JAKi and the Theory of Relativity

Kevin L. Winthrop, MD,MPH

Professor, School of Public Health

Division of Infectious Diseases

Oregon Health & Science University

Disclosures

- Research funding from Pfizer, BMS
- Scientific consultant work for Amgen, Abbvie, Pfizer, UCB, Genentech, BMS, Lilly
- Data safety monitoring boards for RCTs conducted by UCB, Roche, Astellas, Lilly, Janssen, Galapagos, Sanofi, Regeneron

Objectives

- Understand the relative differences and similarities with regard to adverse events between JAK inhibitors
- Appreciate the distinct safety profile of JAK inhibitors relative to biologic therapies
- Understand JAK inhibitors and their role/risk in COVID-19

Polling Question

RA patients over age 50 with cardiovascular risk factors appear to be at higher risk for what event(s) when taking tofacitinib 5mg BID as compared to a TNF blocker? (Select all that apply)

A. Serious infection

B. Herpes zoster

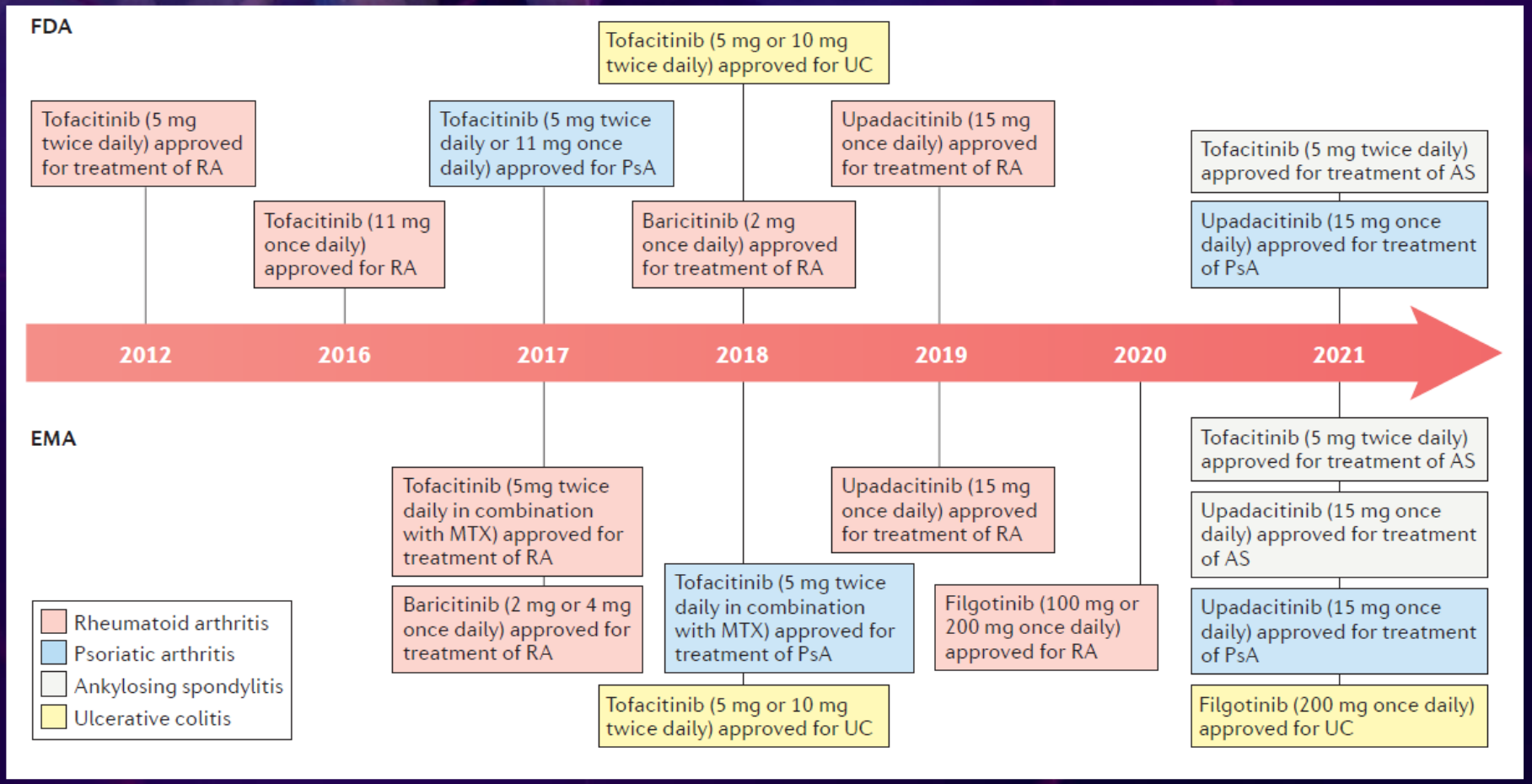
C. Malignancy

D. VTE

E. Melanoma

RA AEs of Interest

- Serious infections, malignancy, cardiovascular disease
- Disease activity increases the risk of these outcomes
- Relative to no disease control, all DMARDs likely decrease the risk
- Safety study evolution
  - Biologics Vs MTX
  - TNFis vs other biologics
  - JAKs versus other biologics



Winthrop KL et al. Nature Rheum (In Press)

TABLE 1 Mean IC_{50} values in enzymatic assay for tofacitinib, baricitinib, upadacitinib, and filgotinib inhibition of JAK1, JAK2, JAK3, and TYK2

	IC_{50} (nmol/L) [n][a,b]			
	JAK1	JAK2	JAK3	TYK2
Tofacitinib	15 [7]	71 [7]	45 [8]	472 [10]
Baricitinib	0.78 [3]	2 [3]	253 [3]	14 [3]
Upadacitinib	0.76 [3]	19 [3]	224 [3]	118 [3]
Filgotinib	45 [3]	357 [3]	9097 [3]	397 [3]

Abbreviations: ATP, adenosine triphosphate; IC_{50}, half-maximal inhibitory concentration; JAK, Janus kinase; TYK, tyrosine kinase.

[a]IC_{50} values represent the geometric mean of independent experiments; [n] denotes the number of experiments.

[b]All reactions were carried out in the presence of 1 mmol/L ATP.

Dowty M et al. Pharmacol Res Persp 2019

Table 3. Mean changes in selected laboratory parameters after drug start by individual JAK inhibitor and its reported JAK selectivity.[±]

	Tofacitinib	Peficitinib	Baricitinib	Decernotinib	Filgotinib	ABT-494
JAK "selectivity"	JAK 1,3	JAK 1,3	JAK 1,2	JAK 3	JAK 1	JAK 1
Lymphocytes	Decreased	No change	No change	Decreased	No change	Decreased
NK cells	Decreased	Not reported	Decrease[¥]	Not reported	No change	Decrease
Neutrophils	Decrease	Decrease	Decrease	Decrease	Decreased	Decrease
Hemoglobin	Increased	Increased	Decrease	No change	Increase	Decrease
Platelets	Decrease	Decrease	No change	Not reported	Decreased	Not reported
LFTs	Increased	Not reported	Increase	increase	No change	Increased
CPK	Increased	Increased	Increase	Not reported	Not reported	Increased
HDL	Increased	Increase	Increased	No change	Increased	Increased
LDL	Increased	Increase	Increased	Increase	No change	Increased
Creatinine	Increased	Increase	Increased	increase	Increase	Increased

[±]These are general trends reported in the development program for each compound. Magnitude of change varies by compound, and within each compound, by dose. In some cases, changes were seen at only certain doses (e.g. high doses). Note: grade changes for laboratory parameters can occur in the opposite direction of mean trends for a given parameter. Also note, in some cases, reported experience involves a very small number of exposed patients such that these estimations of laboratory change are less robust (e.g. decernotinib, peficitinib).

[¥]Initial rise followed by a decrease

Winthrop KL. *Nat Rheum Rev.* 2017.

JAKi and COVID Severity

Table 2 Frequencies and proportions of outcomes in the ordinal COVID-19 severity scale according to baseline use of biologic or targeted synthetic disease-modifying antirheumatic drug for patients with rheumatoid arthritis at the time of COVID-19 onset (N=2869)

COVID-19 severity scale	Overall N=2869 n (%)	Abatacept n=237 n (%)	Rituximab n=364 n (%)	IL-6 inhibitors n=317 n (%)	JAK inhibitors n=563 n (%)	TNF inhibitors n=1388 n (%)
Not hospitalised	2256 (78.6)	181 (76.4)	210 (57.7)	271 (85.5)	409 (72.6)	1185 (85.4)
Hospitalised without oxygenation	137 (4.8)	12 (5.1)	20 (5.5)	13 (4.1)	28 (5.0)	64 (4.6)
Hospitalised with any oxygen or ventilation	319 (11.1)	26 (11.0)	80 (22.0)	24 (7.6)	86 (15.3)	103 (7.4)
Death	157 (5.5)	18 (7.6)	54 (14.8)	9 (2.8)	40 (7.1)	36 (2.6)

IL-6, interleukin 6; JAK, Janus kinase; TNF, tumour necrosis factor.

Table 4 Multivariable* OR of biologic or targeted synthetic disease-modifying antirheumatic drugs at each binary level of the COVID-19 severity scale (N=2869)

	Abatacept		Rituximab		IL-6 inhibitors		JAK inhibitors		
COVID-19 outcome	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	TNF inhibitors
Hospitalised	1.18 (0.76 to 1.82)	0.47	4.53 (3.32 to 6.18)	<0.01	0.84 (0.53 to 1.33)	0.45	2.40 (1.78 to 3.24)	<0.01	Ref
Hospitalised with oxygenation/ventilation or death	1.12 (0.70 to 1.81)	0.63	2.87 (2.03 to 4.06)	<0.01	0.72 (0.43 to 1.20)	0.20	1.55 (1.04 to 2.18)	0.01	Ref
Death	1.46 (0.72 to 2.89)	0.30	4.57 (3.32 to 9.01)	<0.01	1.13 (0.50 to 2.59)	0.77	2.04 (1.58 to 2.65)	<0.01	Ref
Mechanical ventilation (restricted to only hospitalised patients, n=613)	1.41 (0.94 to 2.10)	0.09	4.05 (3.08 to 5.33)	<0.01	0.75 (0.51 to 1.10)	0.14	2.03 (1.56 to 2.62)	<0.01	Ref
Mechanical ventilation or death	1.14 (0.78 to 1.66)	0.50	4.44 (3.39 to 5.82)	<0.01	0.74 (0.50 to 1.09)	0.12	2.02 (1.56 to 2.61)	<0.01	Ref

*Adjusted for age, sex, region, calendar time, obesity, smoking, concomitant csDMARD use, glucocorticoid use/dose, comorbidity count, hypertension/cardiovascular disease, interstitial lung disease, cancer and rheumatoid arthritis disease activity.
csDMARD, conventional synthetic disease-modifying antirheumatic drug; IL-6, interleukin 6; JAK, Janus kinase; Ref, reference; TNF, tumour necrosis factor.

Sparks J et al ARD 2021

Cov-Barrier

- 79% steroids, 19% Rem
- Reduction of mortality
  - 8.1% vs 13.1% (HR: 0.57; 95% CI: 0.41, 0.78)
- Primary endpoint progress to ventilation (non-invasive or mechanical) or death
  - -2.7% (p=0.18)
- Safety
  - SIE 8.5% bari vs 9.8% placebo
  - VTE 2.7% bari vs 2.5% placebo

https://investor.lilly.com/news-releases/news-release-details/lilly-and-incyte-announce-results-phase-3-cov-barrier-study

Tofa and Hospitalized COVID

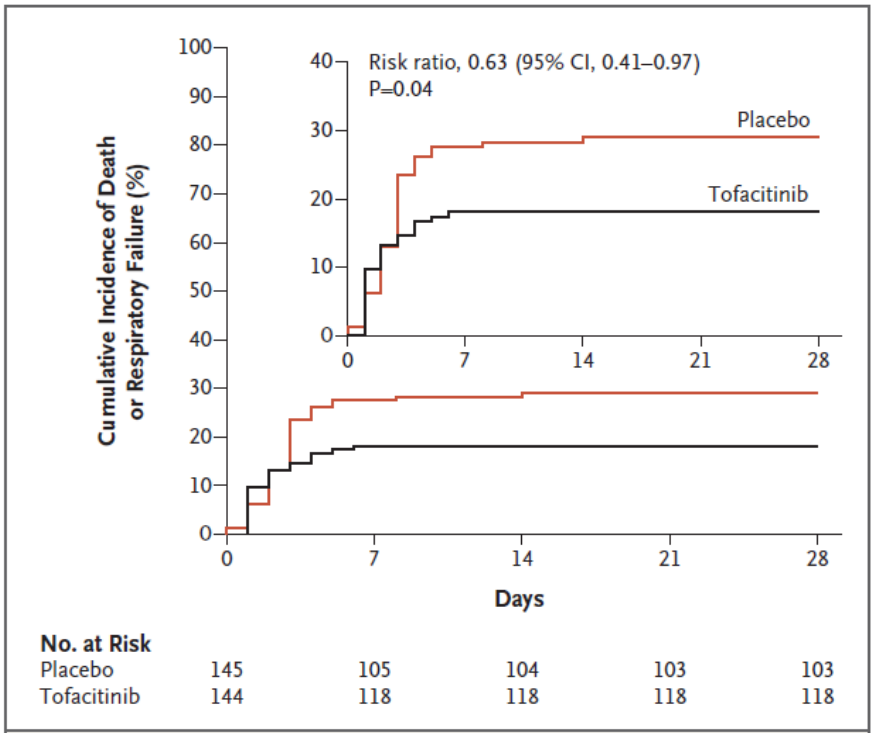
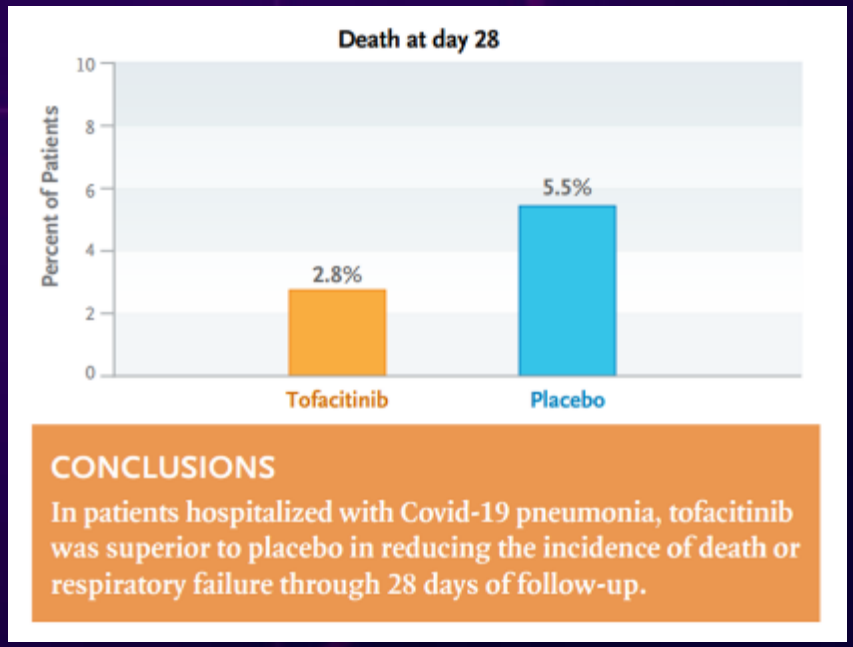


Figure 2. Cumulative Incidence of the Primary Outcome.

The primary outcome was death or respiratory failure through day 28. The risk ratio and P value for the primary outcome were calculated by means of binary regression with Firth correction, with trial group and inclusion of antiviral therapy for Covid-19 as covariates. The inset shows the same data on an expanded y axis.



Guimaraes PO et al. NEJM 2021

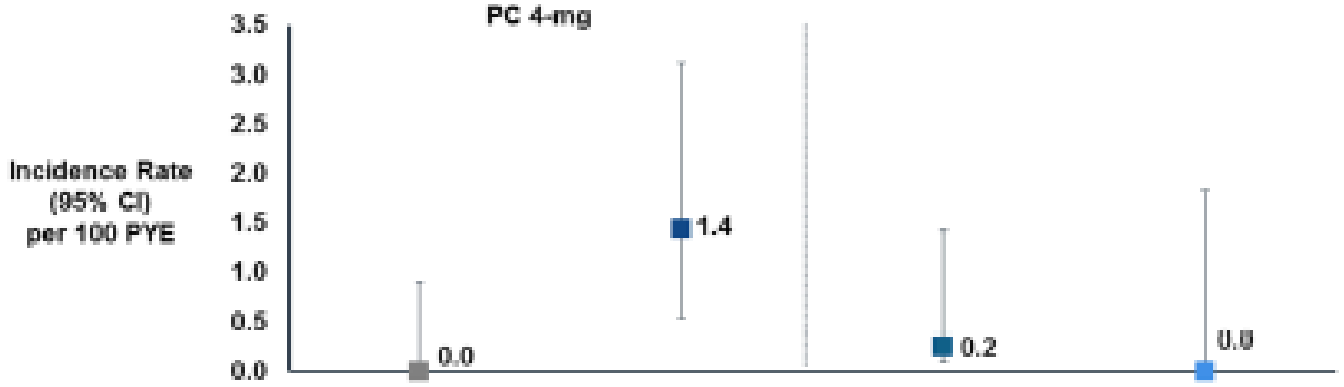
FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions

Approved uses also being limited to certain patients

https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death

VTE Risk and Baricitinib

Figure 25: VTE Incidence Rates during First 24 Weeks of Baricitinib Exposure for the PC 4-mg Dataset and Rescued or Switched Groups

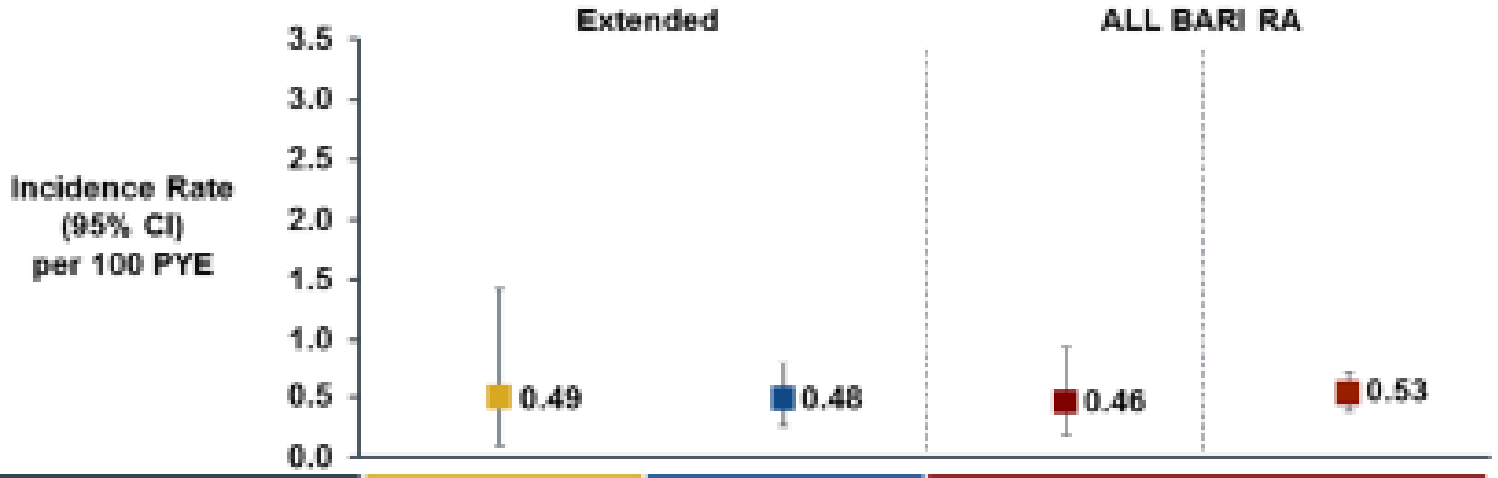


Treatment	PBO	BARI 4 mg	PBO→BARI 4 mg	Active→BARI 4 mg
Time Period	24 wks post-randomization		24 wks post-switch or rescue	24 wks post-switch or rescue
# of Patients	1070	997	928	451
# of Patients with Event(s)	0	6	1	0
PYE	406	418	410	203

https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/arthritisadvisorycommittee/ucm605062.pdf

VTE and Bari

Figure 26: VTE Incidence Rates for Extended and All BARI RA Datasets



Treatment	Bari 2 mg	Bari 4 mg	ALL BARI RA	
Time Period	Overall		0-24 wks	Overall
# of Patients	479	1371	3492	3492
# of Patients with Event(s)	3	14	7	42
PYE	615	2936	1533	7949[a]

Abbreviations: BARI = Baricitinib; CI = confidence interval; PYE = patient years exposure; VTE = venous thromboembolism.
a Includes follow up time

https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/arthritisadvisorycommittee/ucm605062.pdf

VTE Risk in RA (Real World)

Figure 67: Incidence Rates of VTE among RA Patients Reported in Published Observational Studies

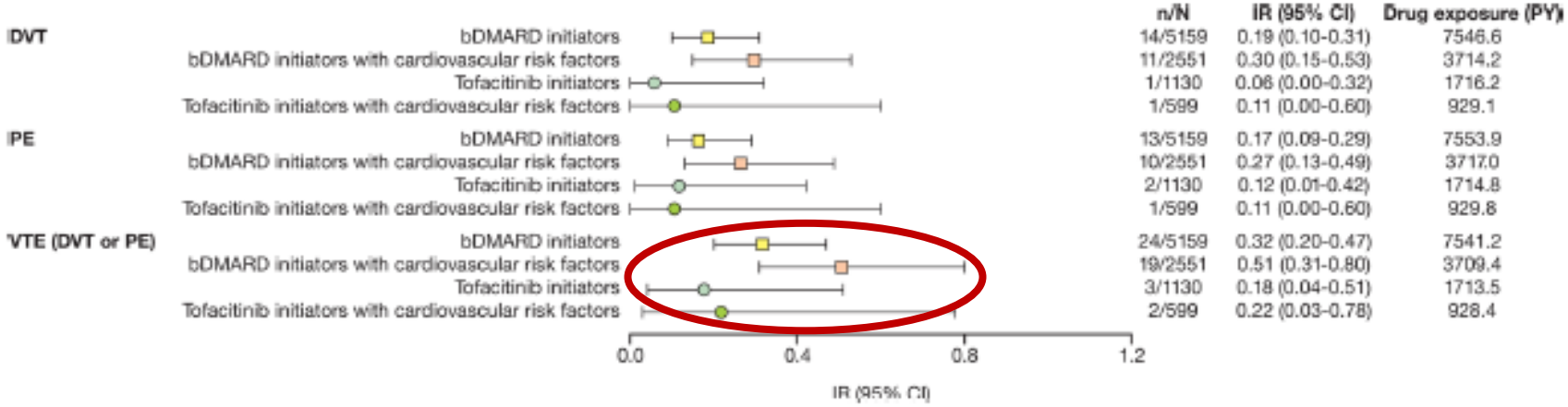
References	RA Cohort	Country	Data Source	N	Incidence Rate per 100 PYs (95% CI)
Ogdie 2017	DMARDS	UK	Medical records	31,336	0.79
Bacani 2012	RA	US	Medical records	464	
Eriksson 2017	RA	Sweden	National Register	43,490	
Kim 2013	DMARDS	US	Claims data	22,143	
Holmqvist 2012	RA (prevalent)	Sweden	National register	37,856	
Yusuf 2015	RA	US	Claims data	70,768	
Holmqvist 2012	RA (incident)	Sweden	National register	7904	
Davies 2011	nbDMARDs	UK	Registry (BSRBR)	3673	
Davies 2011	Anti-TNF	UK	Registry (BSRBR)	11,881	
Choi 2013	DMARD	UK	Medical records	9589	0.33

Abbreviations: BSRBR = British Society for Rheumatology Biologics Registers; DMARD = disease-modifying antirheumatic drug; nbDMARD = non-biologic disease-modifying antirheumatic drug; RA = rheumatoid arthritis; TNF = tumor necrosis factor; UK = United Kingdom; US = United States

https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/arthritisadvisorycommittee/ucm605062.pdf

CORRONA TOFA Real World Risk

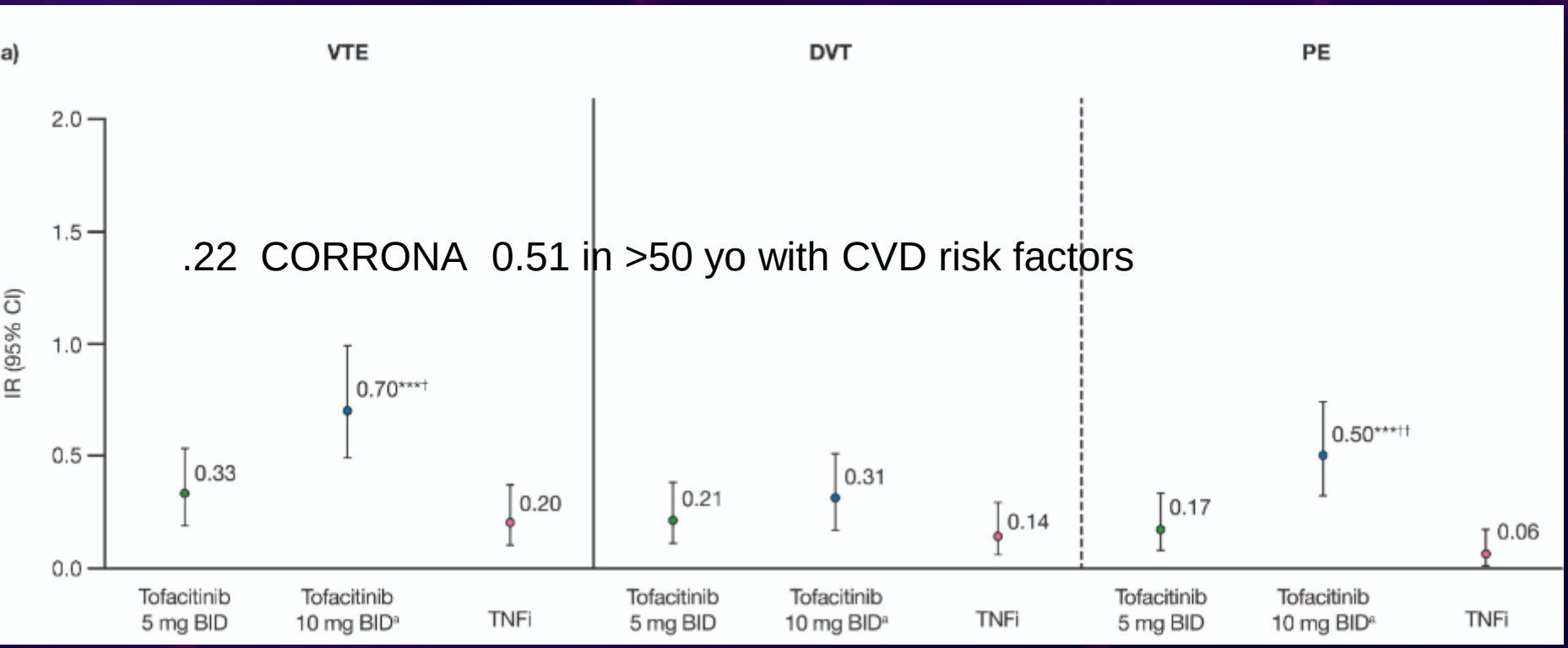
Treatment



	n/N	IR (95% CI)	Drug exposure (PY)
DVT			
bDMARD initiators	14/5159	0.19 (0.10-0.31)	7546.6
bDMARD initiators with cardiovascular risk factors	11/2551	0.30 (0.15-0.53)	3714.2
Tofacitinib initiators	1/1130	0.06 (0.00-0.32)	1716.2
Tofacitinib initiators with cardiovascular risk factors	1/599	0.11 (0.00-0.60)	929.1
PE			
bDMARD initiators	13/5159	0.17 (0.09-0.29)	7553.9
bDMARD initiators with cardiovascular risk factors	10/2551	0.27 (0.13-0.49)	3717.0
Tofacitinib initiators	2/1130	0.12 (0.01-0.42)	1714.8
Tofacitinib initiators with cardiovascular risk factors	1/599	0.11 (0.00-0.60)	929.8
VTE (DVT or PE)			
bDMARD initiators	24/5159	0.32 (0.20-0.47)	7541.2
bDMARD initiators with cardiovascular risk factors	19/2551	0.51 (0.31-0.80)	3709.4
Tofacitinib initiators	3/1130	0.18 (0.04-0.51)	1713.5
Tofacitinib initiators with cardiovascular risk factors	2/599	0.22 (0.03-0.78)	928.4

Mease P et al. ARD 2020

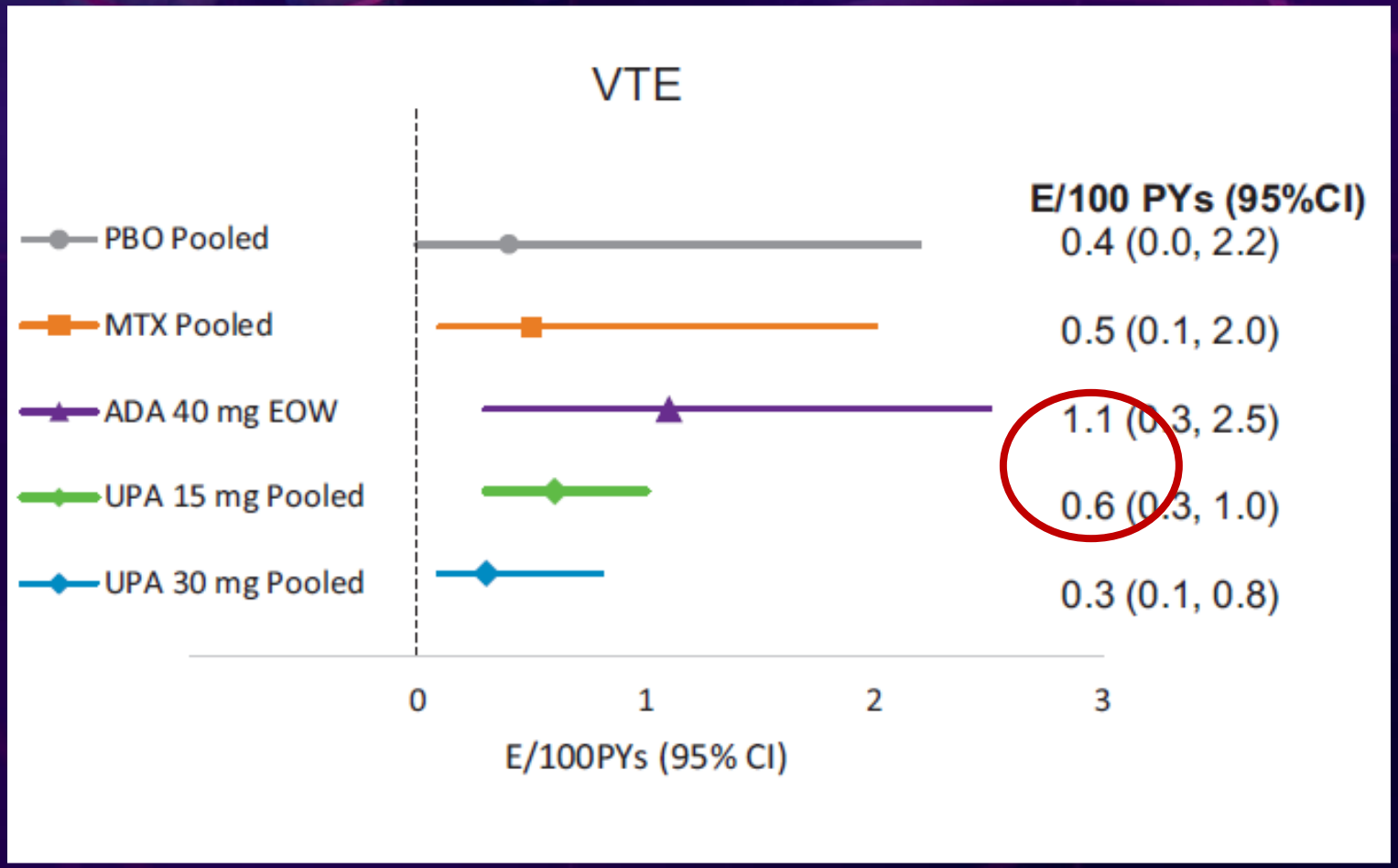
Oral Surveillance VTE



.22 CORRONA 0.51 in >50 yo with CVD risk factors

Charles-Schoeman C et al. ACR 2021

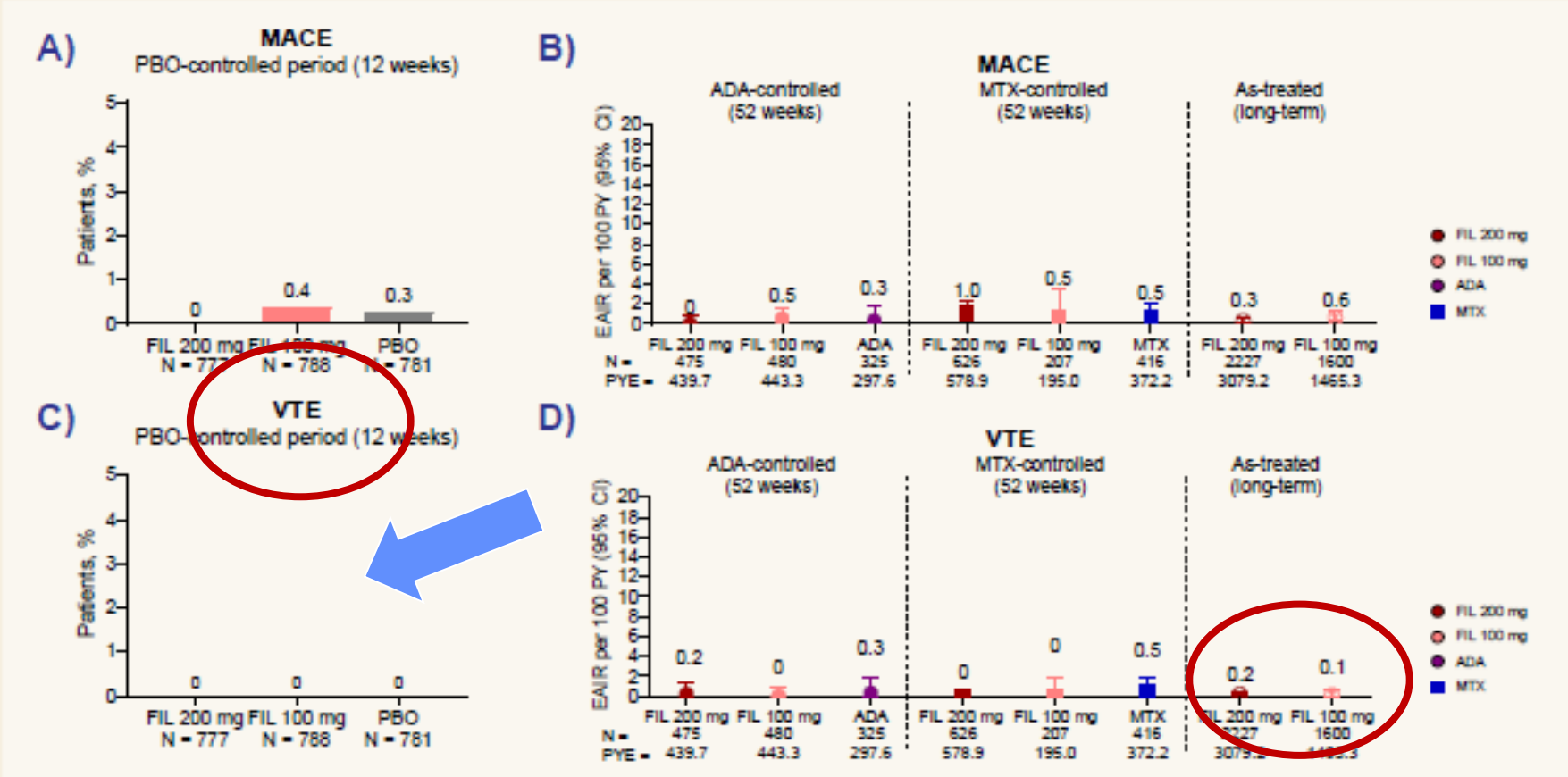
Upa ISS in Phase 3 RA



Cohen SB et al. ARD 2021

Filgo phase 2/3 ISS

Figure 3. MACE and VTE incidence rates in the PBO-controlled set (A, C) and EAIRs in the active-controlled and long-term analysis sets (B, D)



ADA, adalimumab; CI, confidence interval; EAIR, exposure-adjusted incidence rate; FIL, filgotinib; MACE, major adverse cardiovascular event; MTX, methotrexate; PBO, placebo; PY, patient-years; PYE, patient-years exposure; VTE, venous thromboembolism.

Genovese M et al. EULAR 2020

Malignancy and Tofa

Table 2 IRs and SIRs for all malignancies (excluding NMSC), lymphoma, lung and breast cancer for tofacitinib-treated patients with RA (across phase II, III and LTE studies)

	IR Events/100 py (95% CI) Tofacitinib N=5671	SIR[26]* (95% CI) Tofacitinib N=5671
All malignancies (excluding NMSC)	0.85 (0.70 to 1.02)	1.17 (0.96 to 1.41)
Lymphoma	0.08 (0.04 to 0.14)	2.64 (1.27 to 4.86)
Lung cancer	0.19 (0.13 to 0.28)	2.19 (1.39 to 3.29)
Breast cancer	0.18 (0.12 to 0.28)	0.78 (0.47 to 1.22)

Tofacitinib data up to 10 April 2013.
*SEER database (US General Population), SIR data adjusted for age and sex.
IR, incidence rate; LTE, long-term extension; NMSC, non-melanoma skin cancer; py, patient-years; RA, rheumatoid arthritis; SEER, Surveillance Epidemiology and End Result; SIR, standardised incidence ratio as compared with the SEER database.

Curtis JC, et al. *ARD*. 2015.

Tofa Malignancy Vs TNFi

Adjudicated Malignancies Excluding NMSC*

	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID**	Tofacitinib Doses Combined	TNFi
Total number of subjects	1455	1456	2911	1451
Number of subjects with first event within the risk period*** (%)	62 (4.26)	60 (4.12)	122 (4.19)	42 (2.89)
Person-years	5491.48	5311.71	10803.19	5482.30
IR (95% CI) (number of subjects with event/100 person-years)	1.13 (0.87, 1.45)	1.13 (0.86, 1.45)	1.13 (0.94, 1.35)	0.77 (0.55, 1.04)
HR (95% CI) for tofacitinib vs TNFi	1.47 (1.00, 2.18)	1.48 (1.00, 2.19)	1.48 (1.04, 2.09)****	

Including a statistically increased risk of Lung cancer for 10mg BID
MV model---age >65yo and smoking risk factors for malignancy overall

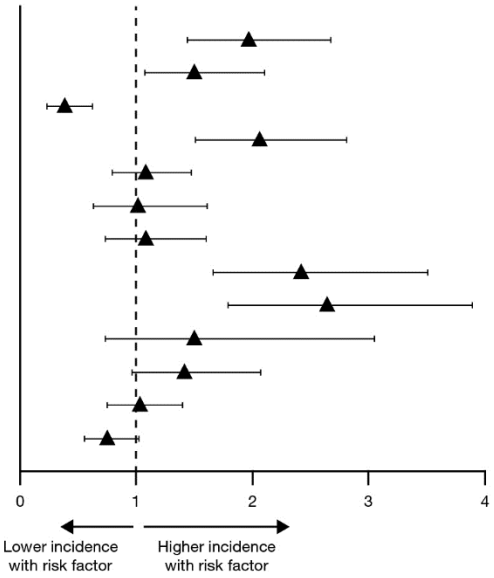
https://www.pfizer.com/news/press-release/press-release-detail/pfizer-shares-co-primary-endpoint-results-post-marketing

Tofa Malignancy MV Model

Figure 1. Risk factors at baseline for all malignancies excluding NMSC in ORAL Surveillance: a) univariate analysis of potential risk factors and their interaction with treatment[a]; b) multivariate analysis of potential independent overall risk[b]

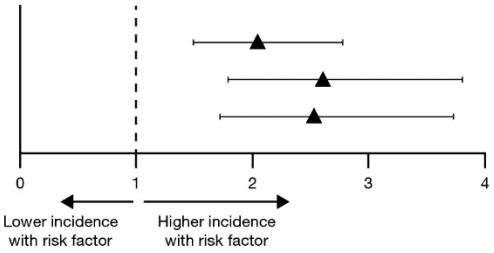
a)

Risk factor (at baseline)	Comparison	HR of risk factor HR (95% CI)	p value	Treatment-by-risk-factor interaction p value
Age ⩾ 65 yrs	Age ⩾ 65 yrs vs 50 – < 65 yrs	1.97 (1.44, 2.67)	< 0.0001	0.7649
Male	Male vs female	1.50 (1.07, 2.10)	0.0194	0.7394
Non-white	Non-white vs white	0.38 (0.23, 0.62)	0.0001	0.0672
Geographic region (by TNFi use), North America[c]	North America vs RoW	2.06 (1.51, 2.81)	< 0.0001	0.4833
BMI ⩾ 30 kg/m² (yes)	Yes vs No	1.08 (0.79, 1.47)	0.6219	0.3402
CRP > 2.87 mg/L (yes)	Yes vs No	1.01 (0.63, 1.61)	0.9772	0.3689
History of diabetes (yes)	Yes vs No	1.08 (0.73, 1.60)	0.7071	0.9694
Current smoker	Current smoker vs never smoked	2.42 (1.66, 3.51)	< 0.0001	0.2524
Past smoker	Past smoker vs never smoked	2.64 (1.79, 3.89)	< 0.0001	
Oral contraceptive or HRT use (yes)	Yes vs No	1.50 (0.73, 3.05)	0.2668	0.6619
Aspirin use (yes)	Yes vs No	1.41 (0.96, 2.07)	0.0776	0.8108
Corticosteroid use (yes)	Yes vs No	1.03 (0.75, 1.40)	0.8609	0.3399
Cox-1 or Cox-2 inhibitor use (without aspirin use) (yes)	Yes vs No	0.75 (0.55, 1.02)	0.0639	0.1713



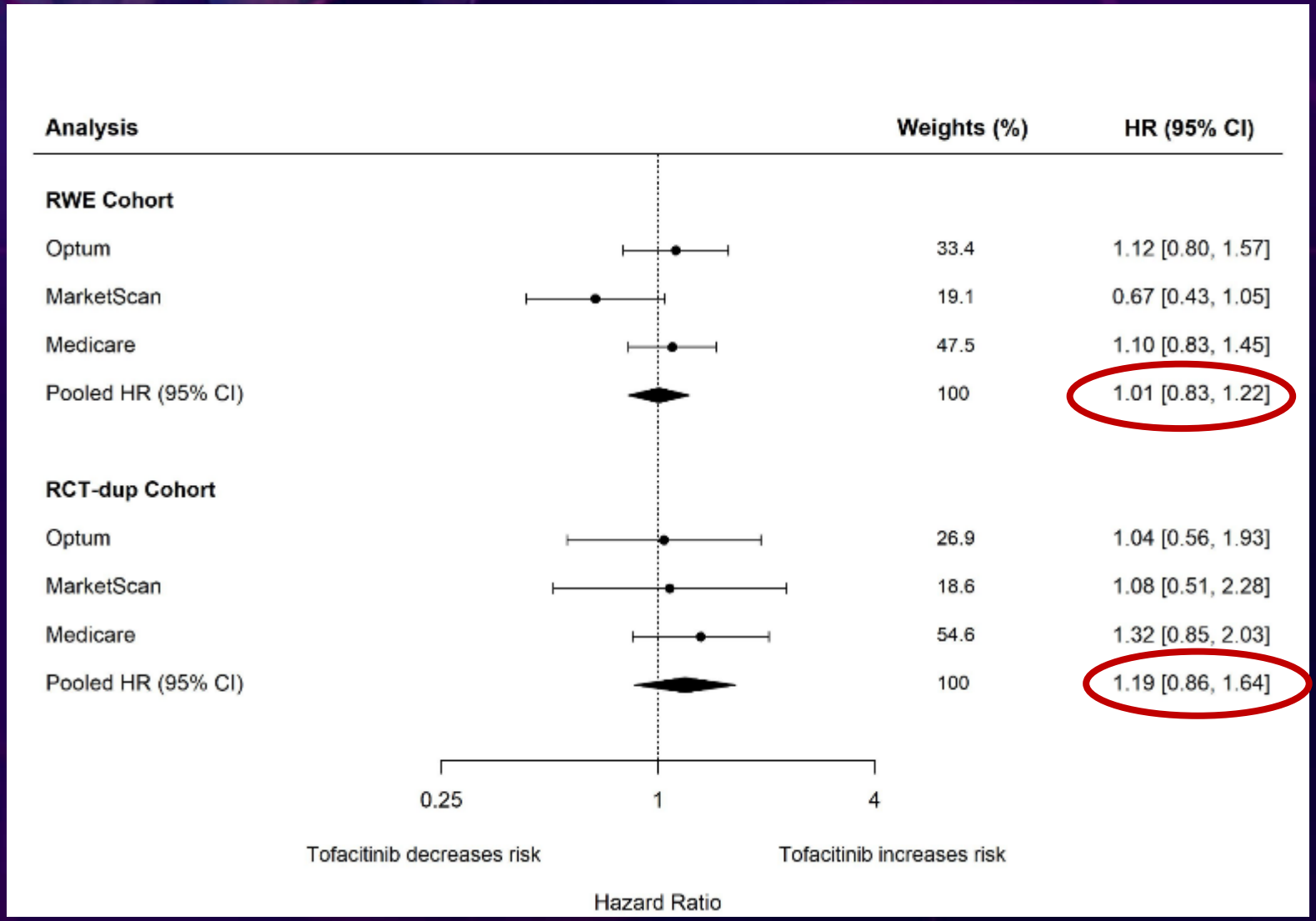
b)

Risk factor (at baseline)	Comparison	HR (95% CI)	p value
Age ⩾ 65 yrs	Age ⩾ 65 yrs vs 50 – < 65 yrs	2.04 (1.49, 2.78)	< 0.0001
Current smoker	Current smoker vs never smoked	2.61 (1.79, 3.81)	< 0.0001
Past smoker	Past smoker vs never smoked	2.53 (1.72, 3.73)	< 0.0001



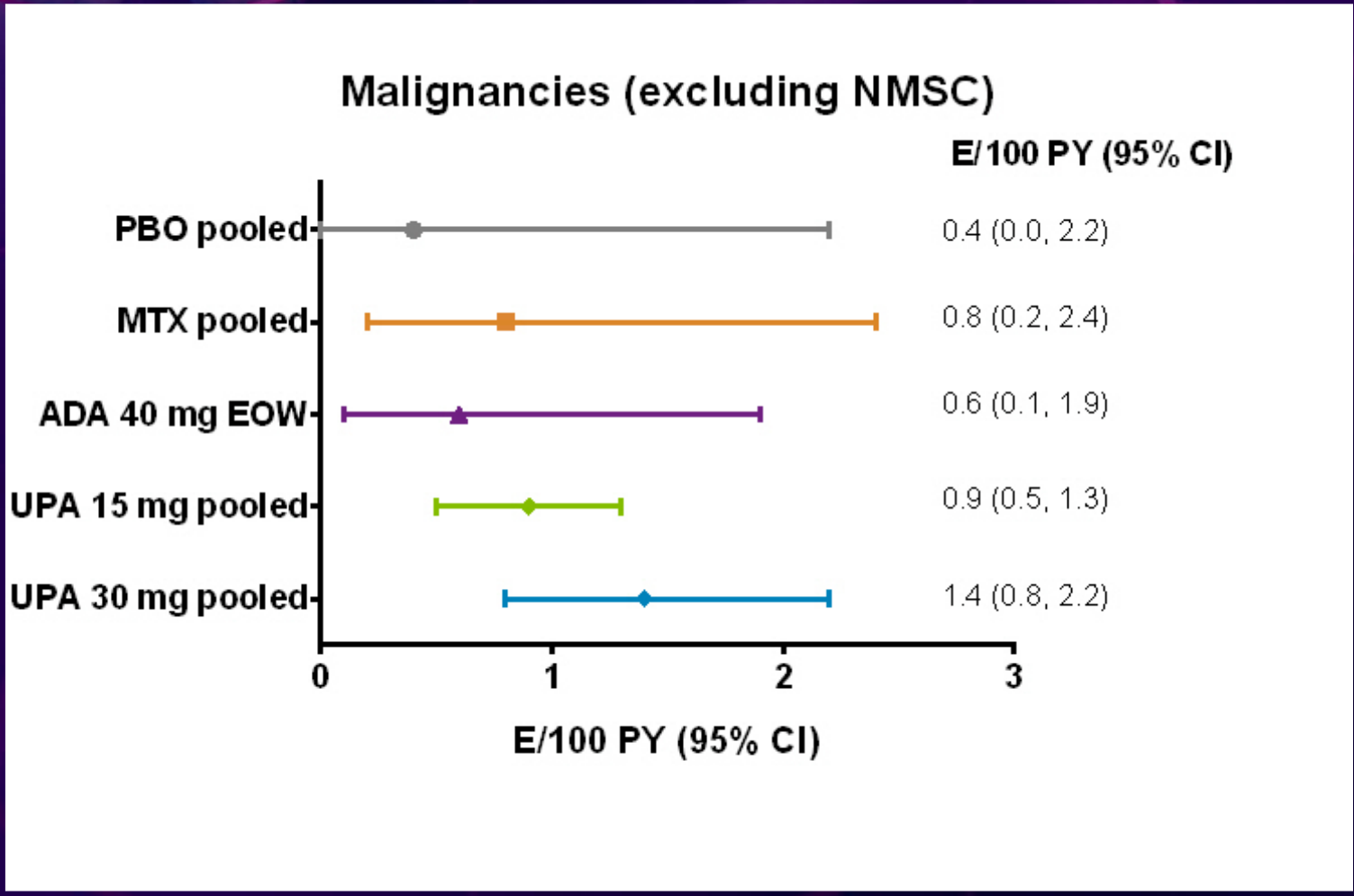
Curtis J et al. ACR 2021

Tofa Vs TNFi
Real World Malignancy



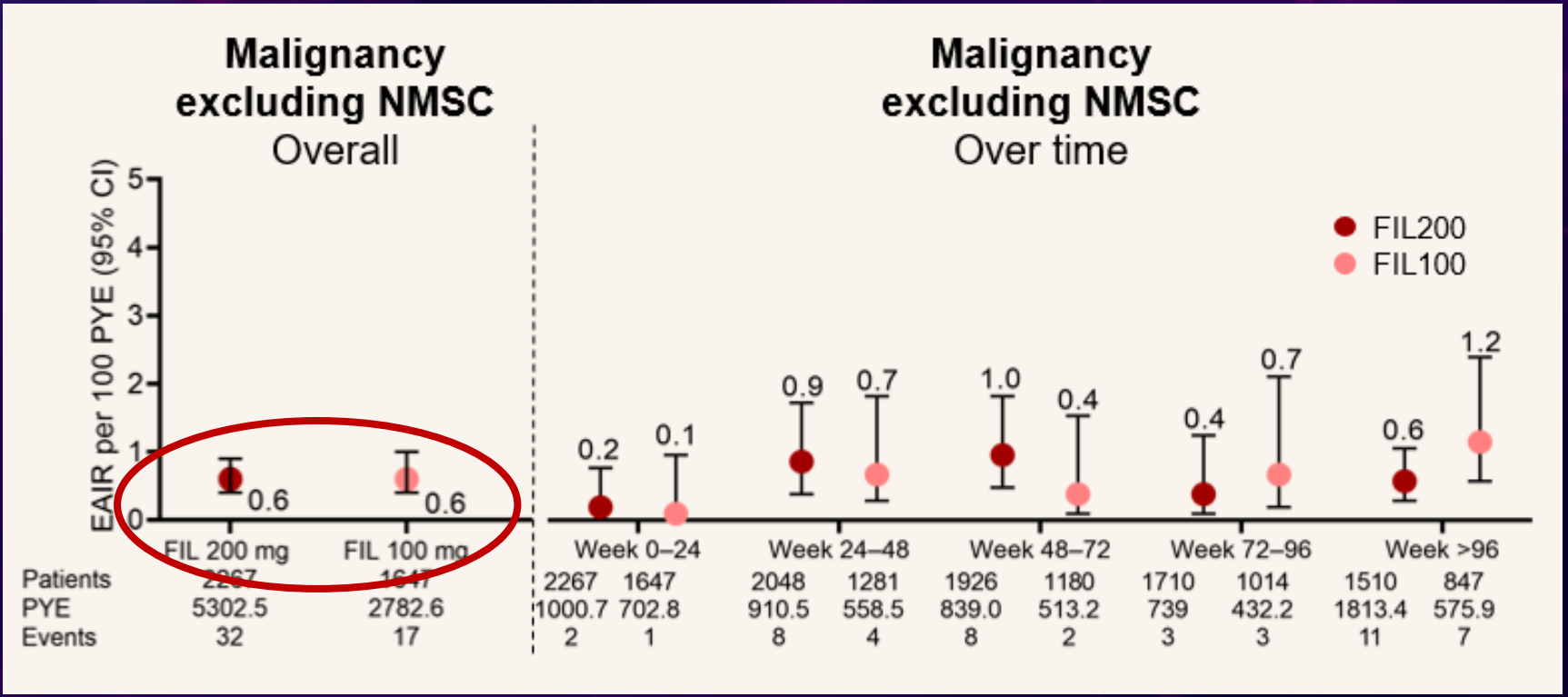
Khosrow-Khavar F et al. ACR 2021

Upa ISS in RA



Cohen SB et al. ARD 2021

Filgo Malignancy



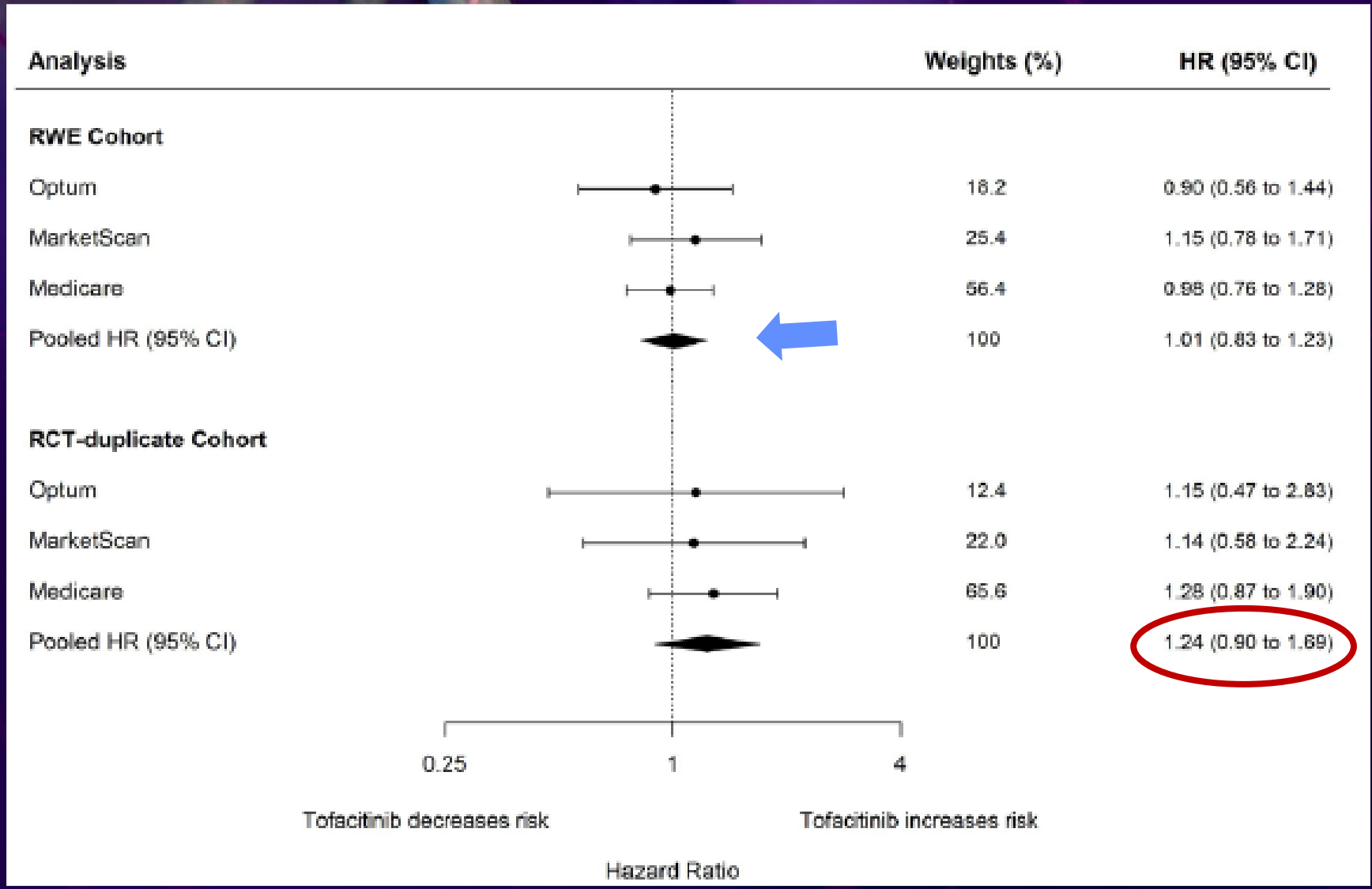
Winthrop KL et al. ACR 2021

MACE Tofa Vs TNFi

Adjudicated MACE*

	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID**	Tofacitinib Doses Combined	TNFi
Total number of subjects	1455	1456	2911	1451
Number of subjects with first event within the risk period*** (%)	47 (3.23)	51 (3.50)	98 (3.37)	37 (2.55)
Person-years	5166.32	4871.96	10038.28	5045.27
IR (95% CI) (number of subjects with event/100 person-years)	0.91 (0.67, 1.21)	1.05 (0.78, 1.38)	0.98 (0.79, 1.19)	0.73 (0.52, 1.01)
HR (95% CI) for tofacitinib vs TNFi	1.24 (0.81, 1.91)	1.43 (0.94, 2.18)	1.33 (0.91, 1.94)****	

https://www.pfizer.com/news/press-release/press-release-detail/pfizer-shares-co-primary-endpoint-results-post-marketing



Khosrow-Kaver F et al. ARD 2022

ENTRACTE Trial

MACE: Tocilizumab Vs. Etanercept

IR was 0.73 ADA in ORALSURV

End point	First events: Etanercept No. (%) first events	Etanercept No. first events/ 100 person-years (95% CI)	Tocilizumab No. (%) first events	Tocilizumab No. first events/ 100 person-years (95% CI)	HR†	95% CI†
Primary end point of MACE, including undetermined cause of death						
ITT population‡	78 (5)	1.70 (1.35–2.10)	83 (5)	1.82 (1.46–2.24)	1.05	0.77–1.43
On-treatment population§	52 (3)	1.28 (0.97–1.66)	57 (4)	1.44 (1.10–1.85)	1.11	0.76–1.62
Sensitivity analysis of primary end point (ITT population)						
MACE, excluding undetermined cause of death	72 (5)	1.57 (1.24–1.97)	74 (5)	1.63 (1.29–2.03)	1.01	0.73–1.40

Active RA and >50 yo with CVD risk factor(s)

Giles J et al. Arth Rheum 2020

ABA vs TNFi in CV Patients

Outcome	Database	HR (95% CI)
Coronary revascularization	MarketScan	0.35 (0.16, 0.77)
	Medicare	0.75 (0.49, 1.14)
	Combined	**0.63 (0.44, 0.92)**
Incident HF	MarketScan	1.00 (0.14, 7.29)
	Medicare	0.76 (0.29, 1.99)
	Combined	**0.80 (0.34, 1.90)**
Incident VTE	MarketScan	2.08 (0.39, 10.95)
	Medicare	1.14 (0.53, 2.48)
	Combined	**1.27 (0.63, 2.57)**
MI	MarketScan	1.01 (0.40, 2.54)
	Medicare	0.58 (0.39, 0.87)
	Combined	**0.64 (0.44, 0.92)**
Stroke/TIA	MarketScan	1.50 (0.90, 2.50)
	Medicare	0.95 (0.64, 1.41)
	Combined	**1.12 (0.82, 1.53)**

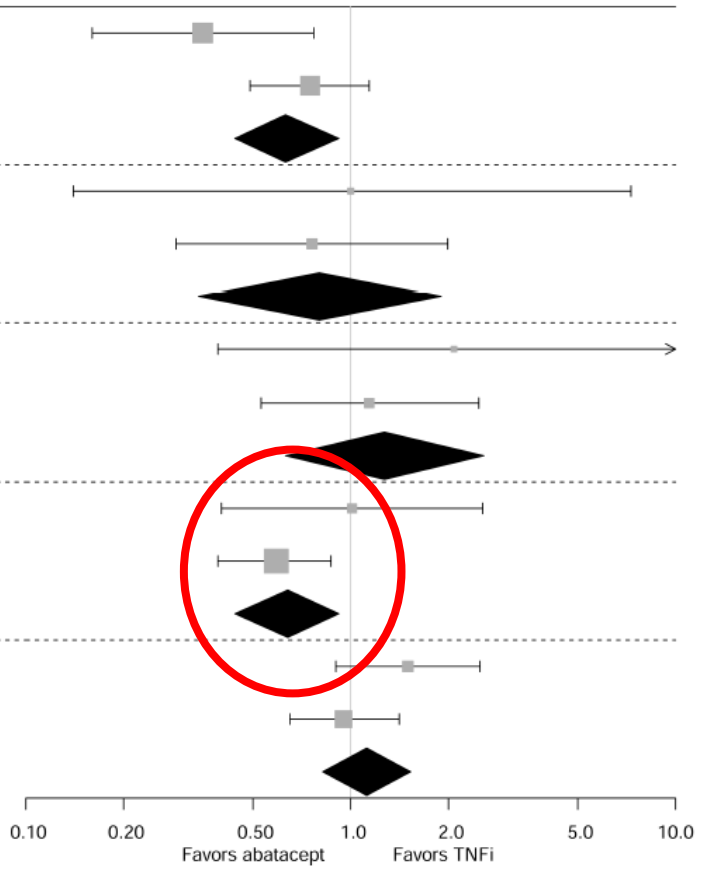


Figure 3. Risk of secondary outcomes for ABA versus TNFi after PS matching in baseline CVD+ subgroup. ABA: abatacept; CVD: cardiovascular disease;

Yinzhu J et al. J Rheum 2018

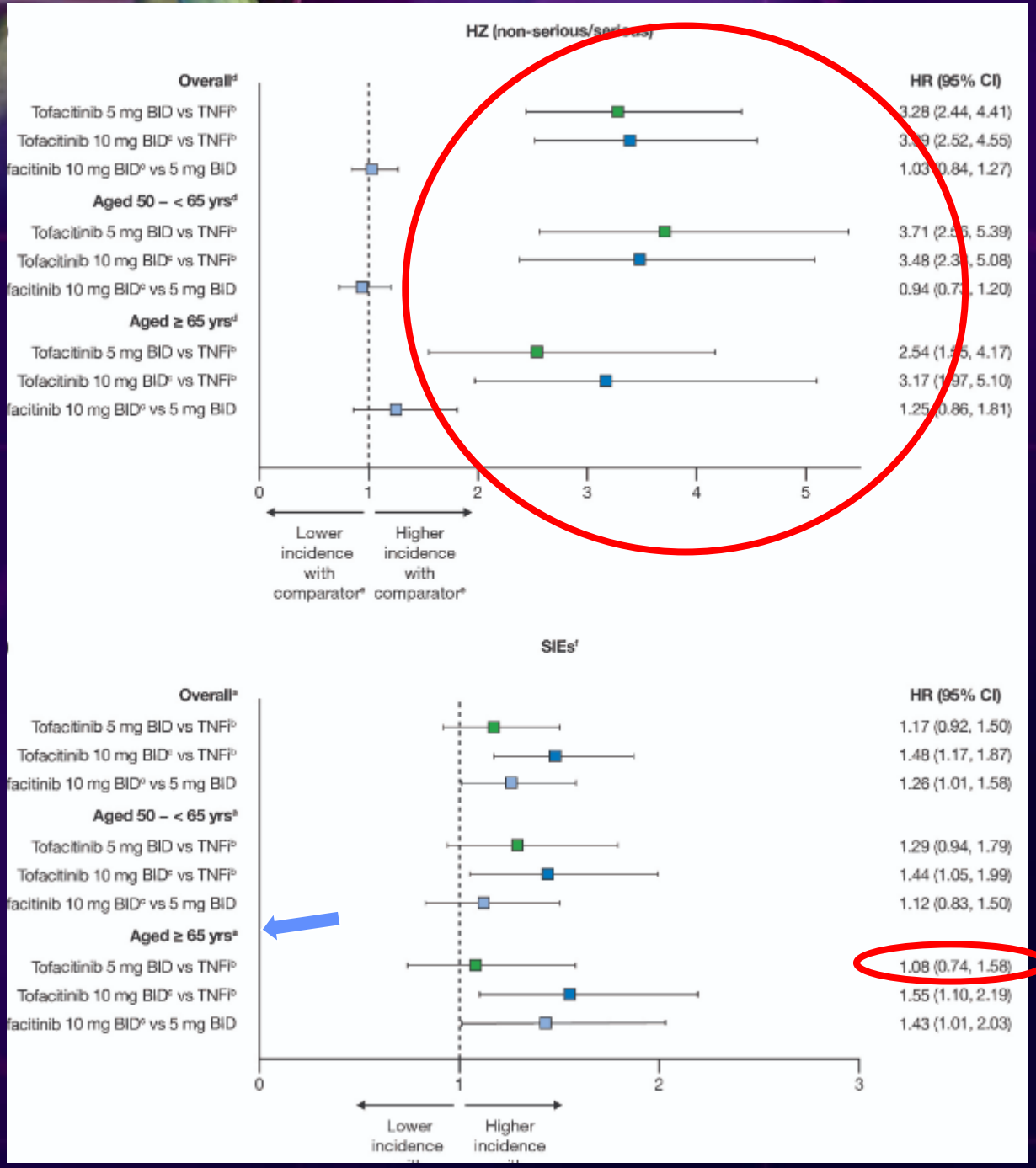
EMA CHMP Announcement

November 15, 2019

- "As a result, tofacitinib should be used with caution in patients with known risk factors for VTE, regardless of indication and dosage. This includes patients who have had a heart attack or have heart failure, cancer, inherited blood clotting disorders or a history of blood clots, as well as patients taking combined hormonal contraceptives or hormone replacement therapy, are undergoing major surgery or are immobile."
- "Other risk factors to be considered when prescribing tofacitinib include age, diabetes, obesity (BMI>30), smoking status and hypertension."
- **"Available data also showed that the risk of serious infections and fatal infections was further increased in elderly patients above 65 years of age, as compared to younger patients. Therefore, tofacitinib should only be considered in these patients if no suitable alternative treatment is available."**

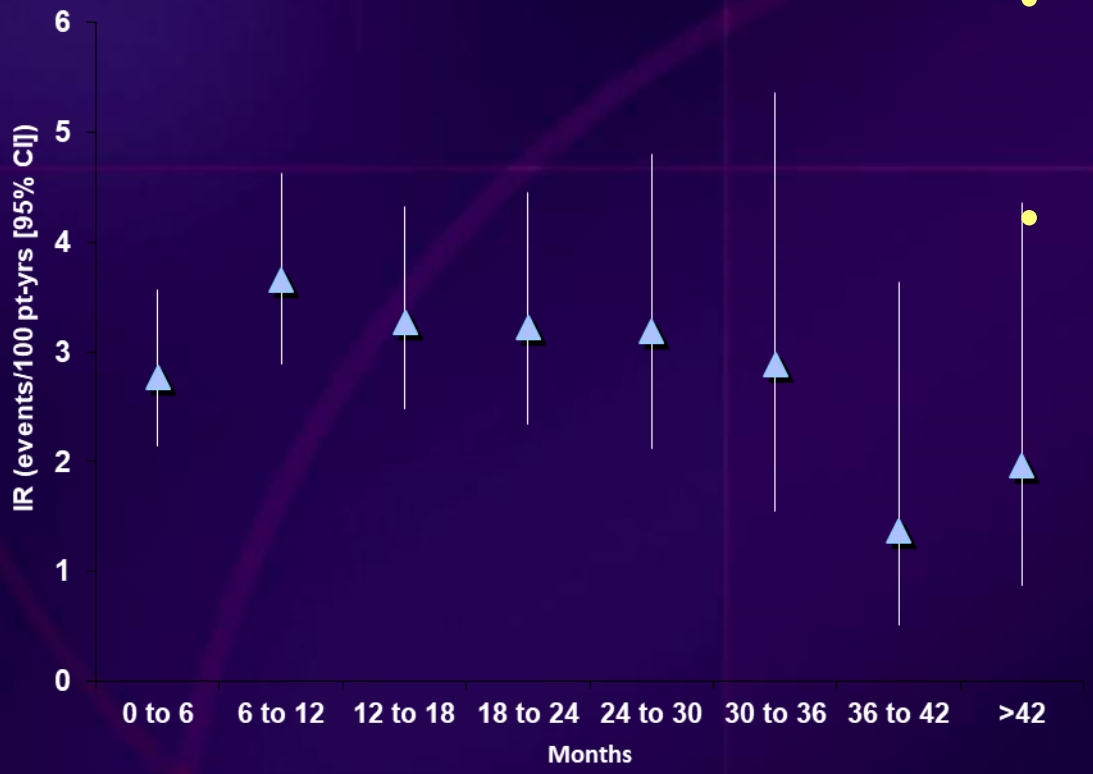
ema-confirms-xeljanz-be-used-caution-patients-high-risk-blood-clots_en

Oral Surveillance Tofa



Balanescu A et al ACR 2021

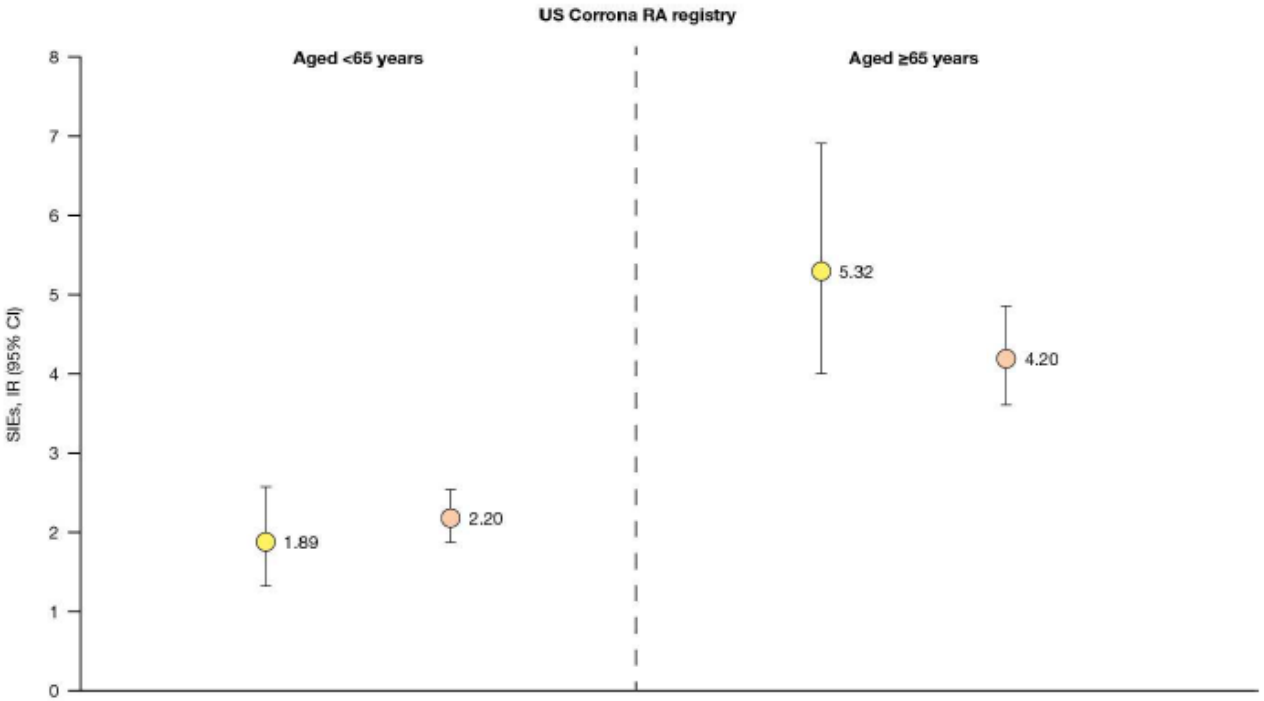
Incidence Rates of Serious Infections (SIs) by 6-Month Intervals



- Overall SI rate reported with tofacitinib:
  - 3.1/100pys
- Rates previously reported in RA clinical trial safety analyses
  - Adalimumab 3.9–5.1/100pys
  - Rituximab 3.9–4.3/100pys
  - Tocilizumab 3.8–5.1/100pys
  - Etanercept 3.8/100pys
  - Abatacept 2.0–3.1/100pys
  - Golimumab 5.09/100pys

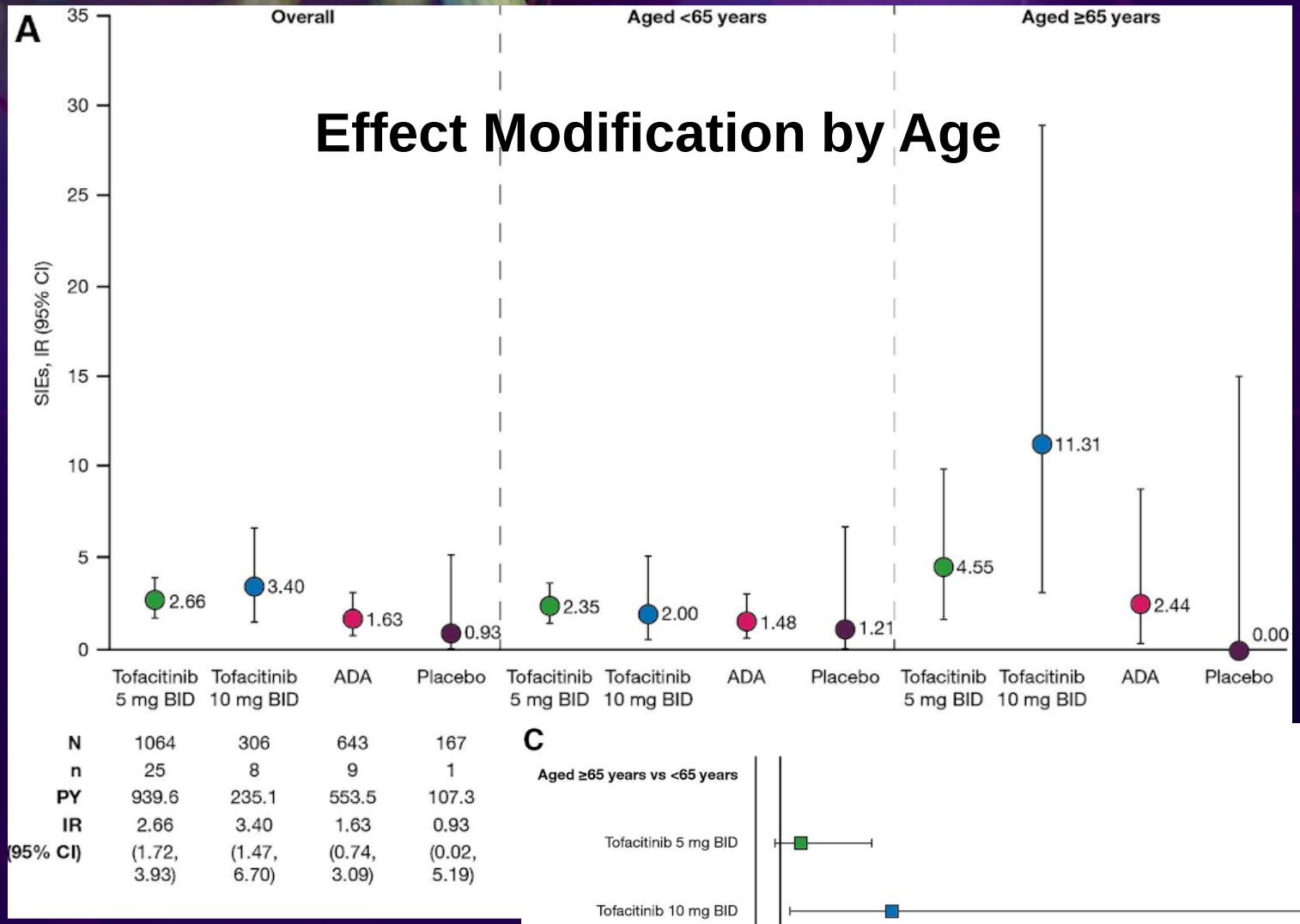
Cohen S, Radominski SC, Gomez-Reino JJ, et al. *Arthritis Rheumatol*. 2014 Jul 21. [Epub ahead of print]. Slide prepared by CSF.

Supplementary figure S2 IRs (95% CI) of SIEs in the US Corrona RA registry, stratified by age (<65 years or ≥65 years).

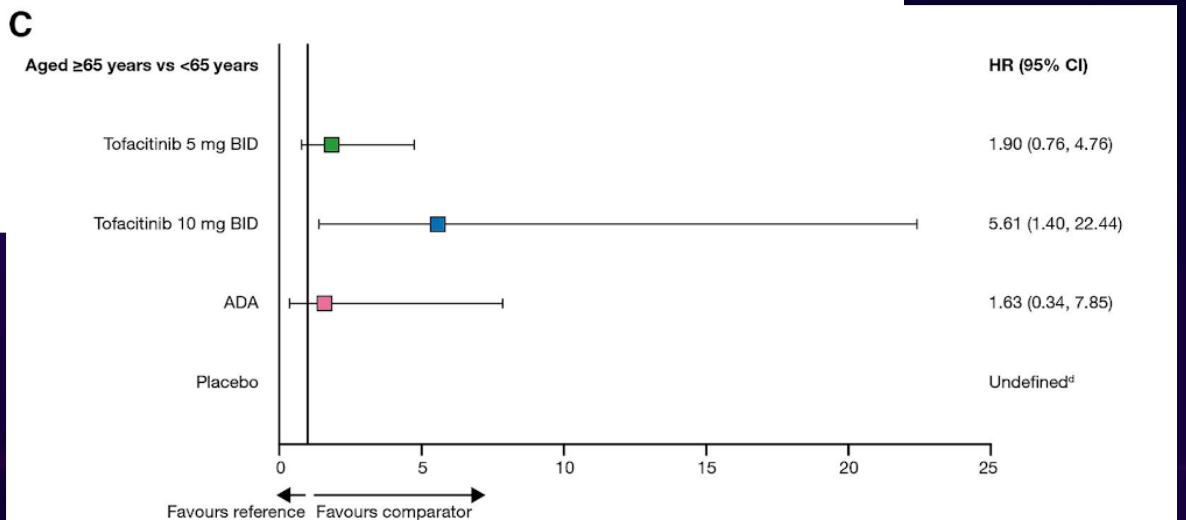


Data from the US Corrona RA registry for patients initiating tofacitinib or bDMARDs between 6 November 2012 and 31 January 2019
Age-/gender-adjusted IR=first events/100 PY
bDMARD, biologic disease-modifying antirheumatic drug; CI, confidence interval; IR, incidence rate; N, number of patients in each treatment group; n, number of patients with event; PY, patient-years; RA, rheumatoid arthritis; SIE, serious infection event

Effect Modification by Age

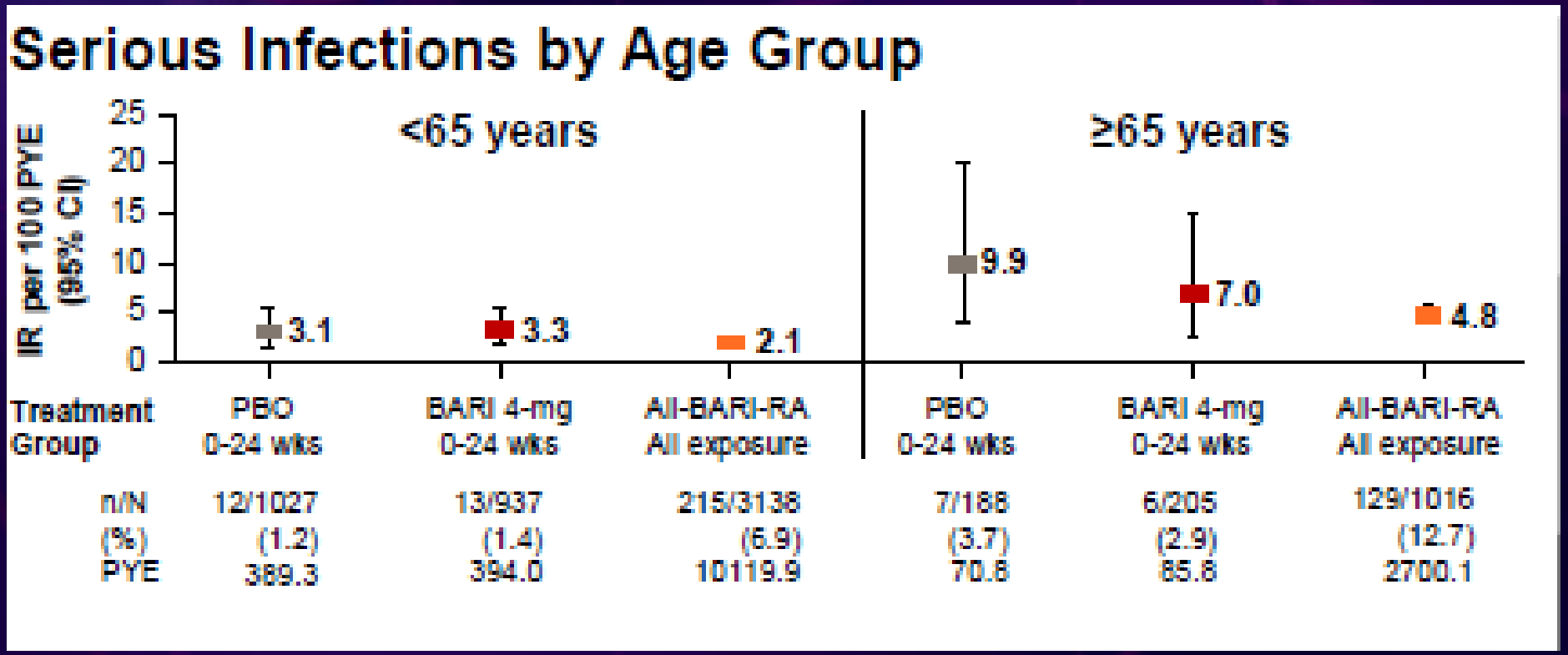


N	1064	306	643	167
n	25	8	9	1
PY	939.6	235.1	553.5	107.3
IR	2.66	3.40	1.63	0.93
(95% CI)	(1.72, 3.93)	(1.47, 6.70)	(0.74, 3.09)	(0.02, 5.19)



Winthrop KL et al. ARD 2020

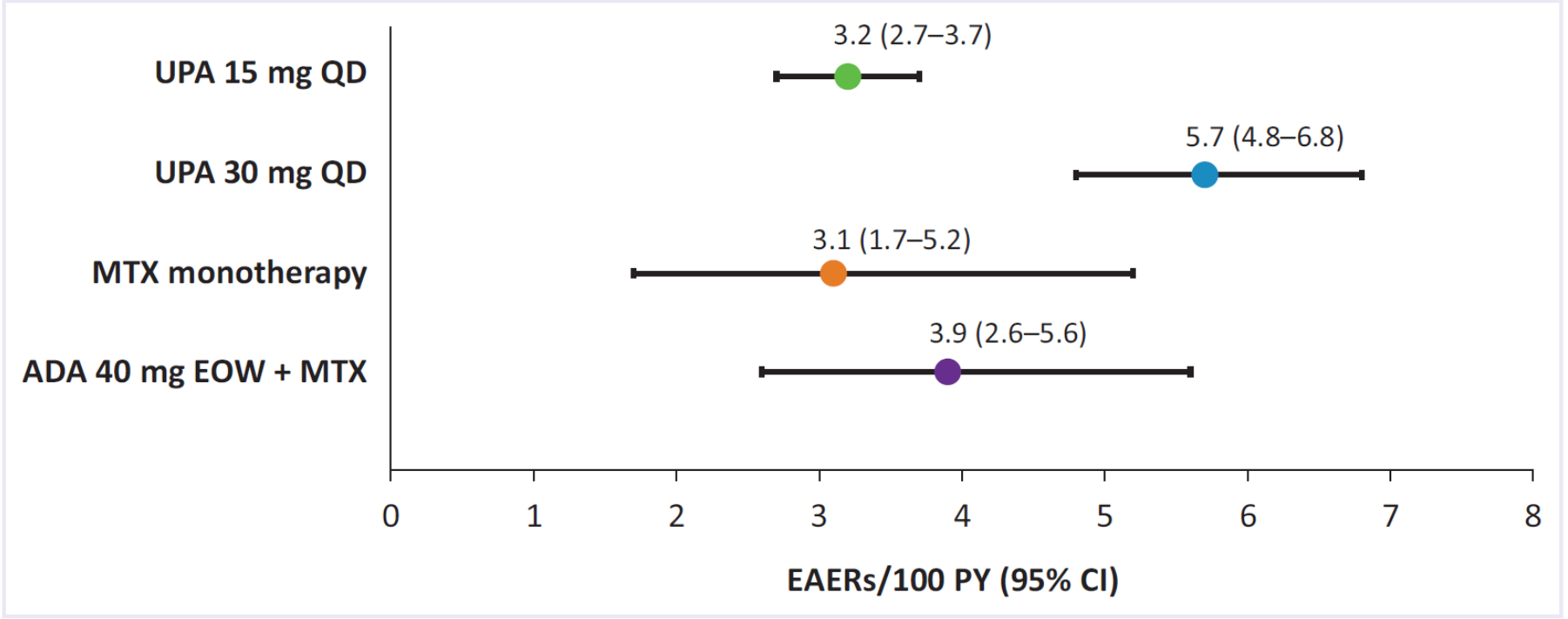
SIE Bari up to 8.5 years



Genovese M et al. EULAR 2020

UPA SIE Phase 3

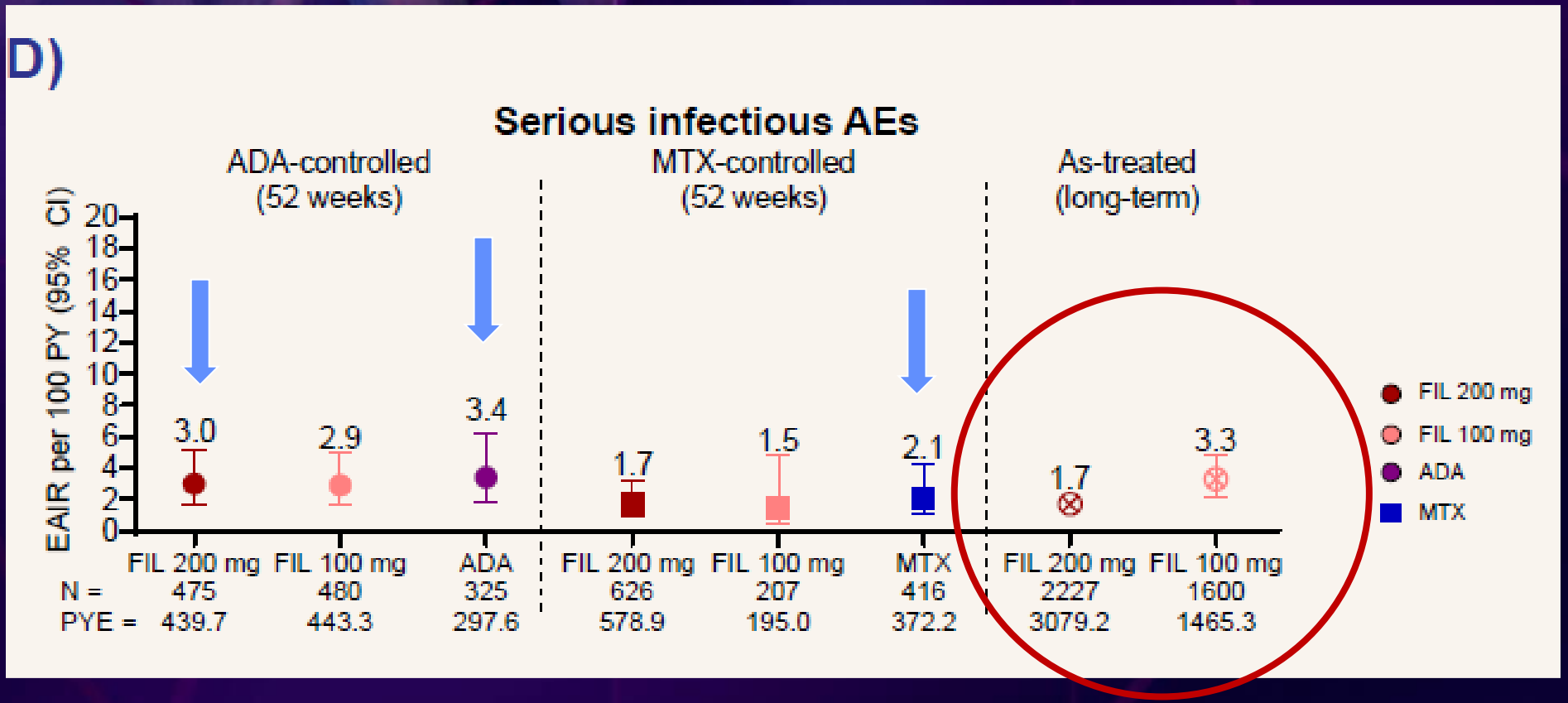
Figure 2. Forest Plot of Exposure-adjusted Serious Infection Rates



ADA, adalimumab; CI, confidence interval; EAERs, exposure-adjusted event rates; EOW, every other week; MTX, methotrexate; PY, patient-years; QD, once daily; UPA, upadacitinib.

Winthrop K et al. EULAR 2020

Filgo phase 2/3 ISS



Genovese M et al. EULAR 2020

Other Potential Opportunistic Infections

All Baricitinib RA Analysis Set

- 8 cases of candidiasis, including involvement of the
  - esophagus (6); none were serious/severe, 2 did not require treatment
  - lung (1); pre-existing bronchiectasis
  - soft tissue (1); serious
- 3 cases of *Pneumocystis jirovecii* pneumonia in Japan
- Single cases of
  - histoplasmosis, paracoccidioidomycosis, and cryptococcal lung infections
  - aspergillosis skin infection
  - Cytomegalovirus
  - Epstein-Barr virus
- No progressive multifocal leukoencephalopathy (PML)

RA=rheumatoid arthritis

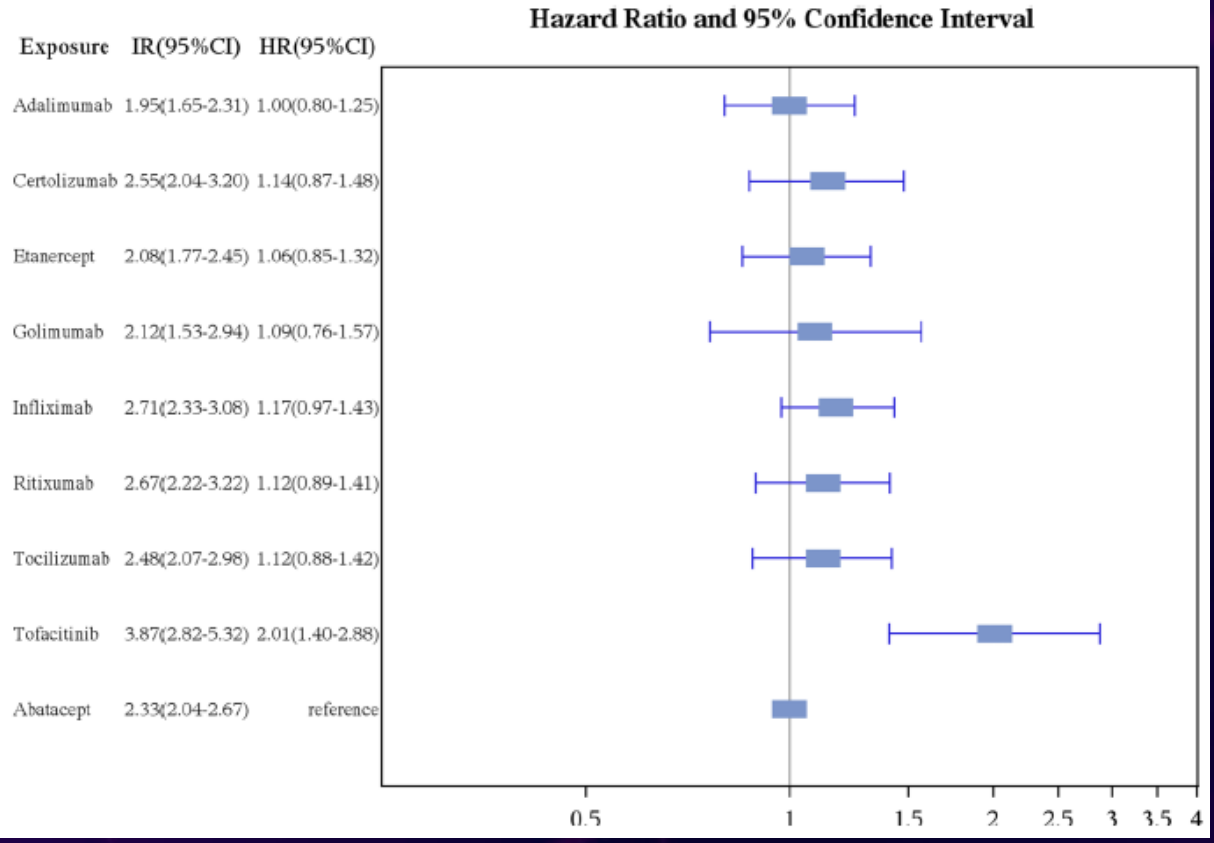
Recurrent zoster is rare

- 17, 413 persons with 1.8 million pys follow-up
  - 9.4/1,000 incidence of first zoster
  - 0.4% persons with second episode
  - Recurrence lowest in 12 months post-first episode
  - Increased risk with female, younger age of first zoster
- Recurrence in JAKi programs was 3-5% on average

Qian J et al. JAAD 2020

Real World HZ with Tofa and Biologics

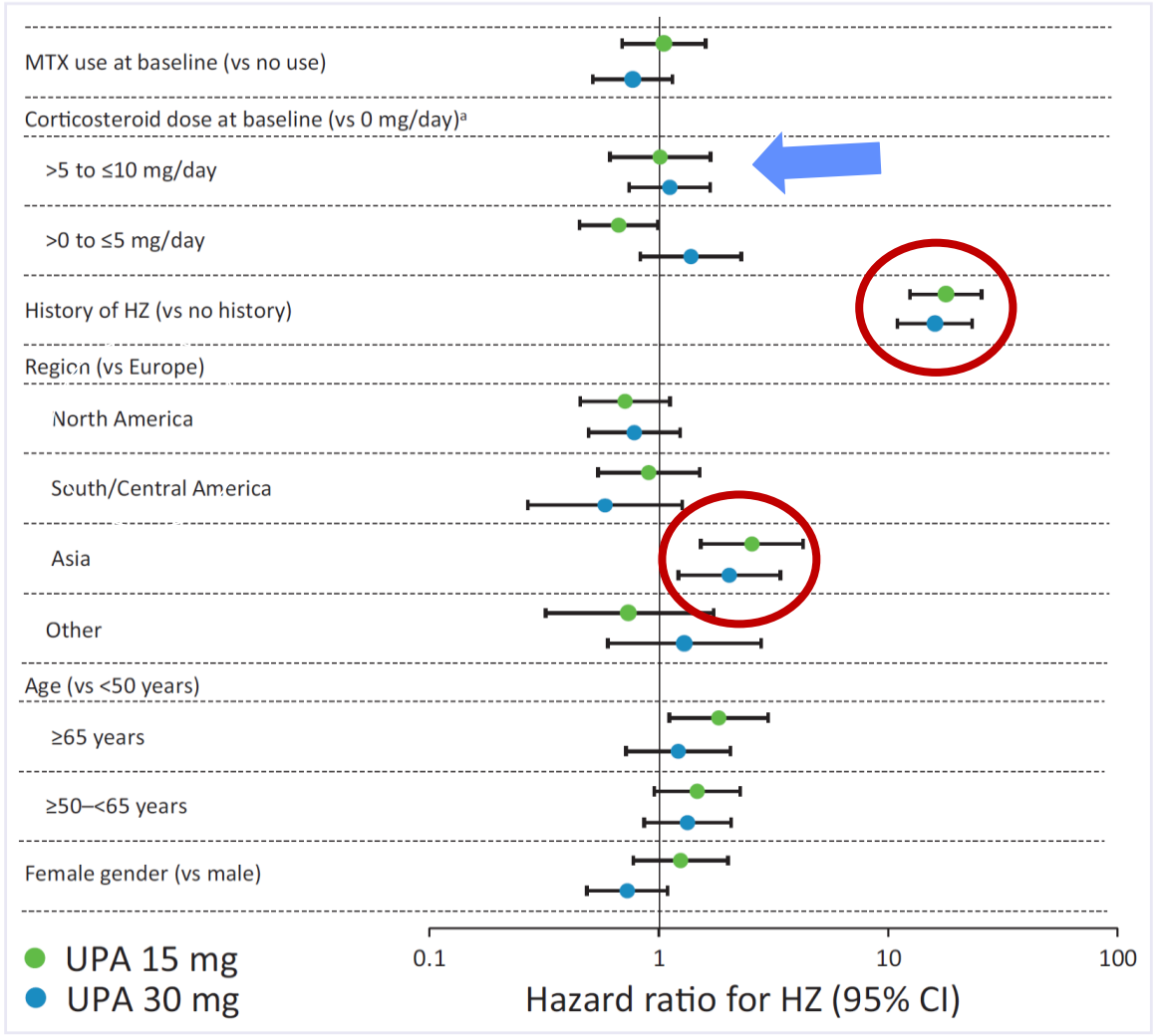
Figure 1 Incidence rates and adjusted* HRs of herpes zoster among tofacitinib and biologic-treated patients with RA. *Adjusted for age, gender, glucocorticoid use, methotrexate, number of biologics used, prior hospitalised infection, prior hospitalisation for other reasons, prior outpatient infection (other than varicella) and zoster vaccination. CI, confidence interval; HR, hazard ratio; IR, incidence rate; RA, rheumatoid arthritis.



Curtis JC, et al. *ARD*. 2016.

Upa Phase 3 RA Program

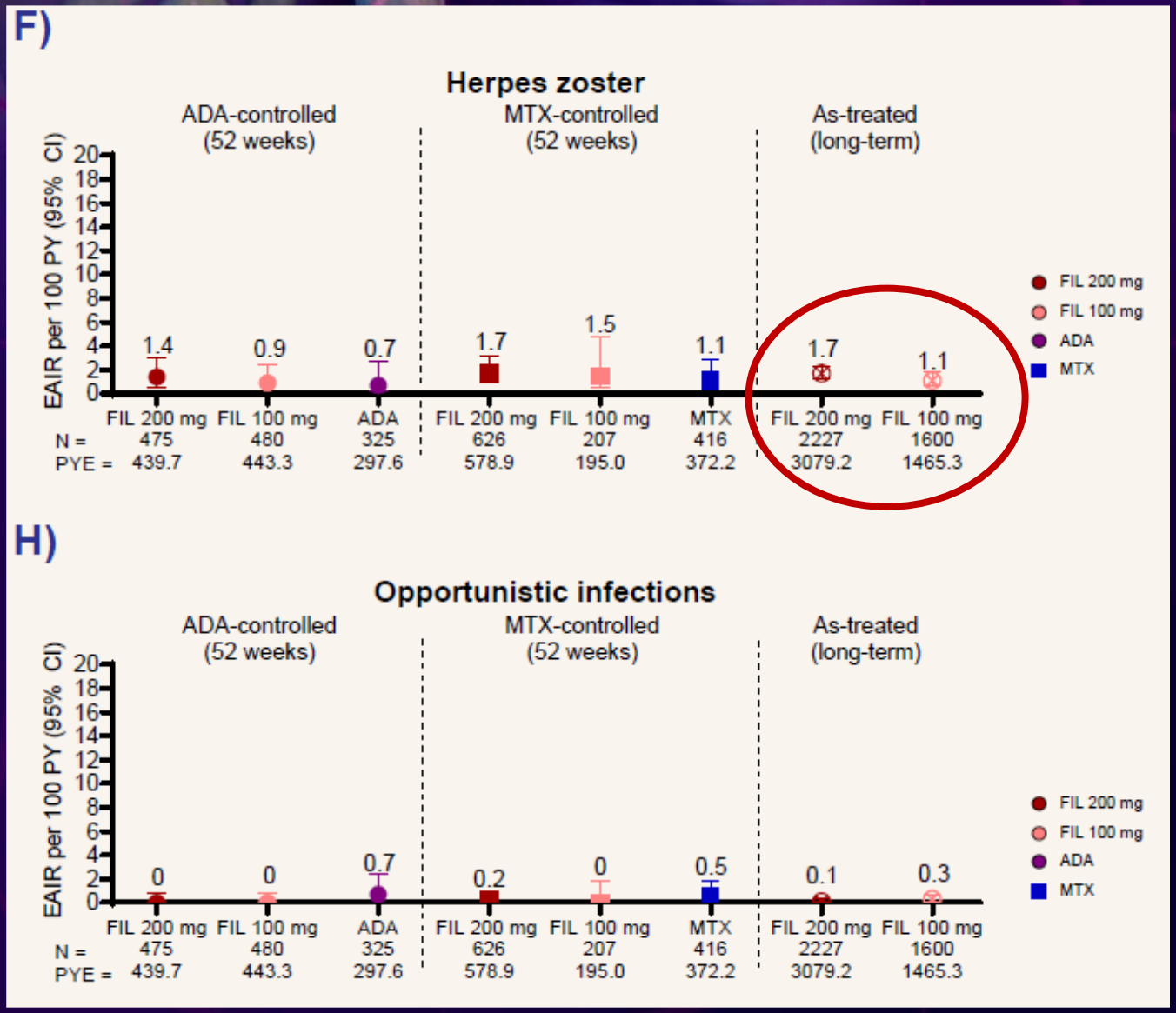
Figure 3. Risk Factors for HZ in Patients Receiving UPA (Multivariate Analysis)



[a]Prednisone or equivalent dose.
CI, confidence interval; HZ, herpes zoster; MTX, methotrexate; UPA, upadacitinib.

Winthrop K et al. http://dx.doi.org/10.1136/annrheumdis-2020-eular.2744

Filgo phase 2/3 ISS



Genovese M et al. EULAR 2020

Abrocitinib (JAK 1) for AD

Table 1 Demographic and baseline characteristics in the placebo-controlled and all-abrocitinib cohorts

	Placebo-controlled cohort[a] $N = 1540$	All-abrocitinib cohort[b] $N = 2856$
Age, y, median (IQR)	33.0 (24.0–46.0)	31.0 (22.0–44.0)

Phase II and III Integrated Safety Analysis of Abrocitinib for Moderate-to-Severe Atopic Dermatitis

Table 4 Summary of infection events in the placebo-controlled and all-abrocitinib cohorts

	Placebo-controlled cohort			All-abrocitinib cohort	
	Placebo $N = 342$	Abrocitinib 100 mg $N = 608$	Abrocitinib 200 mg $N = 590$	Abrocitinib 100 mg $N = 885$	Abrocitinib 200 mg $N = 1971$
Serious infections					
N (%)	2 (0.6)	6 (1.0)	2 (0.3)	17 (1.9)	24 (1.2)
IRs (95% CI)	2.31 (0.28–8.33)	3.80 (1.39–8.27)	1.28 (0.16–4.62)	2.65 (1.55–4.25)	2.33 (1.49–3.47)
Herpes zoster					
N (%)	0	3 (0.5)	8 (1.4)	13 (1.5)	44 (2.2)
IRs (95% CI)	0.00 (0.00–4.25)	1.90 (0.39–5.55)	5.16 (2.23–10.16)	2.04 (1.09–3.49)	4.34 (3.15–5.82)
Herpes simplex[a]					
N (%)	6 (1.8)	19 (3.1)	25 (4.2)	54 (6.1)	116 (5.9)
IRs (95% CI)	7.20 (2.60–14.58)	12.07 (7.26–18.59)	16.22 (10.49–23.67)	8.73 (6.56–11.39)	11.83 (9.77–14.19)
Eczema herpeticum					
N (%)	3 (0.9)	6 (1.0)	0 (0)	15 (1.7)	8 (0.4)
IRs (95% CI)	3.46 (0.71–10.12)	3.81 (1.40–8.28)	0.00 (0.00–2.36)	2.34 (1.31–3.86)	0.78 (0.34–1.53)

CI confidence interval, *IR* incidence rate

[a]Includes events of genital herpes, genital herpes simplex, herpes dermatitis, herpes ophthalmic, herpes simplex, nasal herpes, ophthalmic herpes simplex, and oral herpes

Simpson E et al. AJCD 2021

Abro VTE

- VTE (IR 0.3/100)

100mg (n=885)	200mg (n=1971)
0	5

Simpson E et al. AJCD 2021

TYK2 Inhibitor in PsO

Table 3. Summary of Safety.*

Adverse Event	Placebo (N=45)	BMS-986165				
		3 mg Every Other Day (N=44)	3 mg Daily (N=44)	3 mg Twice Daily (N=45)	6 mg Twice Daily (N=45)	12 mg Daily (N=44)
		number of patients (percent)				
Death	0	0	0	0	0	0
Serious adverse event†	1 (2)	1 (2)	1 (2)	1 (2)	0	0
Adverse event	23 (51)	26 (59)	24 (55)	29 (64)	36 (80)	34 (77)
Adverse event leading to discontinuation of trial regimen‡	2 (4)	1 (2)	2 (5)	1 (2)	3 (7)	1 (2)
Most frequent adverse events§						
Nasopharyngitis	2 (4)	1 (2)	4 (9)	5 (11)	7 (16)	2 (5)
Headache	2 (4)	4 (9)	4 (9)	3 (7)	3 (7)	2 (5)
Diarrhea	2 (4)	1 (2)	1 (2)	2 (4)	2 (4)	4 (9)
Nausea	2 (4)	4 (9)	0	1 (2)	1 (2)	2 (5)
Upper respiratory tract infection	0	1 (2)	3 (7)	1 (2)	4 (9)	1 (2)
Pruritus	2 (4)	0	1 (2)	1 (2)	3 (7)	2 (5)
Acne	0	1 (2)	0	1 (2)	2 (4)	4 (9)
Toothache	1 (2)	1 (2)	1 (2)	1 (2)	3 (7)	1 (2)
Psoriasis	2 (4)	1 (2)	3 (7)	1 (2)	0	0
Aphthous ulcer	0	0	0	3 (7)	0	1 (2)

* Data have been rounded to the nearest integer. Adverse events were events reported by patients that began after the administration of the trial regimen and within 30 days after the last dose.

† Five serious adverse events were reported in four patients: two events in one patient in the placebo group (hemorrhagic anemia and hemorrhoidal hemorrhage) and one event in one patient each in the groups receiving 3 mg every other day (gastroenteritis due to rotavirus), 3 mg daily (accidental eye injury), and 3 mg twice daily (dizziness due to vestibular dysfunction with a history of the same).

‡ For patients who discontinued the trial regimen, data up to 30 days after the last dose were included; for patients who completed the 12-week intervention period, data up to the date of the last dose were included.

§ Shown are adverse events reported by three or more patients in any trial group; events elicited by laboratory testing are not included.

Papp K et al. NEJM 2018

Jak inhibitors: Regulatory Agencies Response to Oral Surveillance

EMA

- The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has recommended that XELJANZ® (tofacitinib) should only be used in patients over 65 years of age, patients who are current or past smokers, patients with other cardiovascular (CV) risk factors, and patients with other malignancy risk factors, if no suitable treatment alternative is available

FDA

- **Health Professionals** should consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Xeljanz/Xeljanz XR, Olumiant, or Rinvoq. This is particularly the case in patients who are current or past smokers, those with other cardiovascular risk factors, those who develop a malignancy, and those with a known malignancy other than a successfully treated nonmelanoma skin cancer. Reserve these medicines for patients who have had an inadequate response or intolerance to one or more TNF blockers. Counsel patients about the benefits and risks of these medicines and advise them to seek emergency medical attention if they experience signs and symptoms of a heart attack, stroke, or blood clot

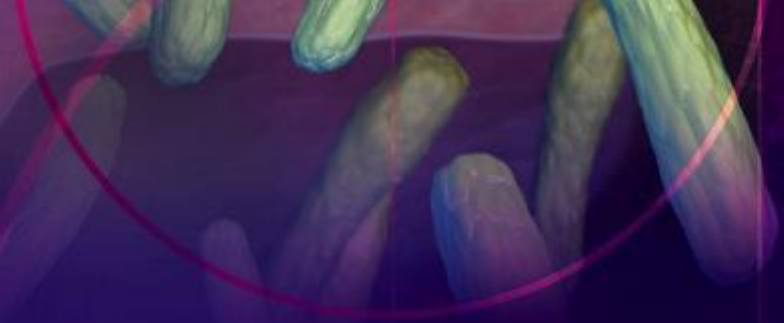
Winthrop KL et al. Nature Rheum 2022

Conclusion

- Maybe TNFi should be in the water?
  - Or maybe ABA
- All JAKs might not be the same
  - Are you more European or more American?
  - Need comparison studies like with Biologics
- For now, place Tofa after TNFi
  - Particularly among those over 50 with CV risk
  - Smokers
- Avoid in those with history of DVT

Acknowledgements

- UAB colleagues
- ACR and EULAR colleagues
- Oregon Health Authority colleagues
- CDC colleagues



APPENDIX

JAKi and COVID Vax

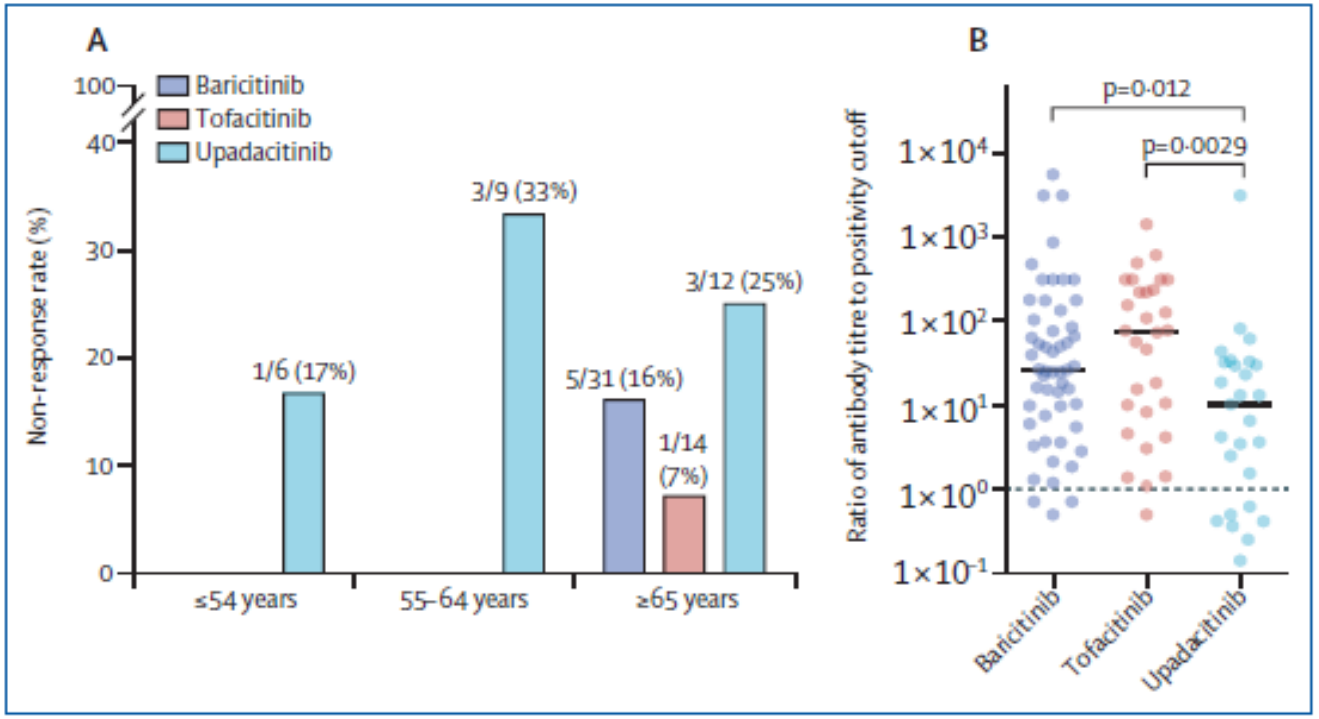
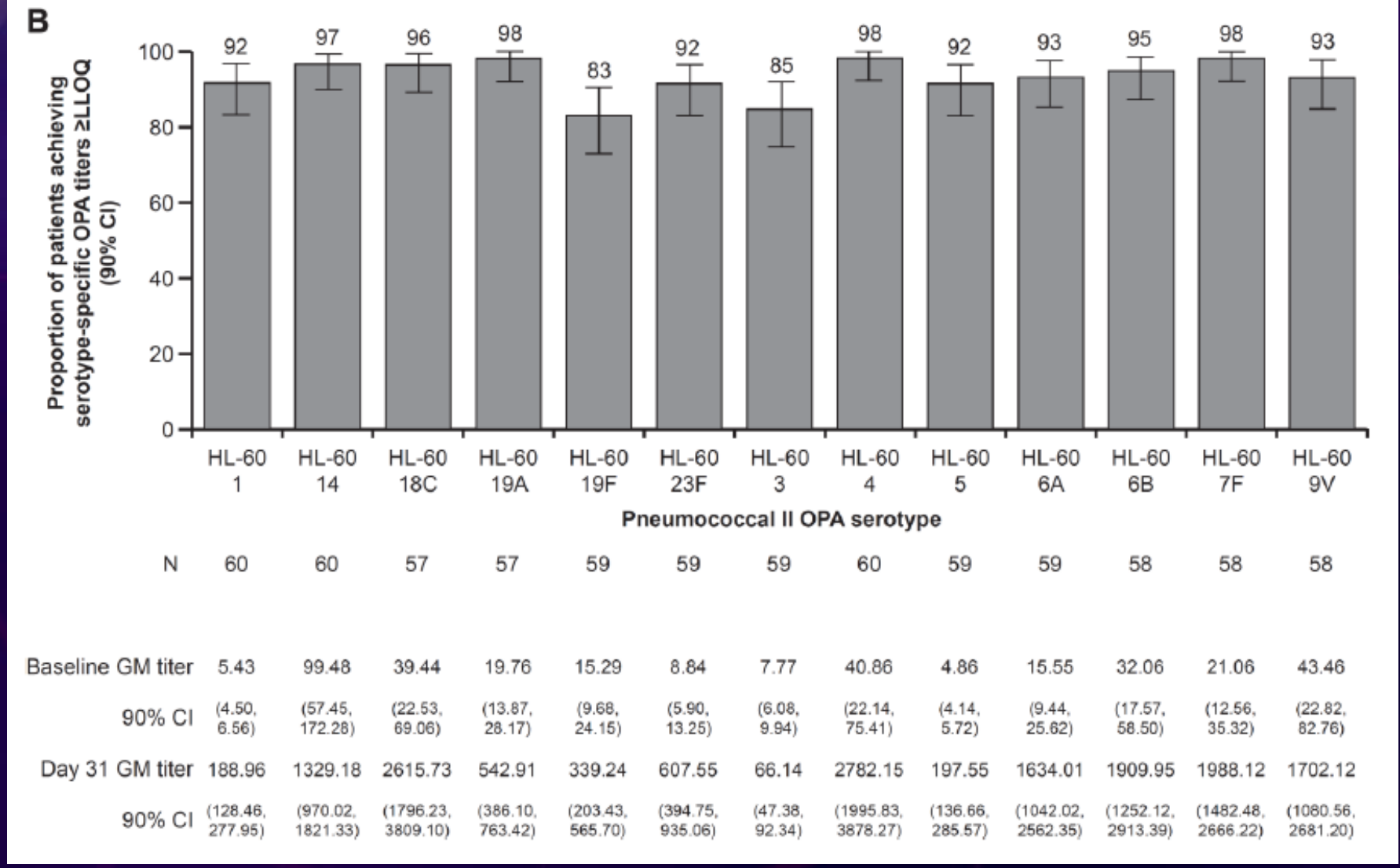


***Figure*: Immune response to COVID-19 vaccination for patient treated with JAK inhibitor**

(A) Proportion of non-responders in each age group (≤54, 55–64, and ≥65 years) according to their JAK inhibitor. (B) Antibody titres (measured as ratio of antibody titre to assay's positivity cutoff) for each patient according to JAK inhibitor. Solid horizontal bars show the median for each inhibitor group and the horizontal dashed line shows the threshold for positive response to the vaccines. Comparisons are based on Kruskall-Wallis analysis of variance on ranks (n=111, the antibody titres were not available for two patients, the result of the serology was only

Seror R et al Lancet Rheum 2021

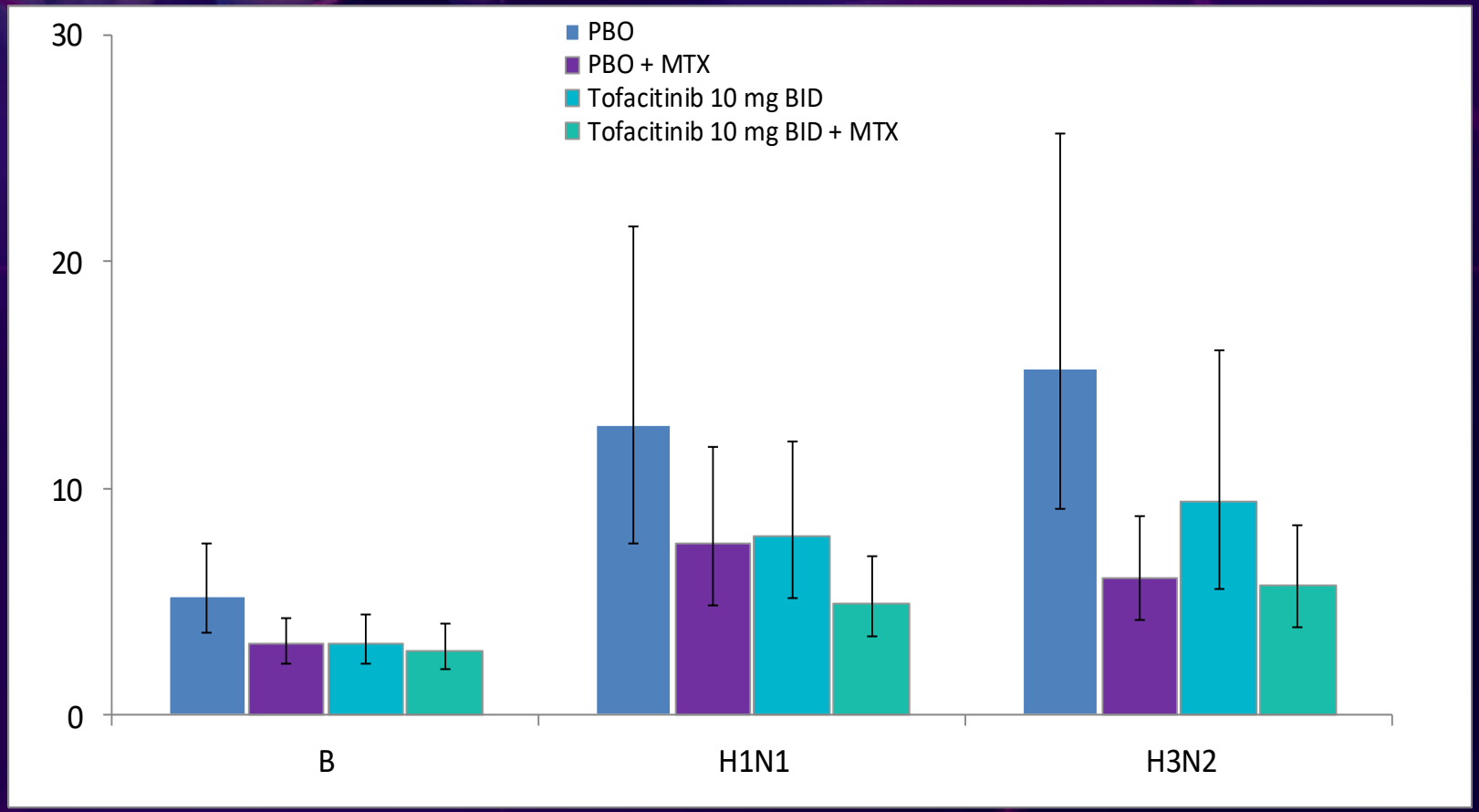
PCV-13 and Tofa



N	60	60	57	57	59	59	59	60	59	59	58	58	58
Baseline GM titer	5.43	99.48	39.44	19.76	15.29	8.84	7.77	40.86	4.86	15.55	32.06	21.06	43.46
90% CI	(4.50, 6.56)	(57.45, 172.28)	(22.53, 69.06)	(13.87, 28.17)	(9.68, 24.15)	(5.90, 13.25)	(6.08, 9.94)	(22.14, 75.41)	(4.14, 5.72)	(9.44, 25.62)	(17.57, 58.50)	(12.56, 35.32)	(22.82, 82.76)
Day 31 GM titer	188.96	1329.18	2615.73	542.91	339.24	607.55	66.14	2782.15	197.55	1634.01	1909.95	1988.12	1702.12
90% CI	(128.46, 277.95)	(970.02, 1821.33)	(1796.23, 3809.10)	(386.10, 763.42)	(203.43, 565.70)	(394.75, 935.06)	(47.38, 92.34)	(1995.83, 3878.27)	(136.66, 285.57)	(1042.02, 2562.35)	(1252.12, 2913.39)	(1482.48, 2666.22)	(1080.56, 2681.20)

Winthrop K et al. JAAD (In Press)

Tofacitinib and HI Titer Rise

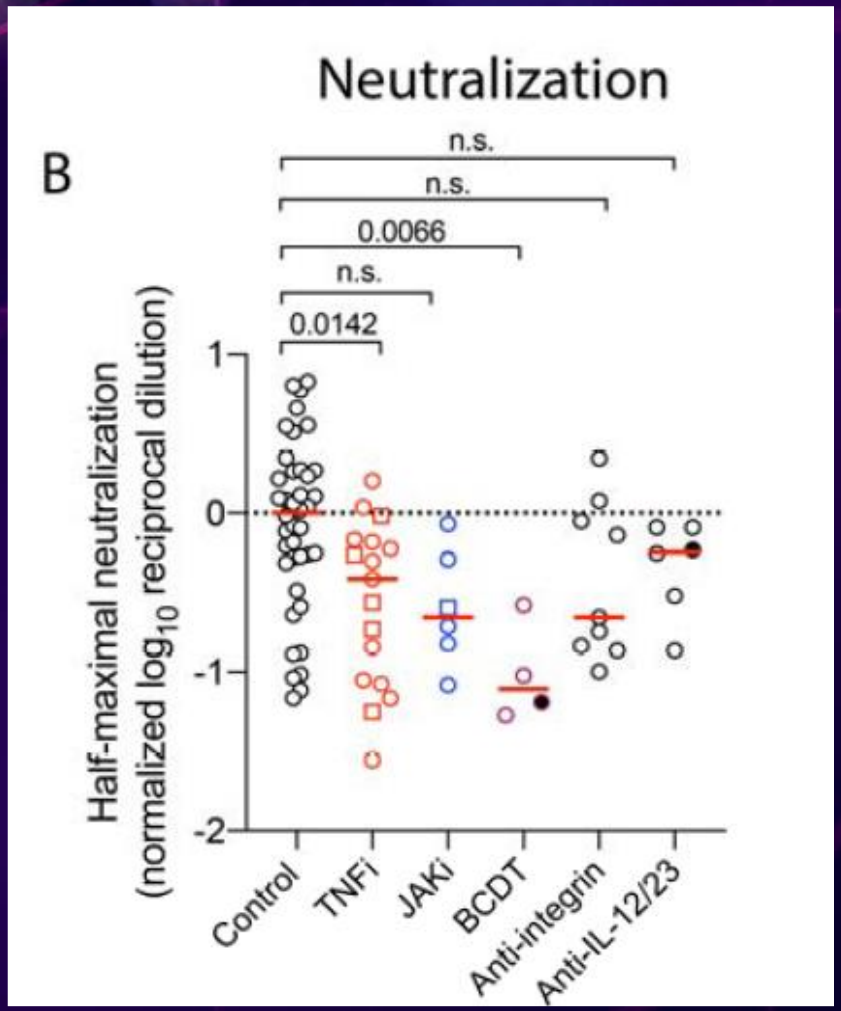


Influenza antibody GMFR 95% CI

Influenza vaccine serotype

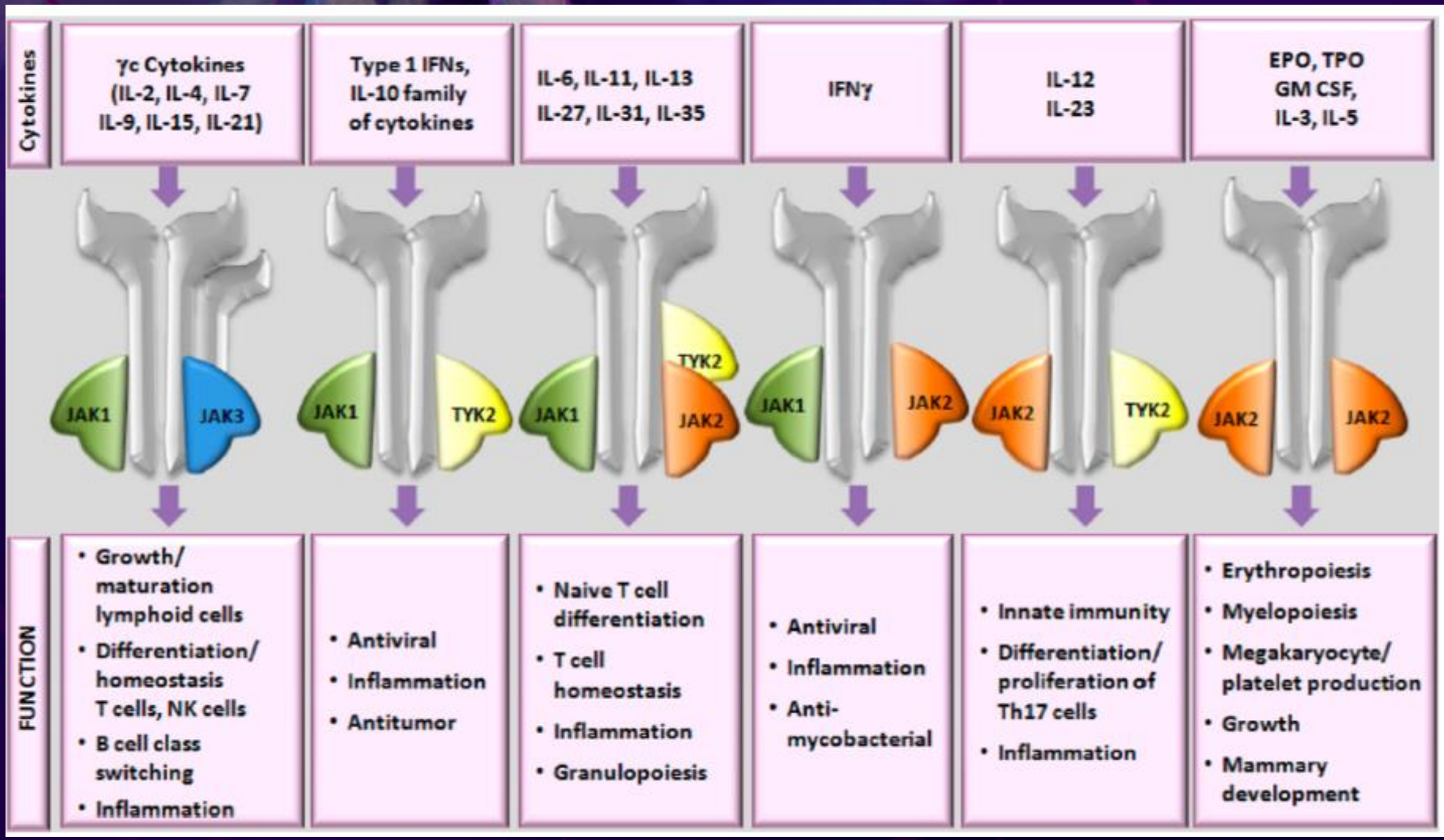
Winthrop K et al. ARD 2015

DMARDs on mRNA Vaccine Response



Mixed IMID, low numbers of disease and therapy groups

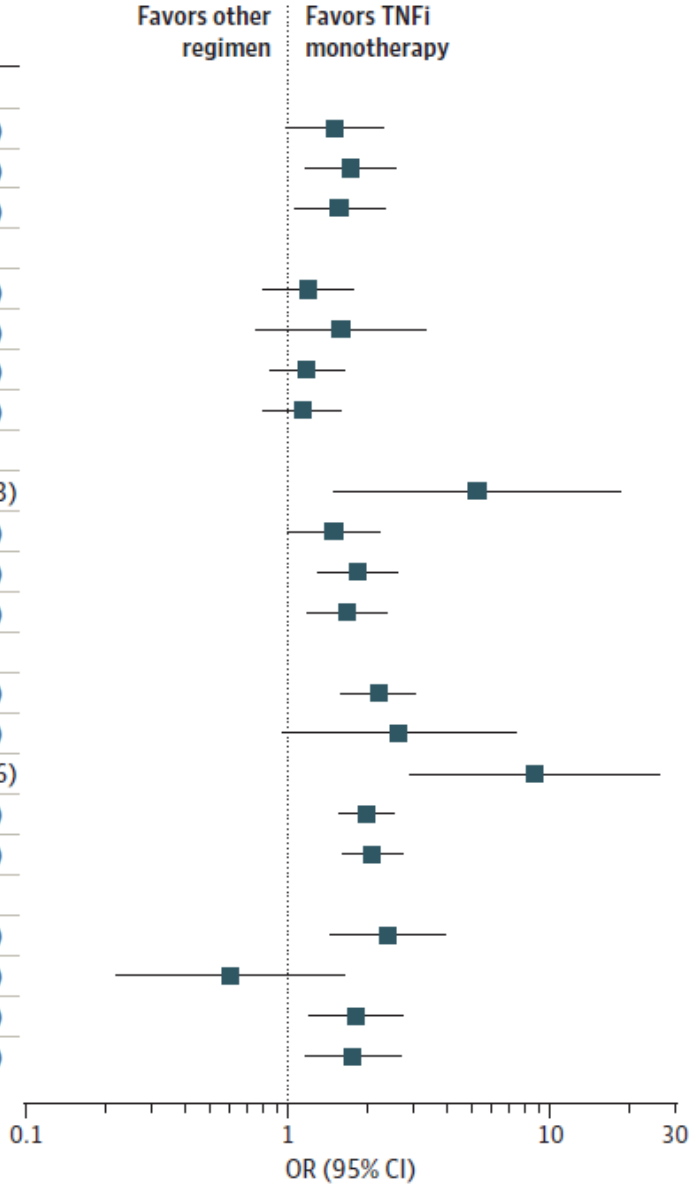
Deepak P et al. Ann Int Med 2021



Clark JD, et al. *J Med Chem.* 2014.

TNFi Protective against COVID Death/Hospitlization

Treatment regimen	OR (95% CI)
TNFi plus AZA/6MP vs TNFi monotherapy	
SECURE-IBD registry	1.51 (0.98-2.31)
Pooled estimate (primary analysis)	1.74 (1.17-2.58)
Pooled estimate (sensitivity analysis)	1.57 (1.06-2.35)
TNFi plus MTX vs TNFi monotherapy	
GRA registry	1.20 (0.80-1.79)
SECURE-IBD registry	1.59 (0.76-3.34)
Pooled estimate (primary analysis)	1.18 (0.85-1.63)
Pooled estimate (sensitivity analysis)	1.14 (0.81-1.60)
AZA/6MP monotherapy vs TNFi monotherapy	
GRA registry	5.28 (1.51-18.43)
SECURE-IBD registry	1.50 (1.00-2.24)
Pooled estimate (primary analysis)	1.8 [illegible]0-2.61)
Pooled estimate (sensitivity analysis)	[illegible]1.19-2.39)
MTX monotherapy vs TNFi monotherapy	
GRA registry	2.21 (1.59-3.08)
SECURE-IBD registry	2.66 (0.95-7.43)
PsoProtect registry	8.76 (2.94-26.06)
Pooled estimate (primary analysis)	2.0[illegible]57-2.56)
Pooled estimate (sensitivity analysis)	[illegible].62-2.72)
JAKi monotherapy vs TNFi monotherapy	
GRA registry	2.41 (1.46-3.99)
SECURE-IBD registry	0.60 (0.22-1.64)
Pooled estimate (primary analysis)	1.82 (1.21-2.73)
Pooled estimate (sensitivity analysis)	1.77 (1.16-2.69)



Izadi Z et al.
JAMA Inf Dis 2021

ORALSURV

Malignancy

The overall rate of malignancy for JAK inhibitors in RA randomized clinical trials and long-term extension studies has been reported to be similar to that seen with bDMARDs, and lower than that observed for tofacitinib in this study. In the ORALSURV study, the incidence rate for malignancy was 1.13 (95% CI 0.87–1.14) for patients treated with tofacitinib 5 mg twice daily and 1.13 (95% CI 0.86–1.14) for those treated with tofacitinib 10 mg twice daily, compared with 0.77 (95% CI 0.55–1.04) for the TNF inhibitor-treated patients (HR 1.48; 95% CI 1.04–2.09). This signal was driven by differential rates of several cancers (particularly lung cancer and lymphoma) primarily seen in the North American strata of the study (compared with the rest of the

Box 1 | **FDA and EMA responses to ORAL Surveillance**

The results of the ORAL Surveillance study[1] have led regulatory authorities such as the FDA and EMA to recommend different changes to the utilization of Janus kinase inhibitors.

EMA[22]

- For patients ≥65 years old, those with a history of smoking and those with risk factors for cardiovascular disease or malignancy, tofacitinib should be used only if no suitable alternatives exist

FDA[2]

- Use of tofacitinib, baricitinib and upadacitinib is recommended for use only in patients who have had an inadequate response to, or intolerance of, one or more TNF inhibitors
- Boxed warnings for tofacitinib, baricitinib and upadacitinib updated to include information about the risks of serious heart-related events, cancer, blood clots and death
- Health-care professionals should consider the benefits and risks for an individual patient prior to initiating or continuing treatment with tofacitinib, baricitinib or upadacitinib, particularly for patients with a history of smoking, those with risk factors for cardiovascular disease and those with a malignancy

Winthrop KL et al. Nat Rheum Rev 2022