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Is There Still a Role for Immunomodulators?

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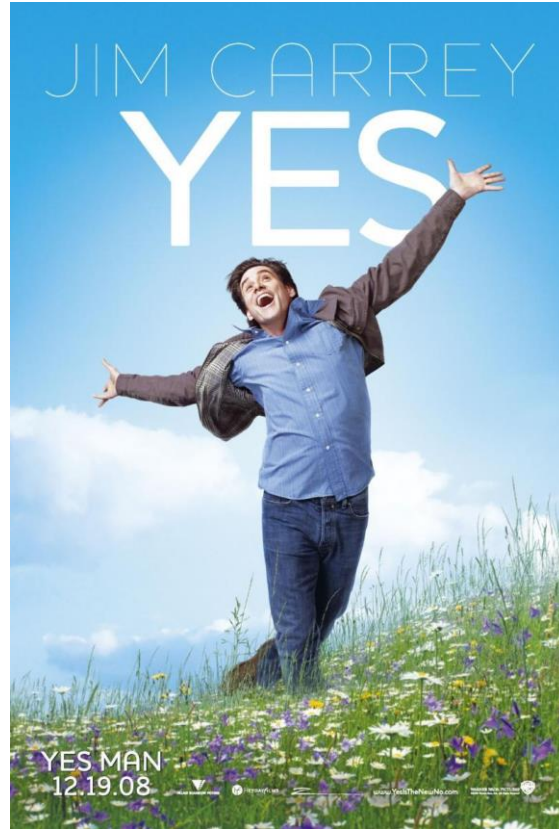
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- There are a no financial relationships to disclose at this time.

Is There Still a Role for Immunomodulators?



Thiopurines in the Era of Biologics

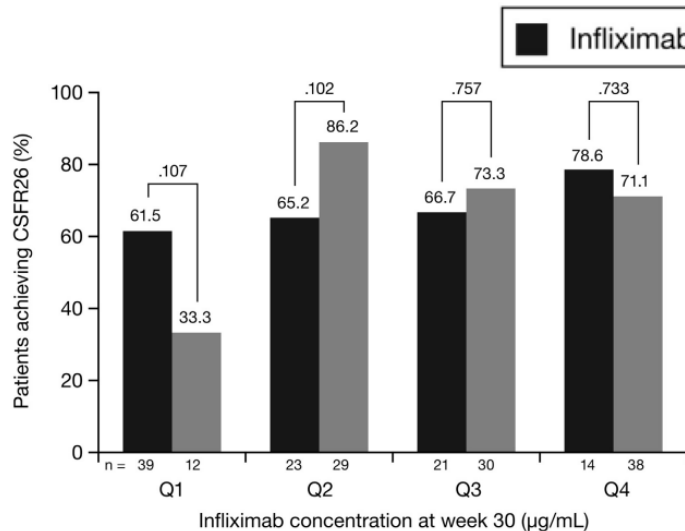
- Combination with anti-TNF agents
- Combination with non-anti-TNF biologics

Thiopurine – anti-TNF Combination Therapy

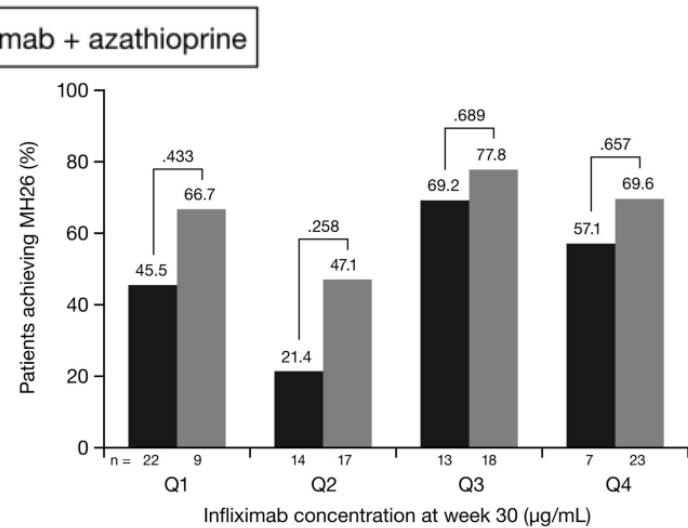
- Improved efficacy in both CD and UC
- Lower incidence of anti-drug antibodies
- Higher anti-TNF trough levels

Thiopurine – anti-TNF Combination Therapy

Corticosteroid-free remission
at week 26 by IFX TL at week 30



Mucosal Healing
at week 26 by IFX TL at week 30



Q1, <0.84 $\mu\text{g/mL}$; Q2, ≥ 0.84 $\mu\text{g/mL}$ to <2.36 $\mu\text{g/mL}$;
Q3, ≥ 2.36 $\mu\text{g/mL}$ to <5.02 $\mu\text{g/mL}$; Q4, ≥ 5.02 $\mu\text{g/mL}$

Network Meta-analysis in Crohn's Disease

Biologic-naïve patients

Clinical Remission									
Clinical Response	Infliximab	0.61 (0.31,1.19)	1.50 (0.54,4.22)	2.65 (0.70,10.02)	1.72 (0.61,4.87)	2.07 (0.63,6.87)	2.28 (0.73,7.06)	4.53 (1.49,13.79)	6.17 (2.54,15.01)
	0.56 (0.36,0.87)	Infliximab + Thiopurine	2.49 (0.73,8.52)	4.38 (0.99,19.45)	2.85 (0.83,9.82)	3.43 (0.87,13.54)	3.76 (1.01,14.03)	7.49 (2.04,27.49)	10.20 (3.34,31.10)
	8.84 (1.95,40.03)	15.88 (3.29,76.64)	Adalimumab	1.76 (0.76,4.08)	1.15 (0.66,1.99)	1.38 (0.51,3.69)	1.51 (0.61,3.74)	3.01 (1.25,7.27)	4.10 (2.31,7.27)
	-	-	-	Adalimumab + Thiopurine	0.65 (0.24,1.77)	0.78 (0.21,2.85)	0.86 (0.25,2.95)	1.71 (0.51,5.77)	2.33 (0.84,6.43)
	7.90 (1.78,35.10)	14.18 (2.99,67.26)	0.89 (0.61,1.31)	-	Ustekinumab	0.83 (0.31,2.21)	1.32 (0.54,3.23)	2.63 (1.10,6.28)	3.58 (2.05,6.25)
	-	-	-	-	-	Risankizumab	1.10 (0.38,3.19)	2.19 (0.77,6.21)	2.98 (1.33,6.64)
	12.76 (2.76,59.08)	22.91 (4.64,113.02)	1.44 (0.75,2.80)	-	1.62 (0.87,3.00)	-	Vedolizumab	1.99 (0.75,5.26)	2.71 (1.34,5.48)
	15.08 (3.46,65.83)	27.08 (5.81,126.25)	1.71 (1.02,2.84)	-	1.91 (1.21,3.00)	-	1.18 (0.67,2.10)	Certolizumab Pegol	1.36 (0.70,2.66)
	22.00 (5.17,93.56)	39.49 (8.68,179.61)	2.49 (1.62,3.82)	-	2.79 (1.94,3.99)	-	1.72 (1.04,2.85)	1.46 (1.11,1.92)	Placebo

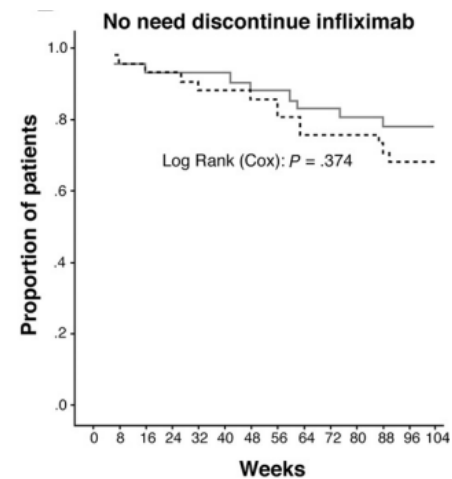
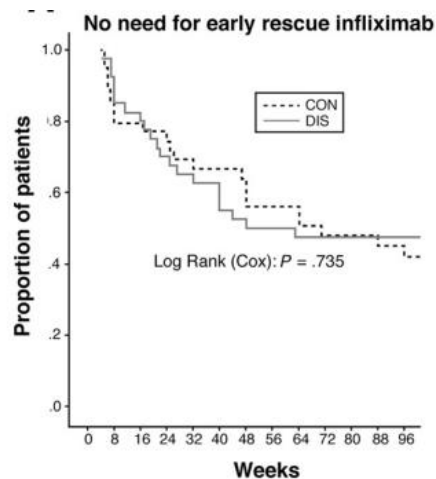
Network Meta-analysis in Crohn's Disease

		Clinical Remission							
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	Infliximab + Thiopurines	0.56 (0.36,0.87)	2.49	1.38	2.85	3.43	3.76	7.49	10.20 (3.34,31.10)
	Adalimumab	8.84	15.88	1.76	1.15	1.38	1.51	3.01	4.10
	-	-	-	0.65	0.78	0.86	1.71	2.33	
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	15.08 (3.46,65.83)	27.08 (5.81,126.25)	1.71 (1.02,2.84)	-	1.91 (1.21,3.00)	-	1.18 (0.67,2.10)	Certolizumab Pegol	1.36 (0.70,2.66)
22.00 (5.17,93.56)	39.49 (8.68,179.61)	2.49 (1.62,3.82)	-	2.79 (1.94,3.99)	-	1.72 (1.04,2.85)	1.46 (1.11,1.92)	Placebo	

Infliximab in combination with azathioprine is the highest ranked treatment for induction of clinical remission in biologic-naïve patients and maintenance of remission

Thiopurine – anti-TNF Combination Therapy: Can thiopurine therapy be withdrawn in CD?

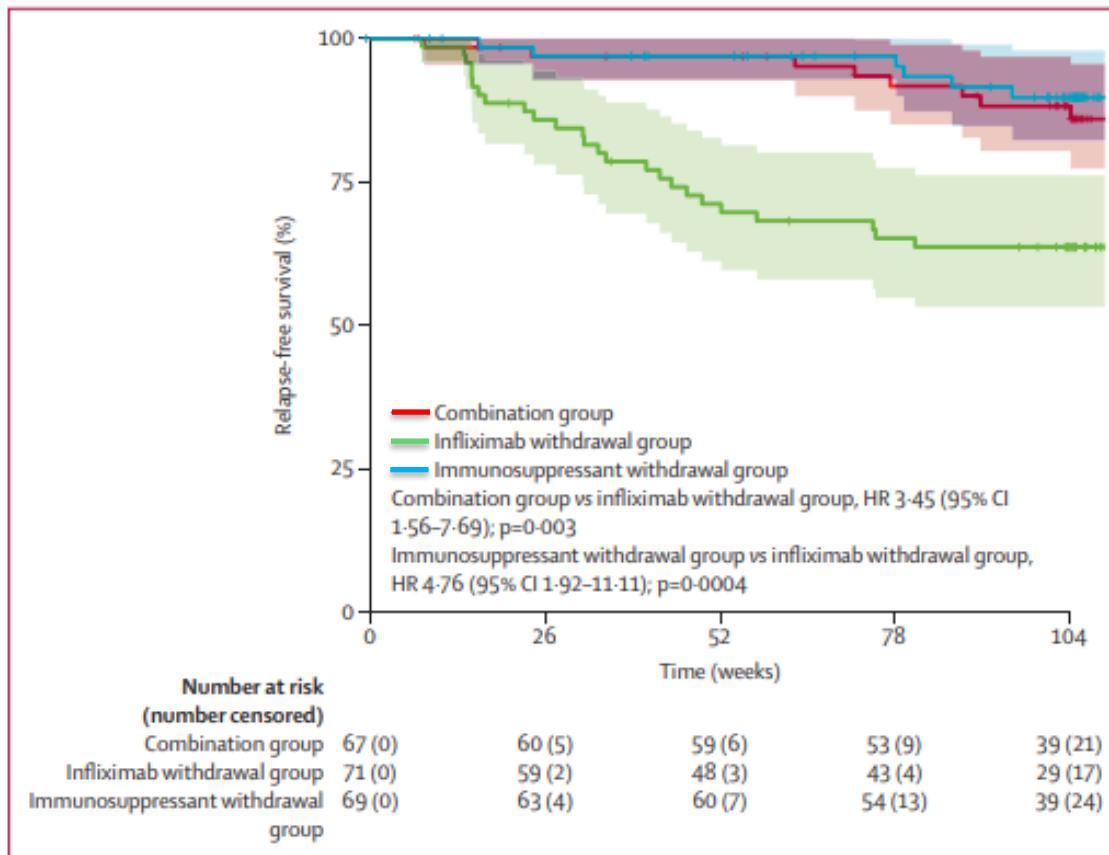
- Open label RCT: Continuing (n=40) vs. discontinuing IS (n=40) ≥ 6 months after IFX
- IFX maintenance for 104 weeks
- **Similar proportions had a change in IFX dosing interval or stopped IFX**
- CRP was higher and IFX trough levels were lower in the Dis group
- Mucosal ulcers absent in 64% (Con) and 61% (Dis) at 104 weeks



Thiopurine – anti-TNF Combination Therapy: Can thiopurine therapy be withdrawn in CD?

- Patients in steroid-free clinical remission for >6 months on combination IFX-IS therapy for >8 months
- Open label RCT:
 - Combination (n=67)
 - IFX withdrawal (n=71)
 - IS withdrawal (n=69)
- Randomization stratified according to
 - Disease duration before start of first anti-TNF treatment (≤ 2 or > 2 years)
 - Failure of IS therapy before start of IFX
 - Presence of ulcers at baseline endoscopy

Thiopurine – anti-TNF Combination Therapy: Can thiopurine therapy be withdrawn in CD?



2-year relapse rates

10% (2–18)

14% (4–23)

36% (24–47)

Predictors of relapse

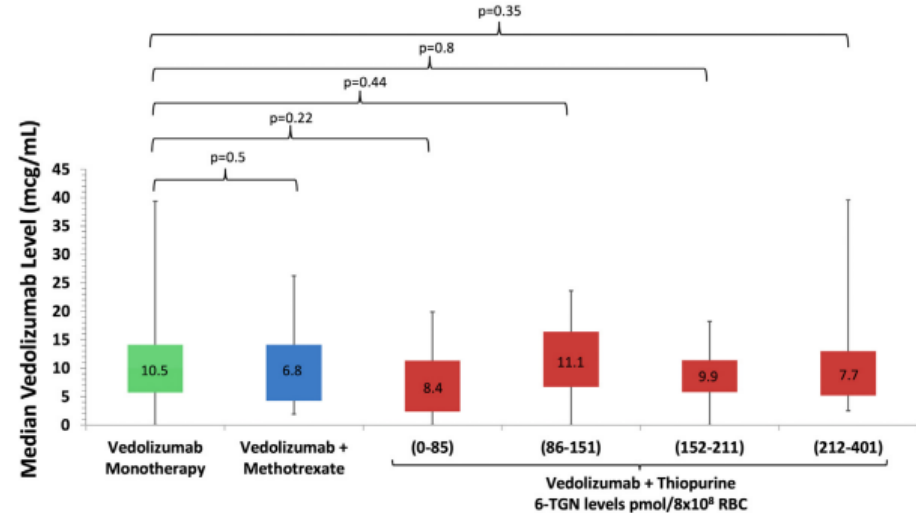
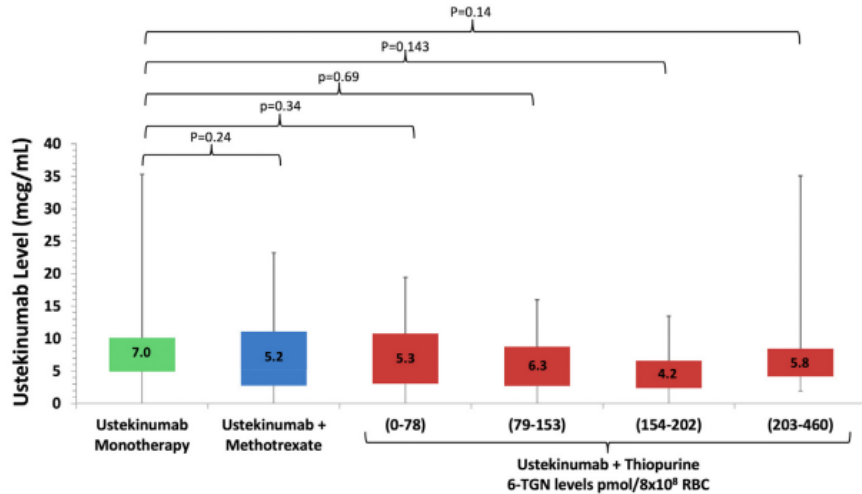
- IFX withdrawal
- Age at dx < 17
- CRP
- FeCal
- CDEIS

Thiopurine – anti-TNF Combination Therapy

- Very effective approach
- Thiopurines may be stopped after ≥ 6 months of remission

Thiopurines combined non-anti-TNF biologics

- No effects on PK (maintenance phase)



MGH/Alberta/Nancy Experience

	Vedolizumab		Ustekinumab	
	Combination(%)	Monotherapy(%)	Combination(%)	Monotherapy(%)
CR week 14	68.2	74.1	54.6	65.8
CR week 30	74.3	75.6	71.6	77.4
CR week 52	78.3	72.9	62.1	67.0
Endoscopic remission	55.2	52.3	58.1	41.2
Treatment failure	48.9	45	54.2	46.1

Retrospective study of patients on vedolizumab (n=549, CD 286 and UC 263, 78 thiopurine, 53 MTX) or ustekinumab (n=363, 359 CD 359 and UC 4, 57 thiopurine, 63 MTX)

MGH/Alberta/Nancy Experience

	Vedolizumab		Ustekinumab	
	Combination(%)	Monotherapy(%)	Combination(%)	Monotherapy(%)
CR week 14	85.2	75.1	64.5	55.8
CR week 30	77.7	72.2	57.9	47.1
CR week 52	78.3	72.9	62.1	67.0
Endoscopic remission	55.5	51.4	58.1	41.2
Treatment failure	48.9	45	54.2	46.1

Multivariate analysis adjusted for disease duration, prior anti-TNF, study site, use of steroids at baseline, and IBD type

Baseline immunomodulator use at VDZ or USTE initiation **did not predict CR** at week 14, 30 or 54

Retrospective study of patients on vedolizumab (n=549, CD 286 and UC 263, 78 thiopurine, 53 MTX) or ustekinumab (n=363, 359 CD 359 and UC 4, 57 thiopurine, 63 MTX)

Decreased Risk of Treatment Failure With Vedolizumab-Thiopurine combination vs. Vedolizumab Monotherapy in CD

- IBD patients starting vedolizumab identified in two US commercial and the French nationwide healthcare databases
- Propensity score matching 1:1
- 10,299 vedolizumab users → 804 CD and 1,088 UC pairs
- Risk of treatment failure with combination therapy:
 - **Crohn's disease: RR 0.85, 95%CI: 0.74 to 0.98**
 - **Ulcerative colitis: RR 0.90, 95%CI: 0.77 to 1.05**
- Findings were consistent across databases

Withdrawal vs. continuation of thiopurines in vedolizumab-treated patients with UC

- Vedolizumab 300 mg q 8 weeks + thiopurine for ≥ 6 months
- Steroid-free clinical remission for ≥ 6 months
- MES ≤ 1 or feCal < 100
- Randomized 1:2 to continuing vs. withdrawing thiopurine
- **Primary endpoint: Vedolizumab TL at week 48**

Withdrawal vs. continuation of thiopurines in vedolizumab-treated patients with UC

- Vedo TL at week 48
 - Continue 14.7 (P=0.36)
 - Withdrawal 15.9

- Anti-drug antibodies
 - Continue 0/20
 - Withdrawal 0/42

Week 48 Secondary Endpoints

Remission	Continue(%)	Withdrawal(%)	P
Clinical	90	79	0.27
FeCal	95	71	0.03
CRP	90	67	0.05
Endoscopic	80	54	0.05
Histological	78	49	0.04
Histoendoscopic	72	32	0.005

Clinical relapse

Partial Mayo score ≥ 3 and feCal > 150 or MES > 1 (or increase from 0 to 1)

- Withdrawal had earlier clinical relapse (HR 2.3; 0.5-10.5)
- Predictors
 - Prior anti-TNF HR 4.65 (1.13-19.18)
 - Histological activity at baseline HR 7.54 (1.70-33.41)

Thiopurines with non-anti-TNF biologics

- 1) No effects on trough concentrations or immunogenicity
- 2) Outcomes – Under investigation

Update on safety

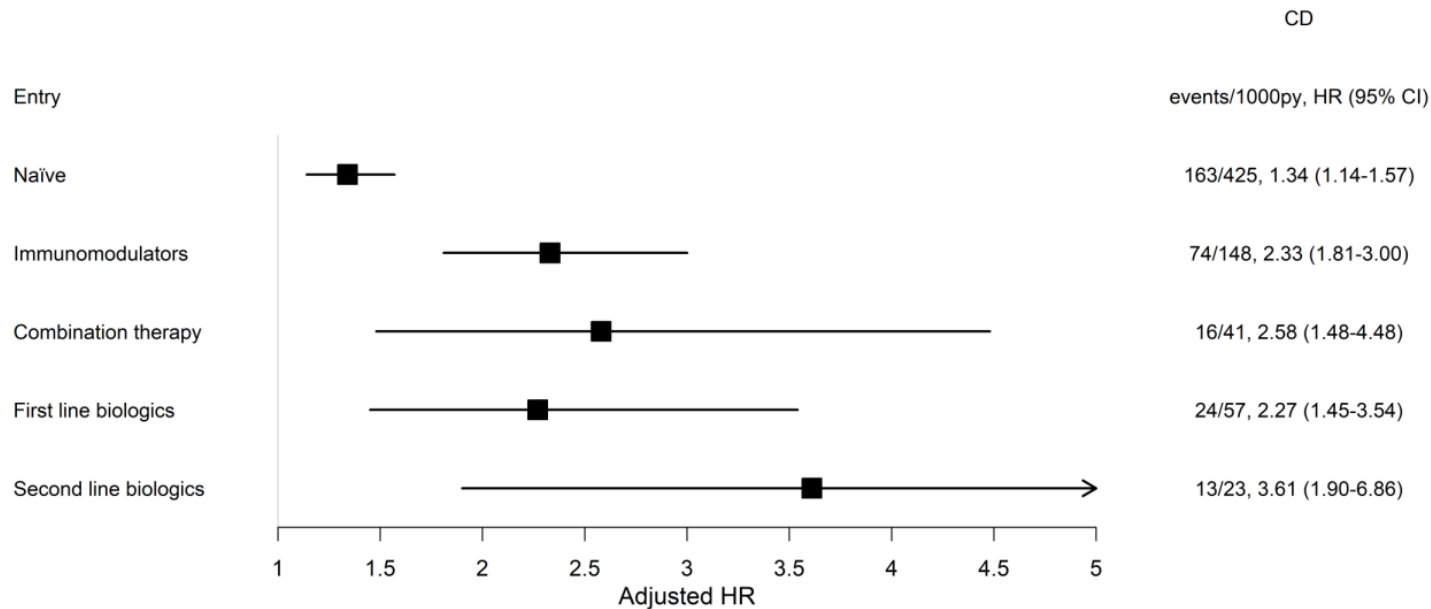
- CA-IBD Cohort Study
 - No increased serious infections from addition of immunomodulators to anti-TNF, ustekinumab or vedolizumab (adjusted HR 1.04, 95%CI 0.71-1.53)
- SR and meta-analysis
 - Paternal thiopurine or methotrexate use were not associated with impairments in fertility or increased odds of adverse pregnancy outcomes

Lymphoma risk

- Swedish and Danish National Registries (1969-2019)
 - 164,716 patients with IBD and 1,639,027 matched reference individuals
 - Lymphoma in 258 CD, 479 UC and 6675 matched reference individuals
 - CD incidence 35/100,000 person-years (vs. 28 in matched individuals)
 - CD HR, 1.32; 1.16–1.50
 - UC incidence 34/100,000 person-years (vs. 33 in matched individuals)
 - UC HR, 1.09; 1.00–1.20
 - HRs have increased in the past 2 decades

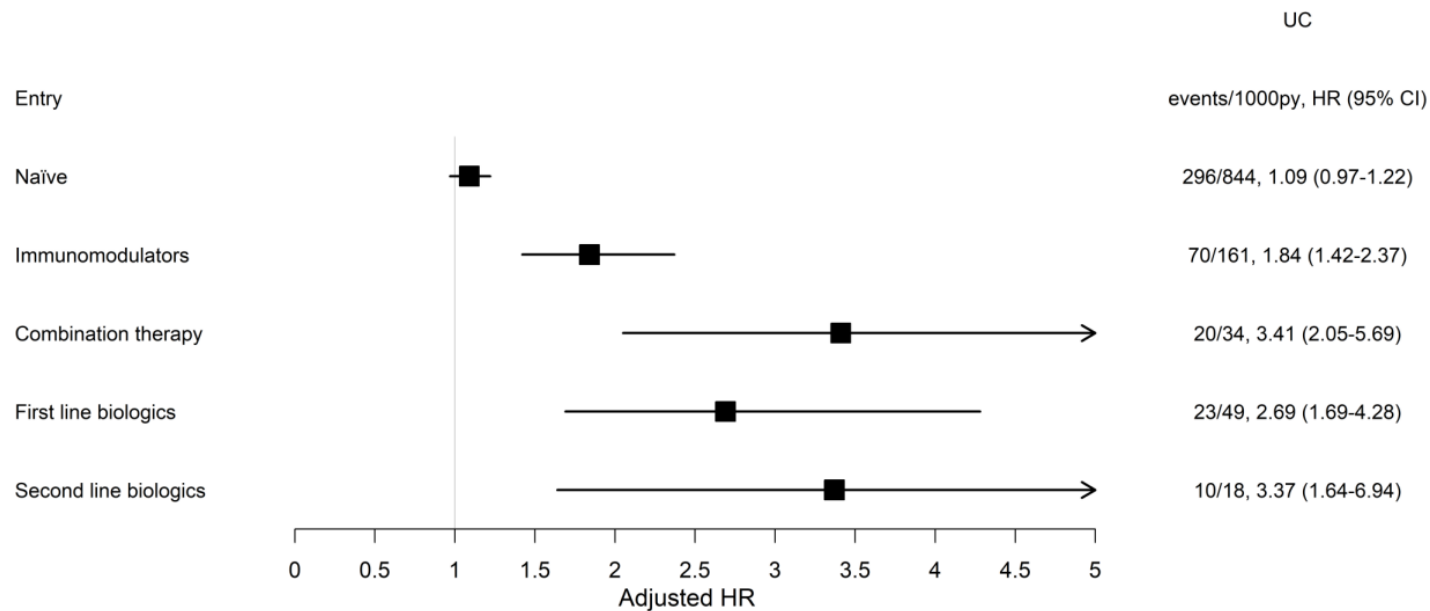
Lymphoma risk

Adjusted HR for lymphoma amongst CD patients on different treatments



Lymphoma risk

Adjusted HR for lymphoma amongst UC patients on different treatments



Thank you