)	1 (UC), 2 (Ps)
Angioimmunoblastic T-cell lymphoma	—	1 (RA)
SPLTCL[e]	2 (RA), 1(AS)	1 (RA)
Anaplastic large-cell lymphoma, T or null cell[f]	1 (UC), 1(AS)	2 (CD), 2 (RA)
Hepatosplenic T-cell lymphoma[g]	1 (CD)	19 (CD), 4 (RA), 5 (UC), 1(Ps)
NK/T-cell lymphoma, nasal-type, aggressive NK leukemia	—	1 (CD), 1 (UC)
NHL, NOS, T cell[h]	6 (RA), 3 (Ps), 4 (CD), 1 (UC)	10 (RA), 4 (CD), 1 (Ps)

Table 4. Histology of T-cell NHL[a] with TNF-α inhibitors (alone or in combination with immunomodulators[b]) compared with T-cell NHL reported in SEER-17 registry

Histology of T-cell NHL	TNF-α inhibitor exposure (%)	SEER-17 registry (%)
T-cell precursor NHL	3	25.49
Mycosis fungoides/Sezary syndrome NHL	20	9.27
Primary cutaneous anaplastic large cell	1	0.60
Peripheral T-cell lymphoma, NOS	4	13.78
Angioimmunoblastic T-cell lymphoma	1	0.83
SPLTCL	4	0.09
Anaplastic large cell lymphoma, T or null cell, systemic	6	2.56
Hepatosplenic T-cell lymphoma	30	0.07
NK/T-cell lymphoma, nasal-type, aggressive NK leukemia	2	0.45
NHL, NOS, T cell	29	42.54

[a]Azathioprine, 6-mercaptopurine, methotrexate, leflunomide, or cyclosporine. [b]Cases subdivided into the total number of cases reported with each approved primary indication for TNF a inhibitor usage. [c]Azathioprine, 6-mercaptopurine, methotrexate, leflunomide, or cyclosporine. [d]Five cases of cutaneous lymphomas reported in literature, not in AERS. [e]One case of SPLTCL reported in literature, not in AERS. [f]One case of anaplastic large cell lymphoma reported in literature, not in AERS. [g]One case of HSTCL reported in literature, not in AERS. [h]One case of T cell NHL, NOS reported in literature, not in AERS.

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T-Cell Non-Hodgkin's Lymphoma: REFURBISH

Table 3. New cases of hepatosplenic T-cell lymphoma[a] with TNF-α inhibitor exposure

	Age	Gender	Diagnosis	Biology	Thiopurine	TCR	Treatment	Outcome
1.	19	M	UC	IFX (2.9 yrs)	AZA (1 yr)	NR	Splenectomy, Chemo	Died
2.	34	F	CD	IFX (3.56 yrs)	AZA (3.56 yrs)	γδ	Splenectomy, Chemo	Alive
3.	68	F	RA	IFX	AZA	NR	Hospice	Died

AZA, azathioprine; CD, Crohn's disease; Chemo, chemotherapy; F, female; γδ, gamma–delta; IFX, infliximab; M, male; NR, not recorded; RA, rheumatoid arthritis; TCR, T-cell receptor; TNF-α, tumor necrosis factor alpha; UC, ulcerative colitis; yrs, years.

[a]Reported to the Food and Drug Administration Adverse Event Reporting System, not in published literature.

Table 5. Test (T-cell NHL and HSTCL) and control events reported[a] with TNF-α inhibitors (alone or in combination with thiopurines) in inflammatory bowel disease patients

	T-cell NHL	Control events	*P* value	Confidence intervals
TNF-α inhibitor with thiopurine	36	12	<0.0001	4.98–354.09
TNF-α inhibitor alone	6	71	1.00	0.13–10.61
Thiopurines alone	19	3	<0.0001	8.32–945.38
Control drugs	1	14	—	—
	HSTCL	**Control events**	***P* value**	**Confidence intervals**
TNF-α inhibitor with thiopurine	23	12	*P*<0.0001	2.99–993.04
TNF-α inhibitor alone	1	71	*P*=1.00	0.02–15.70
Thiopurines alone	17	3	*P*<0.0001	6.90–3045.2
Control drugs	0	14	—	—

HSTCL, hepatosplenic T-cell lymphoma; NHL, non-Hodgkin's lymphoma; TNF-α, tumor necrosis factor alpha.

[a]Reported to the Food and Drug Administration Adverse Event Reporting System only.

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All malignancies: Infliximab ± Immunomodulators

Table 4. Summary of malignancies (excluding nonmelanoma skin cancers) by treatment both overall and during the main portions of all infliximab IBD studies[a] and by immunomodulator use during the controlled portions of the pivotal phase 3 IBD trials[b]

	Crohn's disease		Ulcerative colitis		All inflammatory bowel disease	
	Placebo[c]	Infliximab	Placebo[c]	Infliximab	Placebo[c]	Infliximab
Overall among all infliximab IBD studies[a]						
Pts. treated	217	1,427	248	493	465	1,920
Total/median pt-yrs of follow-up	124/0.5	1,229/1.0	210/0.6	832/1.0	334/0.6	2,061/1.0
All malignancies						
No. (%) of pts. with malignancy	2 (0.9%)	6 (0.4%)	0 (0.0%)	5 (1.0%)	2 (0.4%)	11 (0.6%)
P-value[d]	0.286		0.175		1	
Incidence per 100 pt-yrs	1.61	0.49	0	0.6	0.6	0.53
95% CI[e]	(0.19, 5.82)	(0.18, 1.06)	(0.00, 1.43)	(0.20, 1.40)	(0.07, 2.16)	(0.27, 0.95)
	No immuno-modulator[f]	**Immuno modulator[g]**	**No immuno-modulator[f]**	**Immuno modulator[g]**	**No immuno-modulator[f]**	**Immuno-modulator[g]**
Controlled portions of 5 pivotal IBD studies[b]						
Pts. treated	166	337	394	334	560	671
All malignancies						
Total/median pt-yrs of follow-up	129/1.0	250/0.9	250/0.6	220/0.6	378/0.6	470/0.7
No. (%) of pts. with malignancy	0 (0.0%)	2 (0.6%)	1 (0.3%)	1 (0.3%)	1 (0.2%)	3 (0.5%)
P-value	1		1		0.631	
Incidence per 100 pt-yrs	0	0.8	0.4	0.45	0.26	0.64
95% CI	(0.00, 2.33)	(0.10, 2.89)	(0.01, 2.23)	(0.01, 2.53)	(0.01, 1.47)	(0.13, 1.87)
Expected no. of pts.[h]	0.43	0.71	1.22	0.88	1.65	1.6
SIR[i]	0	2.8	0.82	1.13	0.61	1.88
SIR 95% CI	(0.00, 6.92)	(0.34, 10.11)	(0.02, 4.58)	(0.03, 6.30)	(0.02, 3.38)	(0.39, 5.48)

Lichtenstein GR, et al. *Am J Gastroenterol.* 2012;**107:**1051-1063

All malignancies: Adalimumab ± Immunomodulators

ADA monotherapy[a]			ADA + thiopurine[b]			ADA + methotrexate[b]		
Malignancy	N of patients	N of events	Malignancy	N of patients	N of events	Malignancy	N of patient	N of events
Malignancies other than NMSC								
Anal cancer	1	1	Acute myeloid leukemia	1	1	Bronchial carcinoma	1	1
Breast cancer (in situ)	1	1	Bladder cancer	1	1	Lymphoma	1	1
Colon cancer	1	1	Breast cancer	1	1	Renal cell carcinoma	1	1
Langerhans cell histiocytosis	1	1	Glioblastoma multiforme	1	1	Thyroid cancer	1	1
Thyroid cancer	1	1	Hepatic neoplasm malignant	1	3			
Vaginal cancer (recurrent)	1	1	Lung adenocarcinoma[c]	1	1			
			Non-Hodgkin lymphoma	1	1			
			Ovarian cancer	1	1			
			Prostate cancer	1	1			
			Vulval cancer	1	1			
NMSC								
Basal cell carcinoma	3	4	Basal cell carcinoma	6	7	Basal cell carcinoma	1	1
Skin cancer[d]	2	2	Bowen disease[c]	1	1	Squamous cell carcinoma	1	1
			Squamous cell carcinoma	4	6			

ADA, adalimumab.
[a]In the monotherapy group 1 patient had both basal cell carcinoma and skin cancer reported.
[b]In the ADA + thiopurine and the ADA + methotrexate groups, 1 patient each had both squamous cell carcinoma and basal cell carcinoma reported.
[c]The patient with lung adenocarcinoma also had Bowen disease.
[d]Not otherwise specified.

Osterman MT, et al. *Gastroenterology* 2014;**146:**941-949.