



Διαχείριση Αυτοάνοσων νοσημάτων το 2020. Τι αλλάζει; Ρευματοειδής αρθρίτιδα

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Διευθυντής Ρευματολογικής Κλινικής
Ναυτικού Νοσοκομείου Αθηνών**

**12ου Πανελλήνιο Συνέδριο ΕΠΕΜΥ
Βόλος 29/10 -1/11 2020**

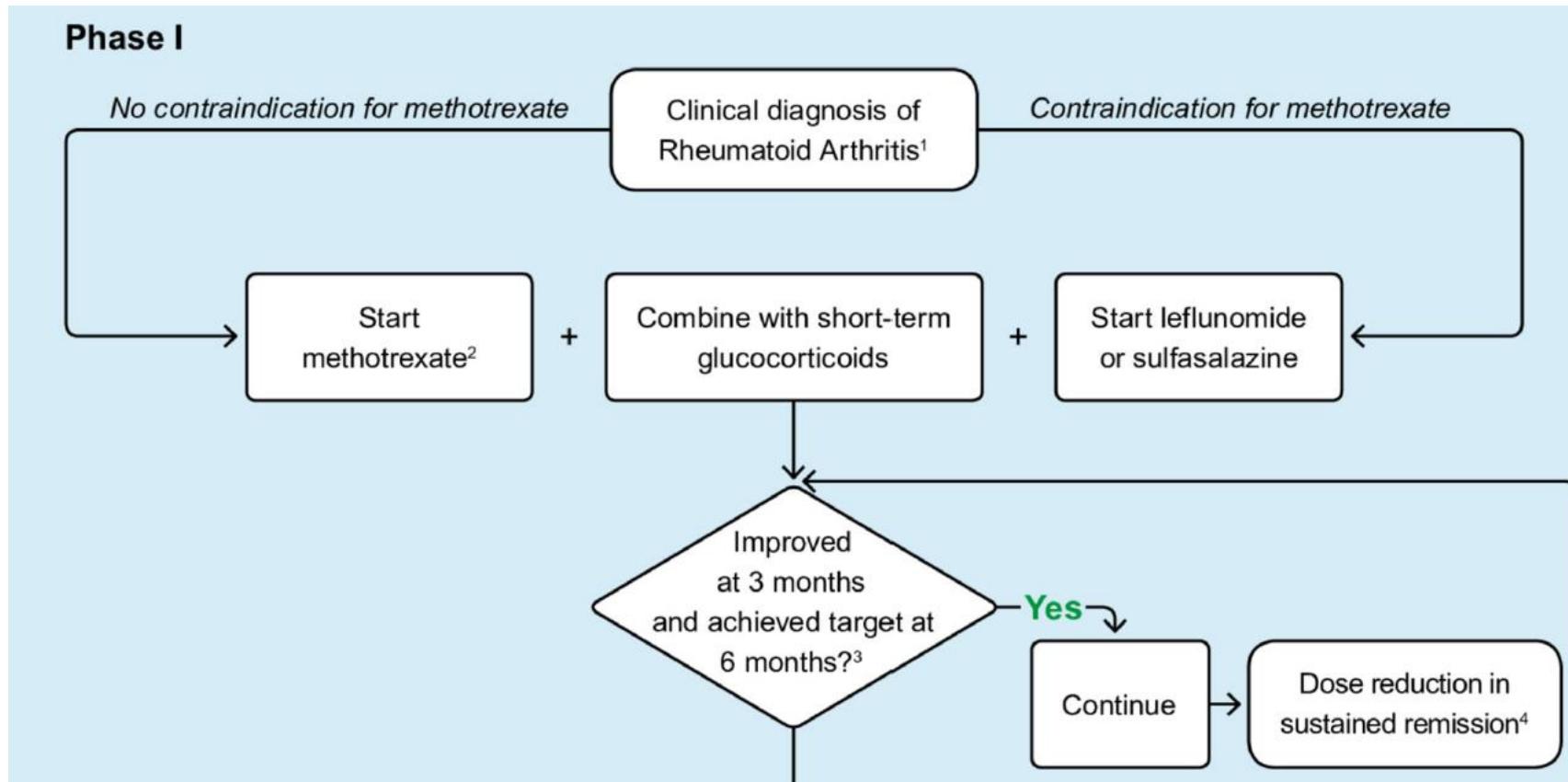
Σύγκρουση συμφερόντων

- Αμοιβή για την παρουσίαση από την Pfizer
- Εκπαιδευτικές-ερευνητικές-συμβουλευτικές επιχορηγήσεις την τελευταία διετία:
MSD, Abbvie, BMS, Novartis, UCB, Roche, Celgene, Janssen, Aenorasi

“Για όλα τα φαρμακευτικά προϊόντα που αναφέρονται παρακαλείσθε να συμβουλεύεστε τις εγκεκριμένες Περιλήψεις Χαρακτηριστικών των Προϊόντων”.

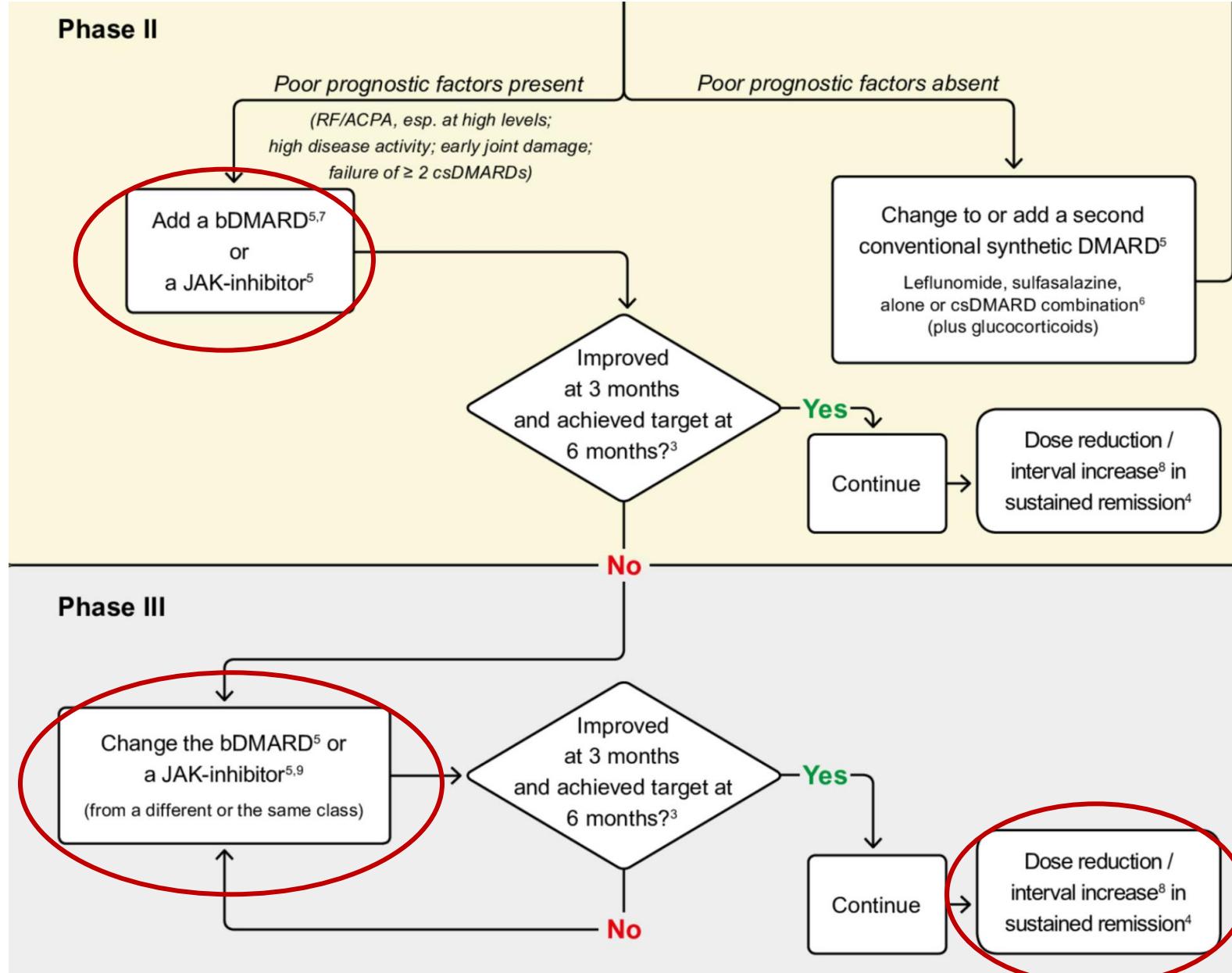
“Η Pfizer έχει ελέγξει το περιεχόμενο ώστε να ανταποκρίνεται στις ειδικές προδιαγραφές της αλλά δεν έχει επιβεβαιώσει ότι οι βιβλιογραφικές παραπομπές έχουν παρατεθεί ορθά.”

Algorithm of RA management based on EULAR updated recommendations



Smolen J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020

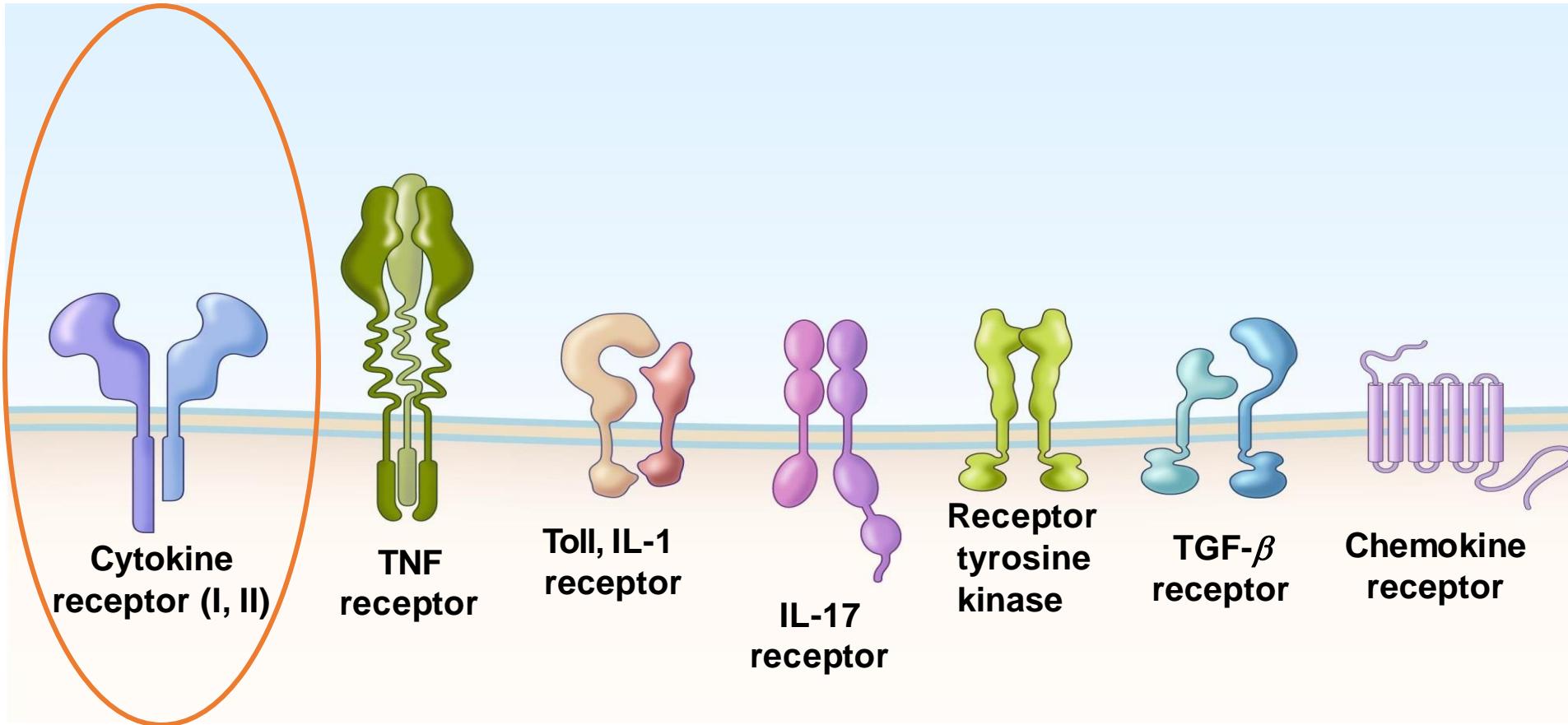
Algorithm of RA management based on EULAR updated recommendations



Δεν ανταποκρίνονται όλοι οι ασθενείς στην θεραπεία

- Στην MTX ~ 50% των ασθενών
- Στους TNFi
 - ~ ACR20 60%, ACR50 40%, ACR70 20%
 - ~ Δευτερογενής αποτυχία ~ 50%

Cytokine receptor superfamilies



- >200 “cytokines” in the human genome: interferons, interleukins, cytokines, growth factors, colony stimulating factors, hormones, etc
- only Type I/II
- critical for host defense, immunoregulation
- major drivers of autoimmunity

O’Shea JJ and Gadina M. *Nature Reviews Rheumatology* 2019
Gadina et al. *Rheumatology* 2019
Gadina et al. *J Leukoc Biol.* 2018
Schwartz et al. *Nat Rev Drug Discov.* 2017

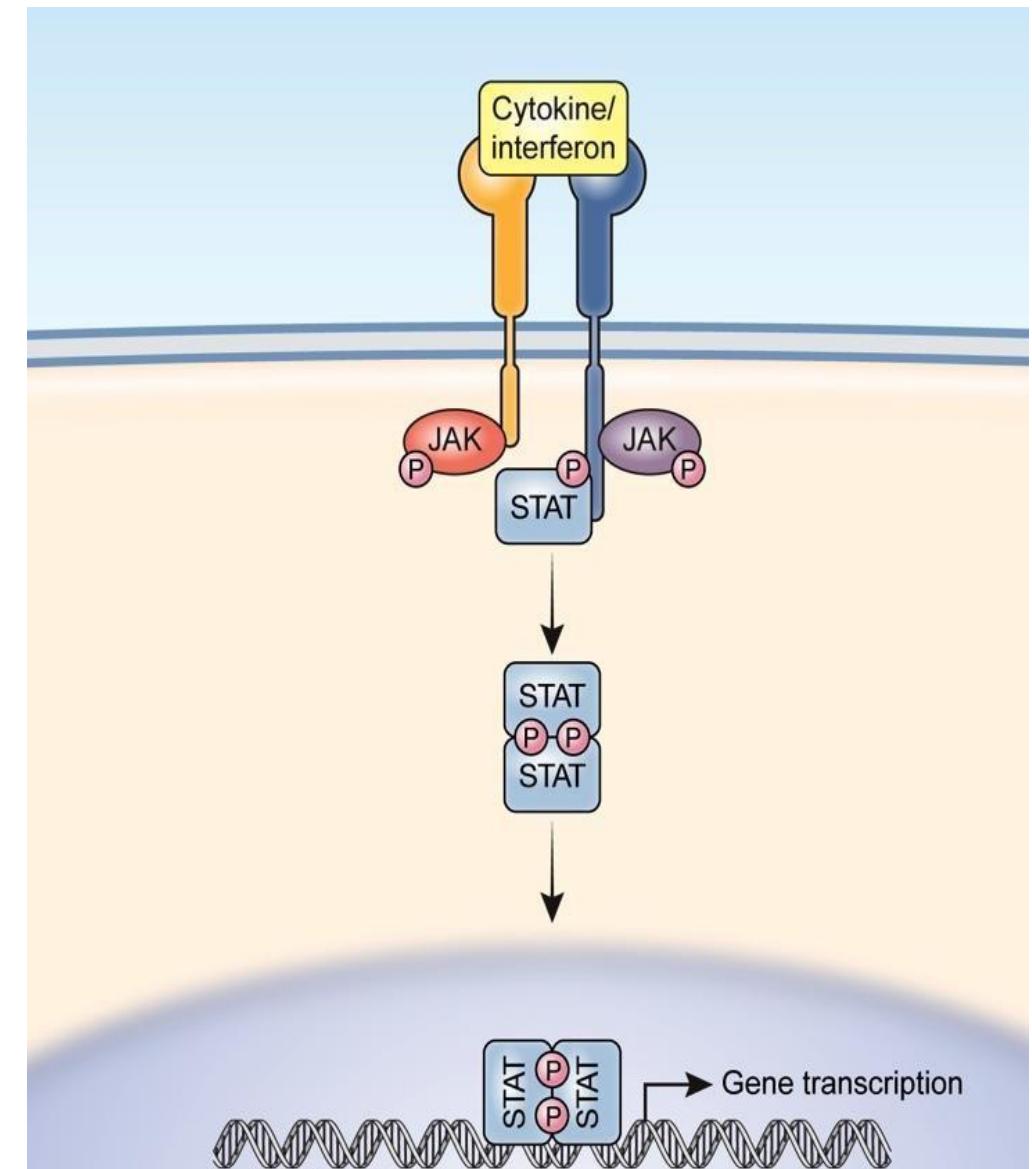
Signaling by Cytokines, Interleukins, Interferons, Colony stimulating factors

Discovery of Jaks

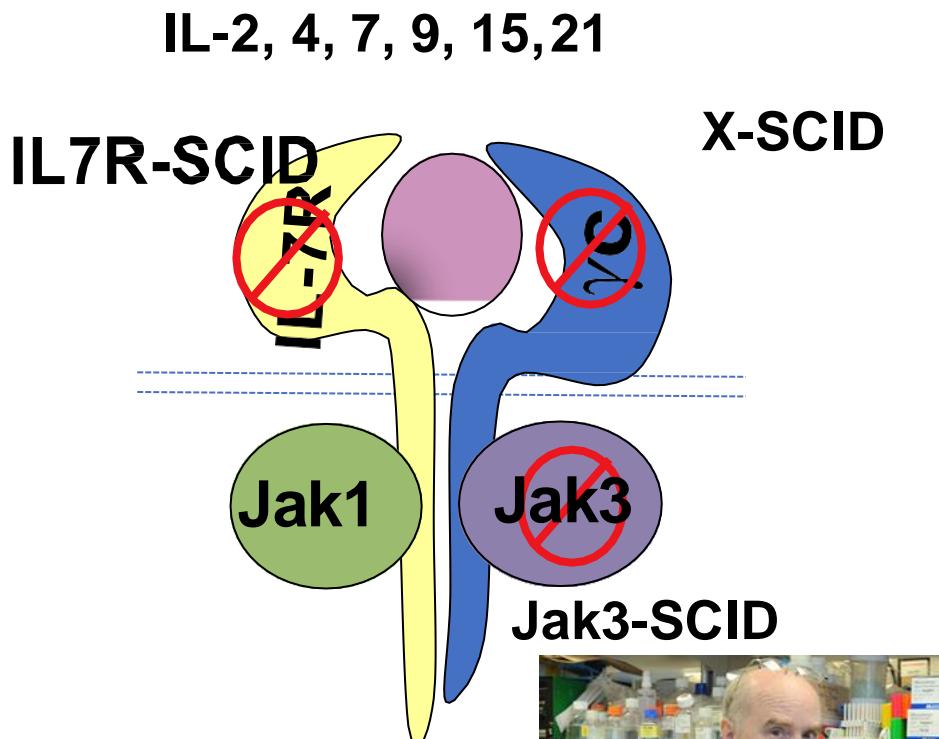
- Screening libraries for kinases
- reconstitution of IFN-resistant cell lines

Velazquez et al Cell 1992

- Conserved flies to mammals
- Mutagenized cell lines established criticality
- In vivo?

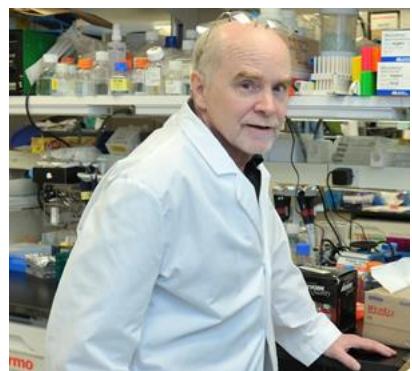


Jaks essential for Type I/II cytokine signaling – genetic evidence



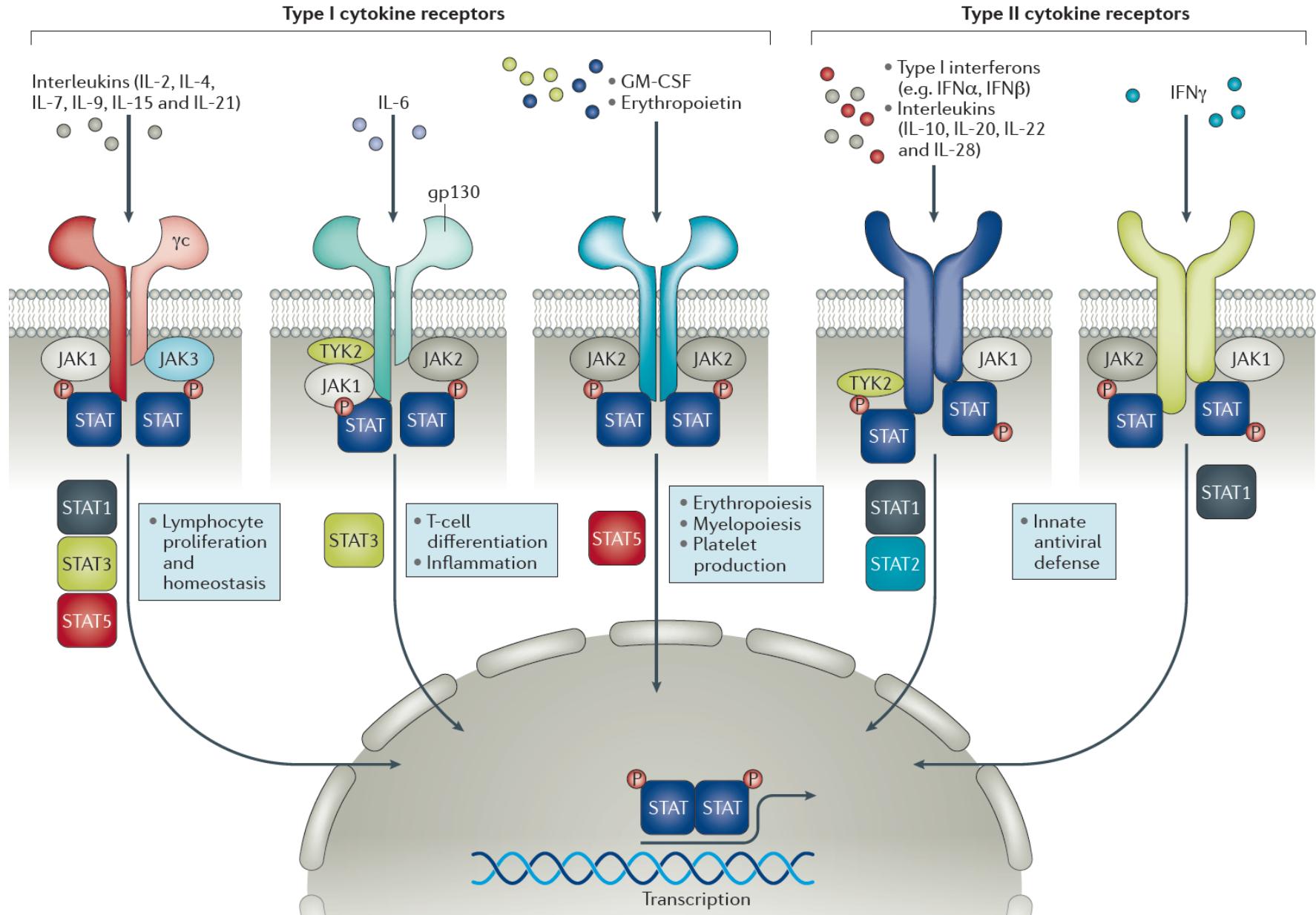
- First “knockout” in JAK–STAT pathway
- Human primary immunodeficiency

Macchi Pet al, Nature, 1995



Russell et al, Science 1995

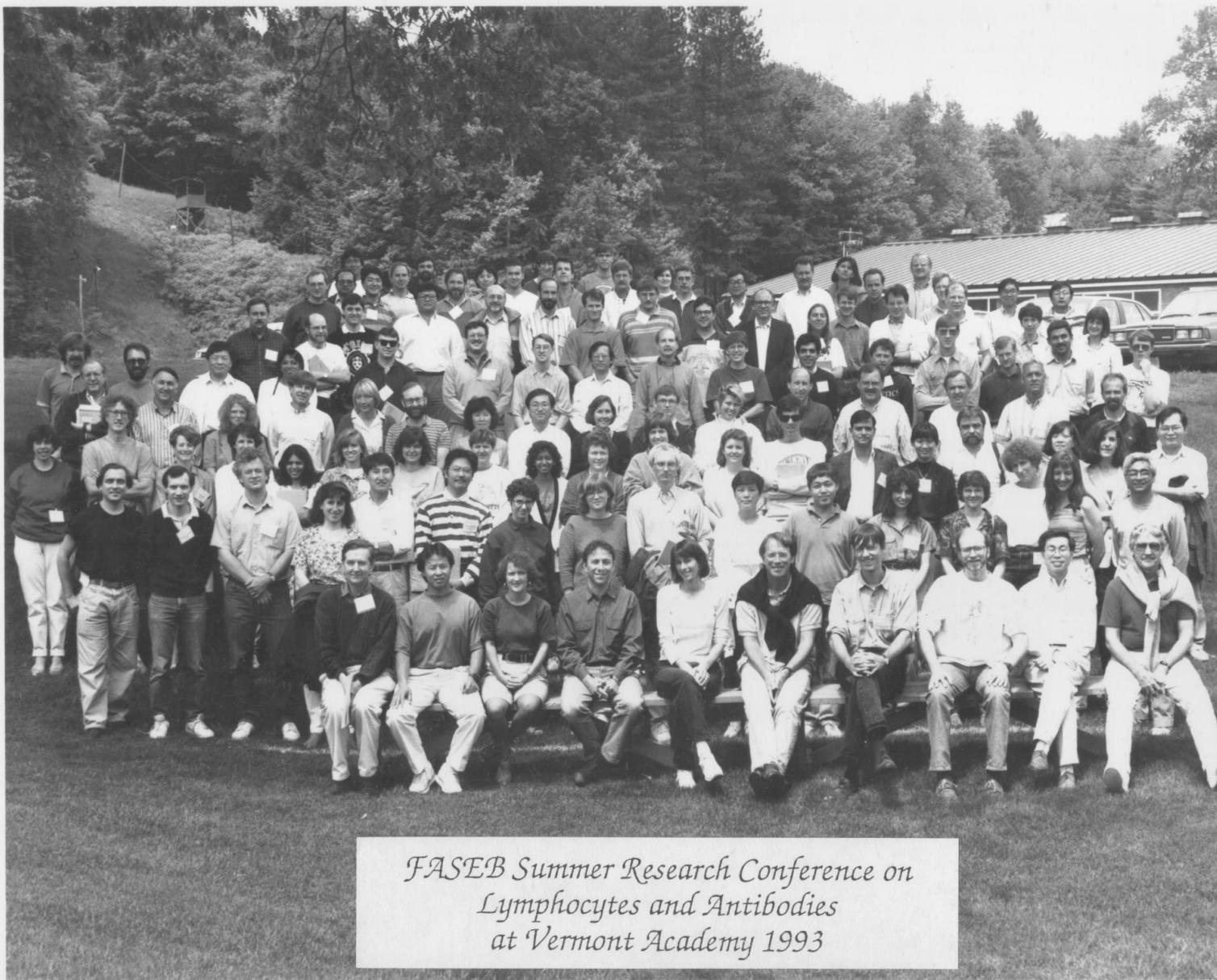
JAKs work in pairs



4 JAKs and 57 cytokines

JAK	CYTOKINE
JAK1	γ_c cytokines: (IL-2, -4, -7, -9, -15, -21); IL-13 TSLP gp130 cytokine family: IL-6, IL-11, IL-31, OSM, CNTF, LIF, CT-1, NNT-1 IFN- γ , IFN α , IFN β , IFN λ , IL-10-like cytokines (L-10, IL-19, IL-20, IL-22, IL-24, and IL-26)
JAK2	β_c cytokines: (IL-3, -5, GM-CSF) TSLP gp130 cytokine family: (IL-6, IL-11, IL-31, OSM, CNTF, LIF, CT-1, NNT-1) Leptin, GH, Prolactin, EPO, TPO, IFN γ , IL-13 IL-12, IL-23
JAK3	γ_c cytokines: IL-2, -4, -7, -9, -15, -21
TYK2	IFN α , IFN β , IFN λ , <u>gp 130 cytokines *</u> IL-10-like cytokines (L-10, IL-19, IL-20, IL-22, IL-24, and IL-26), IL-12 IL-13 IL-23, IL-27

O'Shea JJ and Gadina M. Nature Reviews Rheumatology 2019
 Gadina et al. Rheumatology 2019
 Gadina et al. J Leukoc Biol. 2018
 Schwartz et al. Nat Rev Drug Discov. 2017



*FASEB Summer Research Conference on
Lymphocytes and Antibodies
at Vermont Academy 1993*

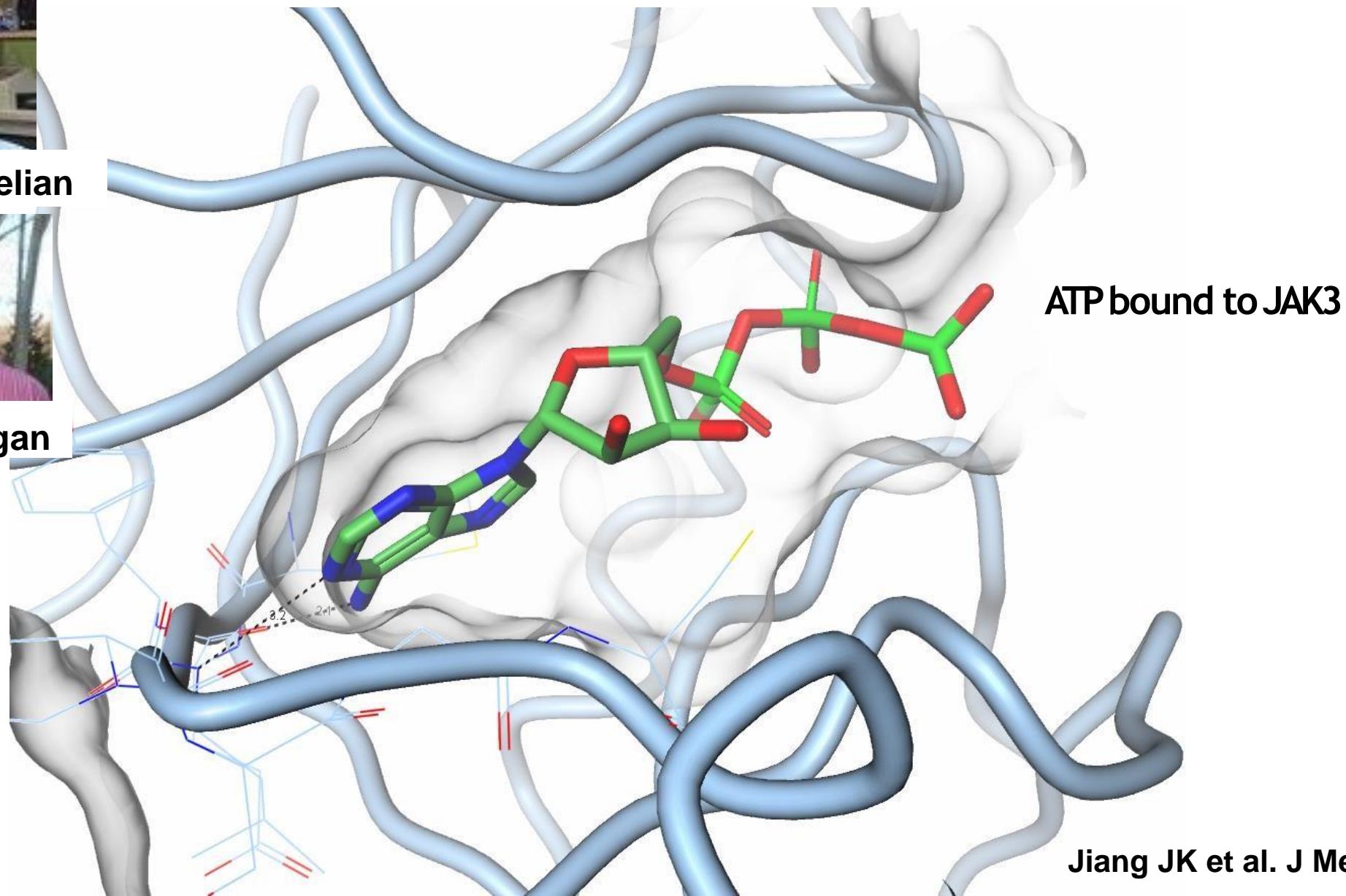
Tofacitinib: ATP Competitive Inhibitor



Paul Changelian

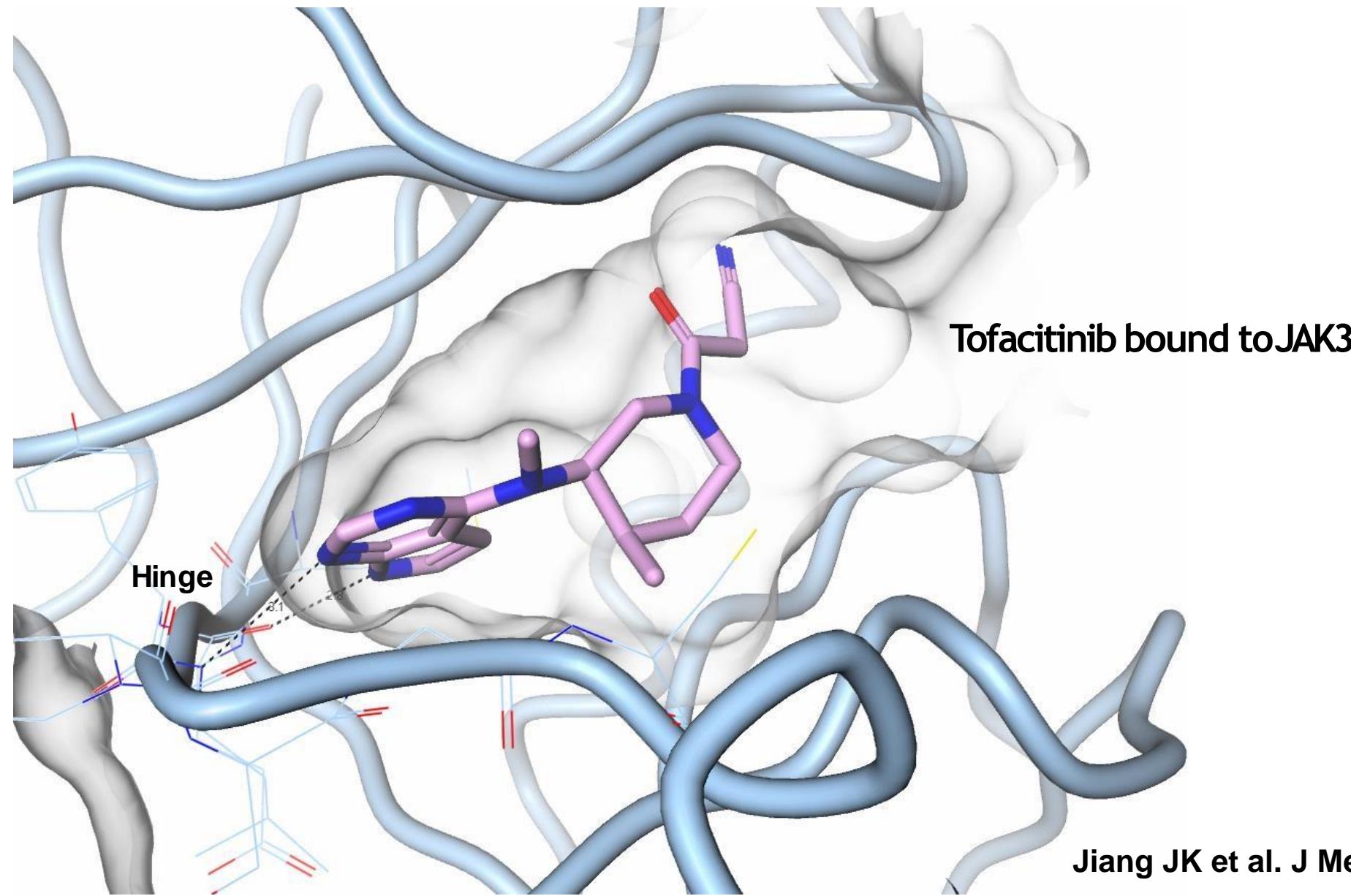


Mark Flanagan



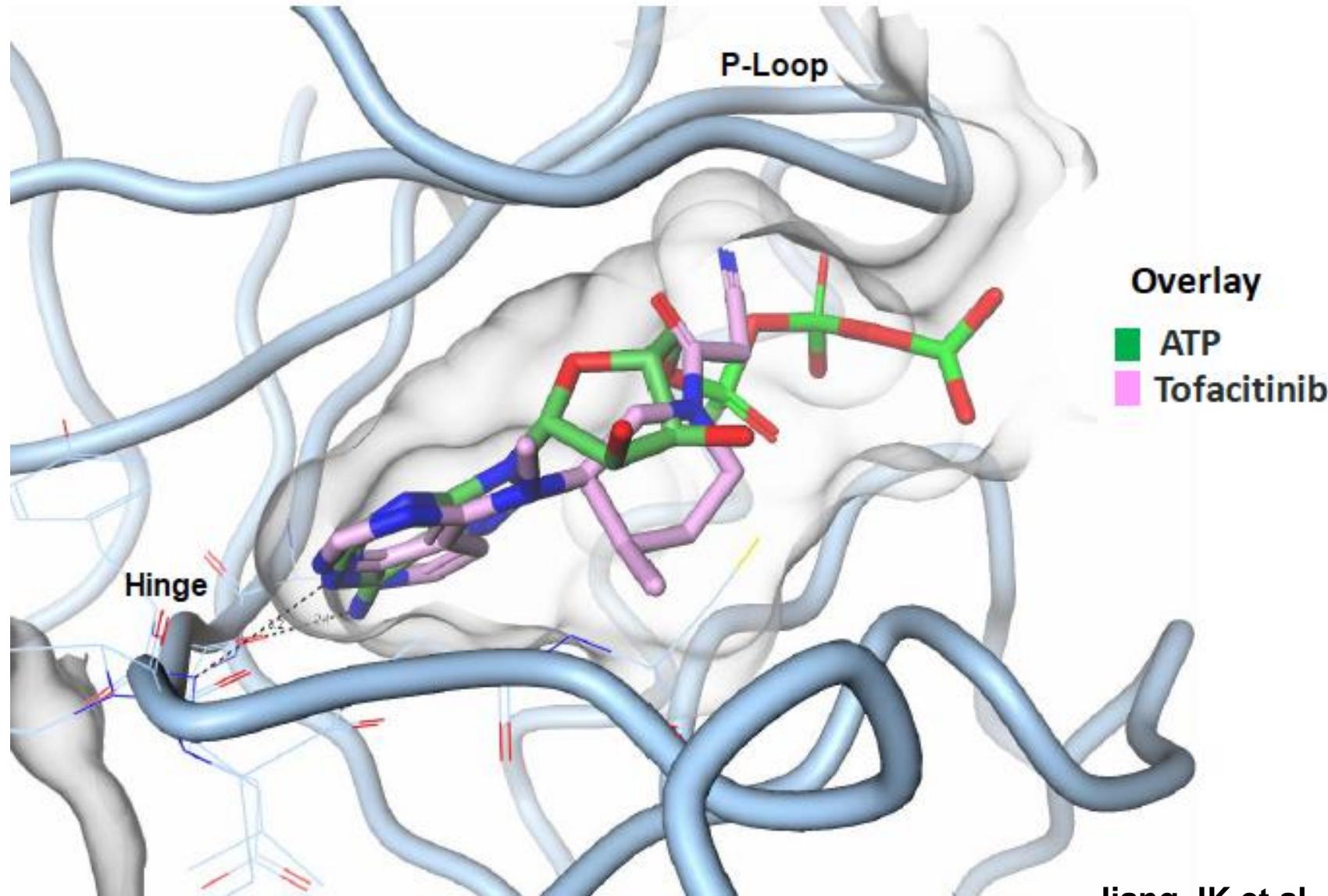
Jiang JK et al. J Med Chem. 2008

Tofacitinib: ATP Competitive Inhibitor



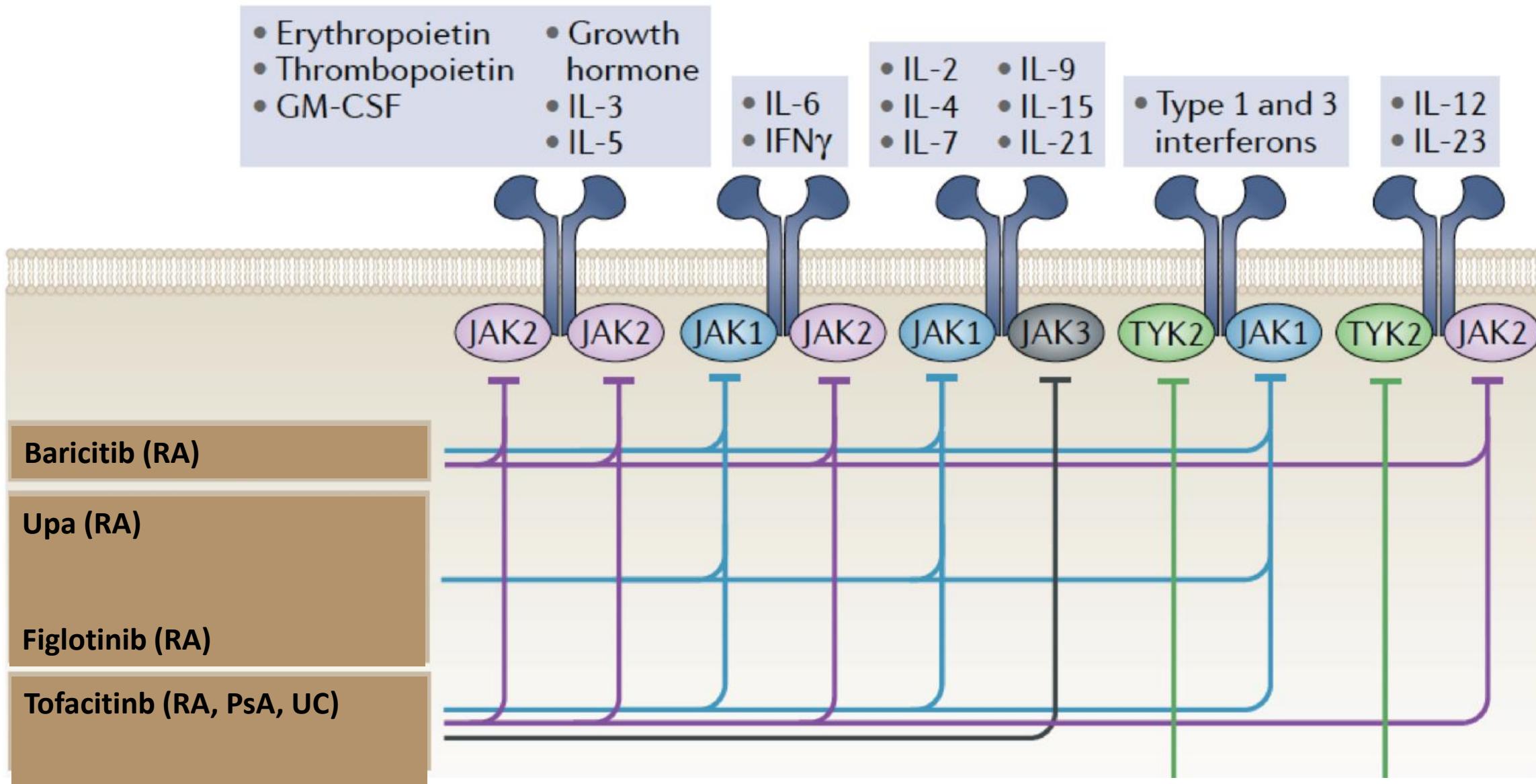
Jiang JK et al. J Med Chem. 2008

Tofacitinib: ATP Competitive Inhibitor

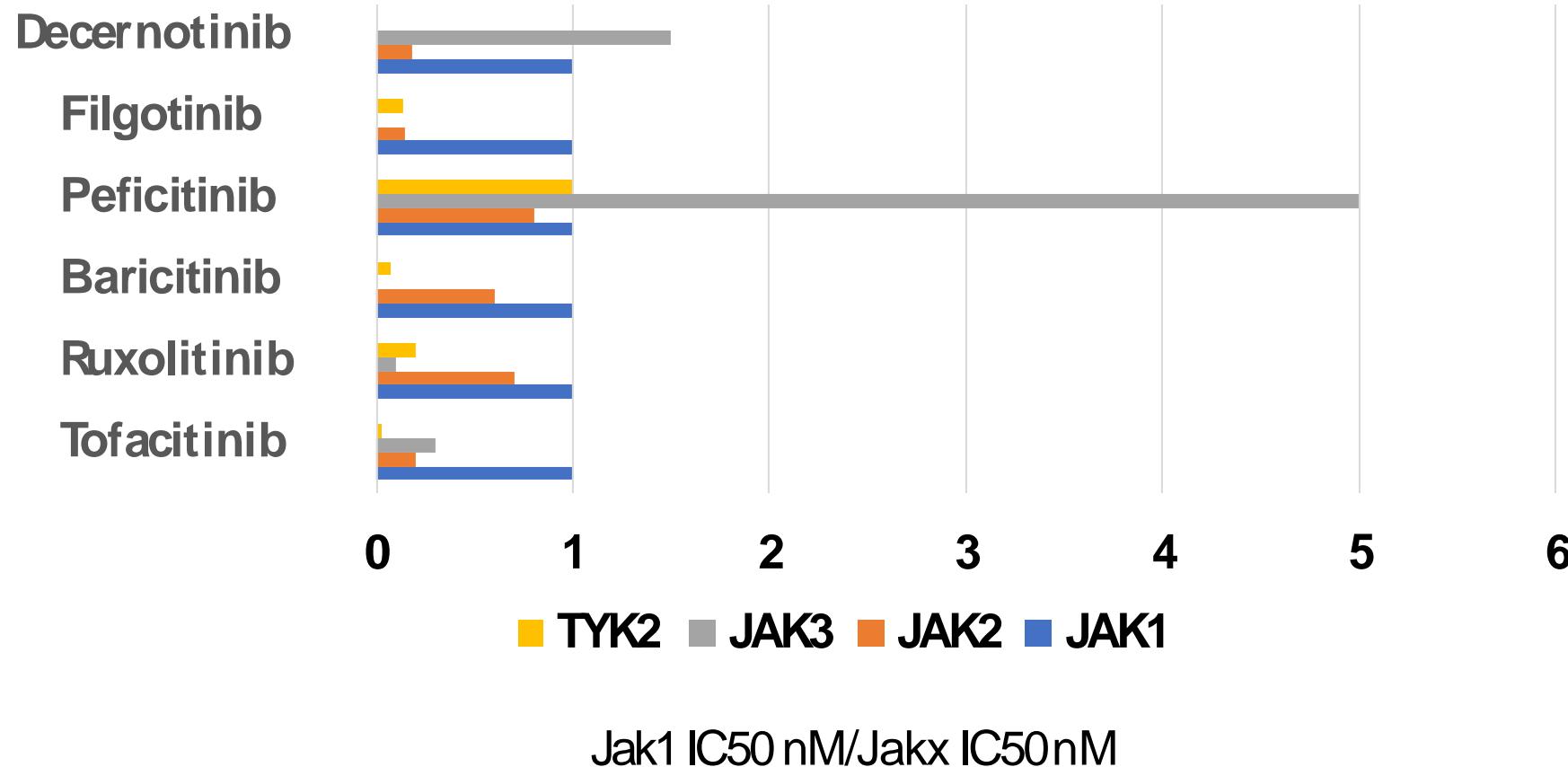


Jiang JK et al. J Med Chem. 2008

Jakinibs



Selectivity – in vitro kinase assays



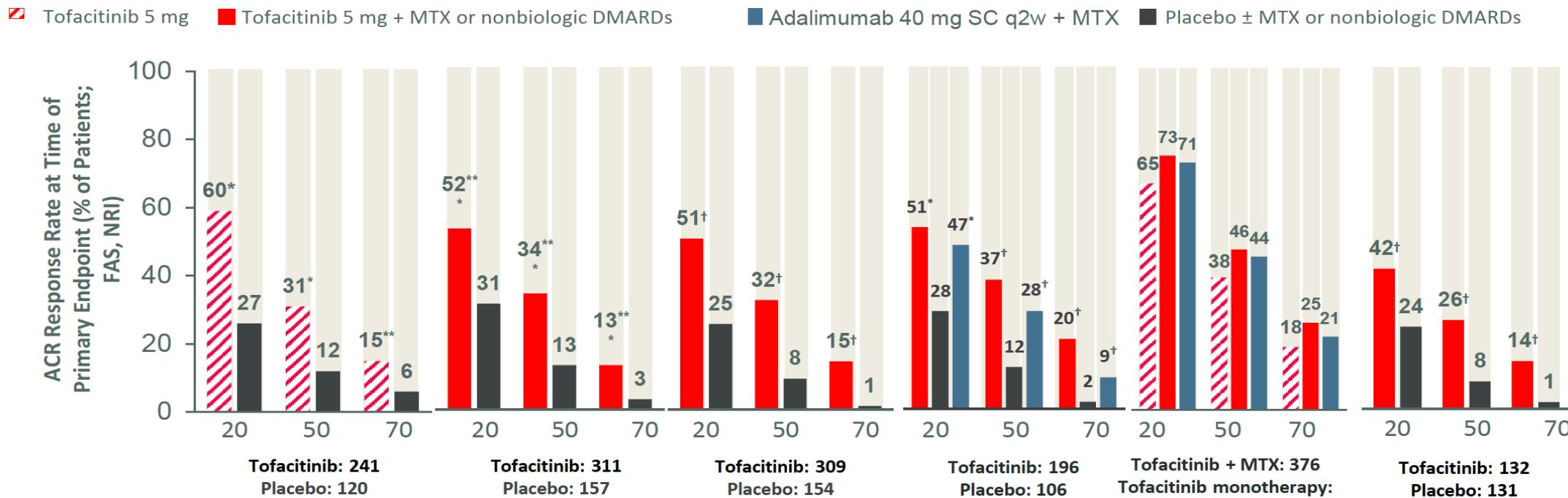
Tofacitinib

- Jak 1, Jak 3, Jak 2 inhibitor
- Approved for RA, PsA, UC
- Dose for **RA , PsA** 5mg BID
- Dose for **UC** 10mg bid for 8 weeks, taper if possible

SmPC Xeljanz 9/2020

- >80,000 pt-yrs experience
Kivitz et al Semin Arthritis Rheum 2017

ACR response rates across tofacitinib Phase 3/4 studies

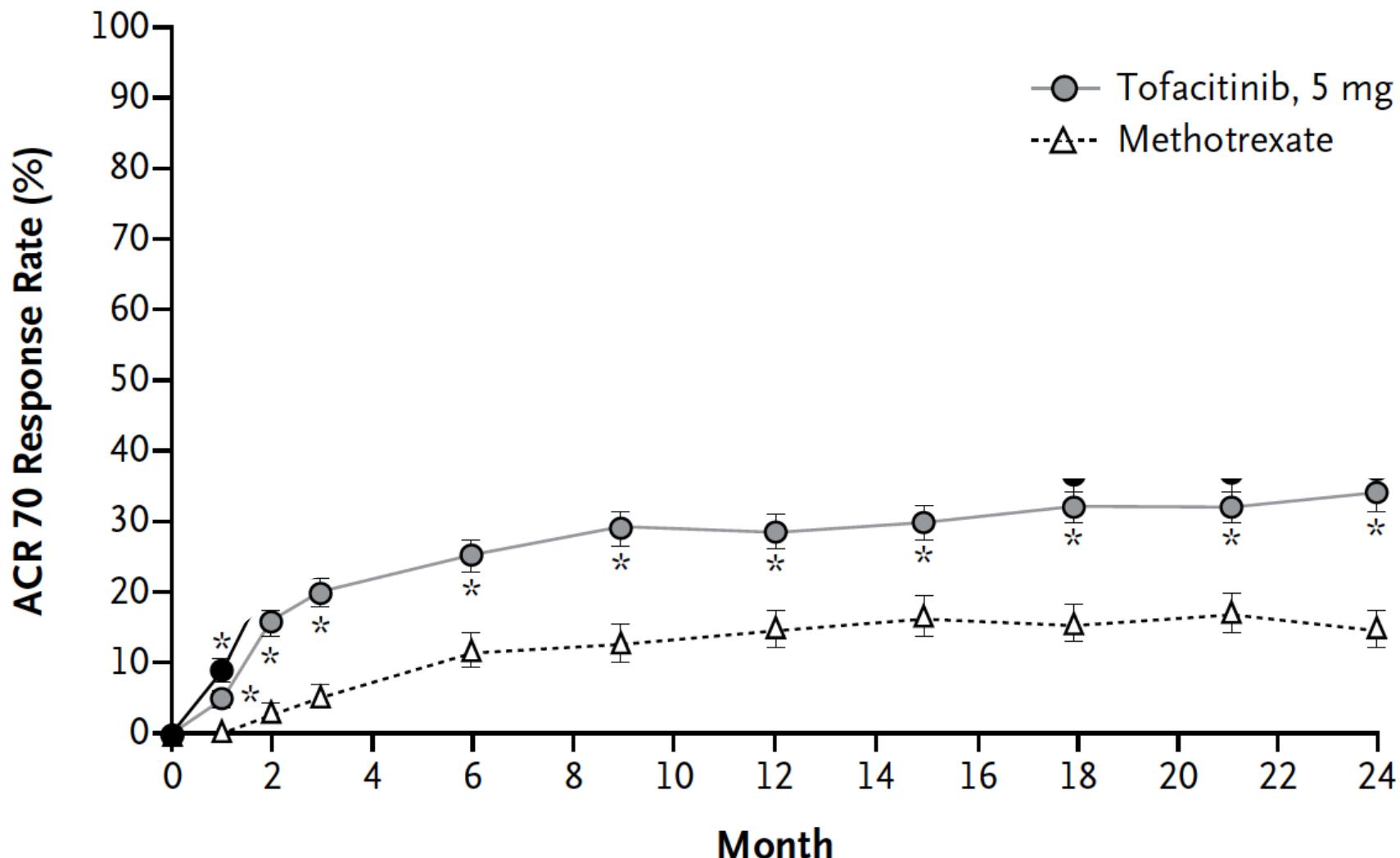


	Solo ¹ (N=610)	Sync ² (N=792)	Scan ³ (N=797)	Standard ⁴ (N=717)	Strategy ^{5§} (N=1152)	Step ⁶ (N=399)
Patient type	DMARD-IR	DMARD-IR	MTX-IR	MTX-IR	MTX-IR	TNFi-IR
Background treatment	None	nonbiologic DMARDs	MTX	MTX	MTX / none	MTX
Feature	Monotherapy	Background DMARDs	X-ray	Active control (adalimumab)	Tofa+MTX vs ADA+MTX Tofa vs Tofa+MTX Tofa vs ADA+MTX	TNFi failure
Time of primary endpoint (mo)	3	6	6	6	6	3

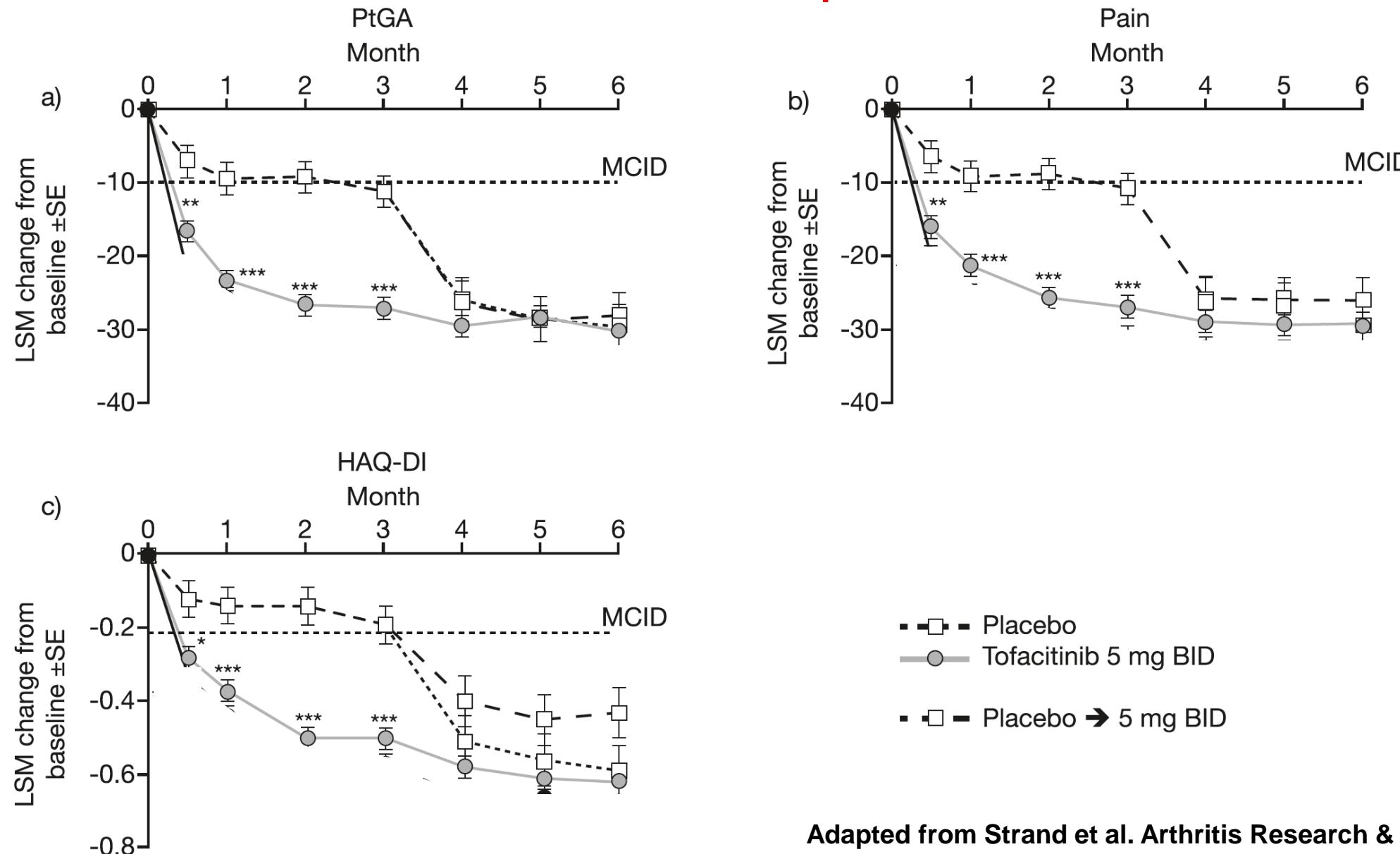
1. Fleischmann et al. N Engl J Med 2012 2. Kremer et al. Ann Intern Med 2013 3. van der Heijde et al. Arth Rheum 2013 4. van Vollenhoven et al. N Engl J Med 2012

5. Fleischmann R et al. Lancet 2017 6. Burmester et al. Lancet 2013

Monotherapy with tofacitinib, as compared with methotrexate monotherapy in naïve RA patients (ORAL Start)

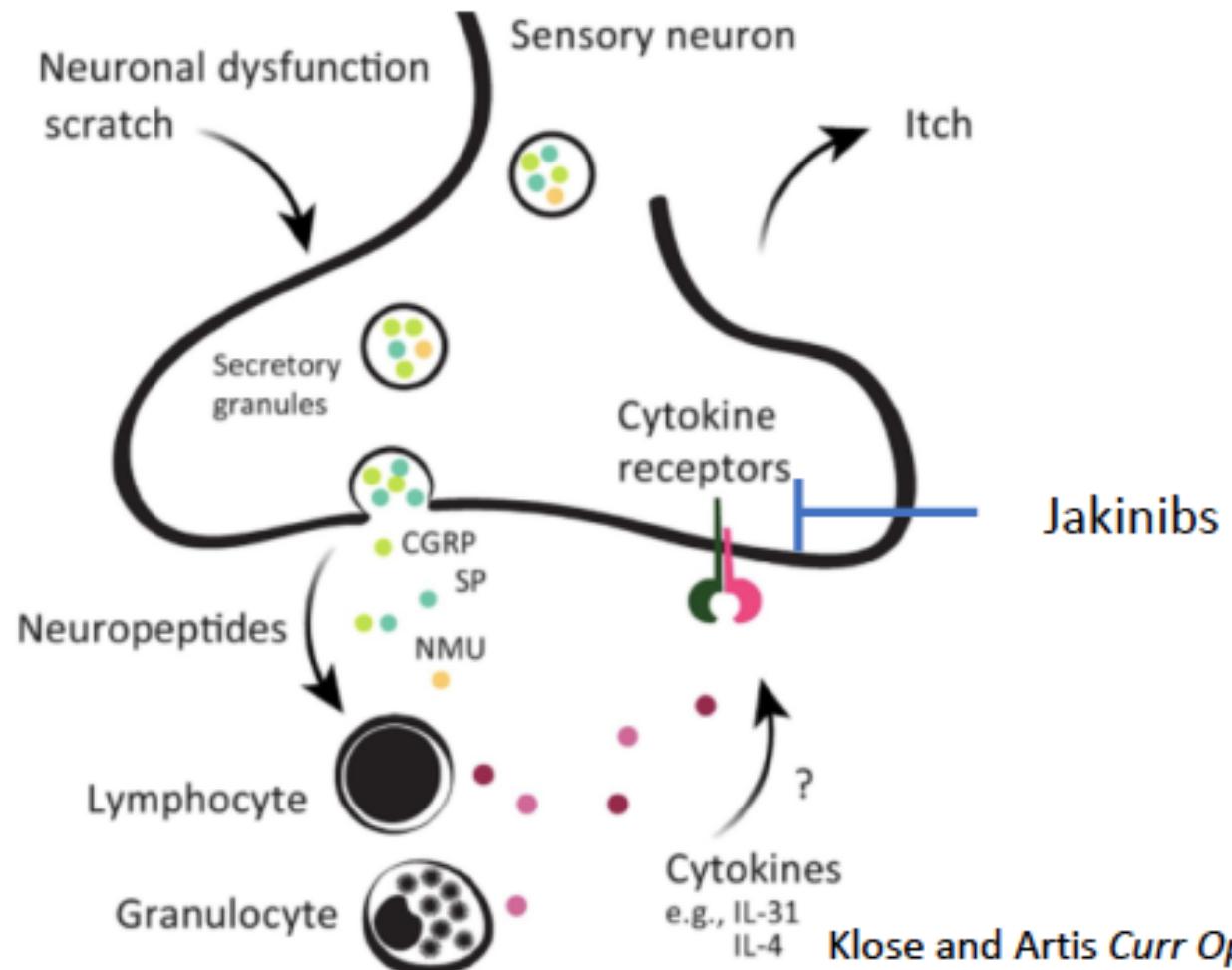


**Rapid Effects of tofacitinib monotherapy on PROs
in a phase 3 RCT of RA pts with inadequate responses to DMARDs**
ORAL Solo – 611 pts



Adapted from Strand et al. Arthritis Research & Therapy 2015

Jakinibs and Cytokines in Pain and Itch: Neural Immune Crosstalk



Klose and Artis *Curr Op Immunol* 2019

Viega-Fernandes and Artis *Science* 2018

Trier and Kim, *Curr Op Immunol* 2018

Mack and Kim *Trends Immunol* 2018

Oetjen LK et al, *Cell* 2017

Ανεπιθύμητες ενέργειες Jakinibs

- Infection – equivalent to biologics, including serious and opportunistic infections
- Including: TB, nontuberculous mycobacteria, *Candida*, *Pneumocystis jirovecii*, *Cryptococcus*, toxoplasmosis
- Viral infection
 - Herpes zoster – more common than biologics
 - 1.5 to 2 fold higher; more common in Asian populations
 - Related to IFN α antagonism?
 - VZV reactivation also seen with Sifalimumab in SLE
 - Small number of CMV infections

Winthrop KL et al Nat Rev Rheum 2017

Kivotz A. et al Sem Arthr Rheum 2018

Ανεπιθύμητες ενέργειες Jakinibs

- Cytopenias: anemia, leukopenia, neutropenia
 - Jak2 inhibition? IL-6?
- DVT – Drug vs Class effect? Mechanism?
 - Yun et al Abstr 824 ACR 2018
 - Desai et al Abstr L09, ACR 2018
- Increased lipids
 - Significance for CV disease? HDL may also be increased
 - Taylor et al ARD 2018
- GI perforation
 - Efficacious in IBD (?)
- Increased transaminases
- Increased CPK
- Increased creatinine
 - Decreased creatinine clearance, no long term renal impairment
- Malignancy – no evidence of increased risk at this time

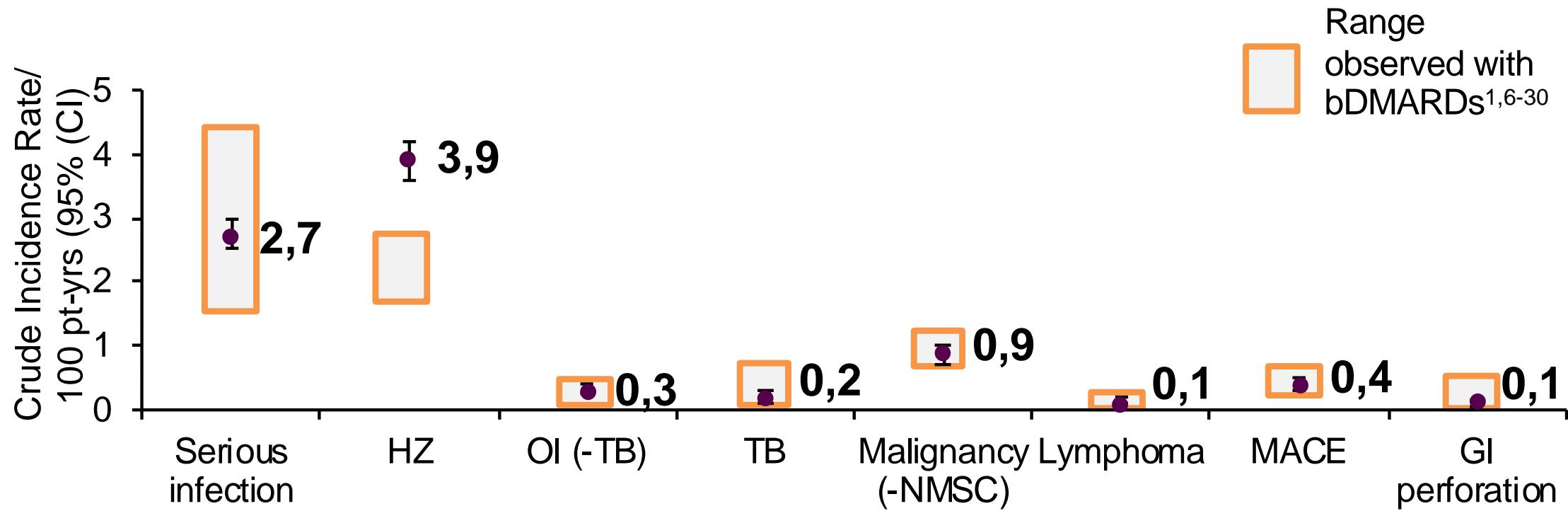
Winthrop KL et al Nat Rev Rheum 2017

Kivitz A. et al Sem Arthr Rheum 2018

Incidence rate for AEs of special interest with tofacitinib are comparable to bDMARDs, except for HZ

AEs of special interest

(Overall tofacitinib population—phase 123 LTE)^{1,2}



Incidence rate for AEs of special interest with tofacitinib are comparable to bDMARDs, except for HZ



Incidence rate is stable over time¹⁻⁴



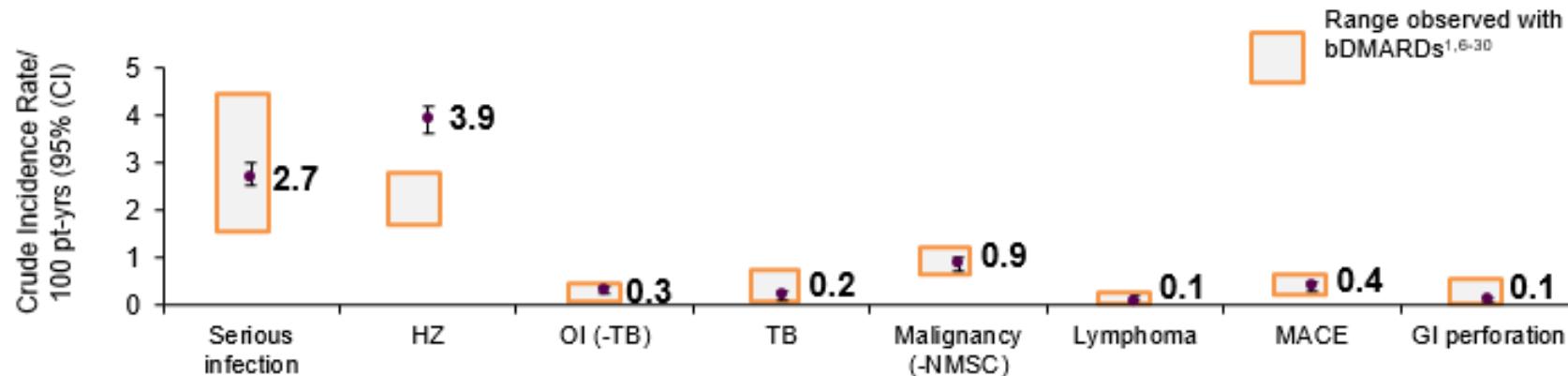
HZ events were medically manageable⁵



Incidence rate is similar to bDMARDs except for HZ^{1,6-30}

AEs of special interest

(Overall tofacitinib population—phase 123 LTE)^{1,2}



AE, adverse event; bDMARD, biologic disease-modifying antirheumatic drug; CI, confidence intervals; GI, gastrointestinal; HZ, herpes zoster; LTE, long-term extension; MACE, major adverse cardiac event; NMSC, non-melanoma skin cancer; OI, opportunistic infections; RA, rheumatoid arthritis; RCT, randomized controlled trial; TB, tuberculosis.

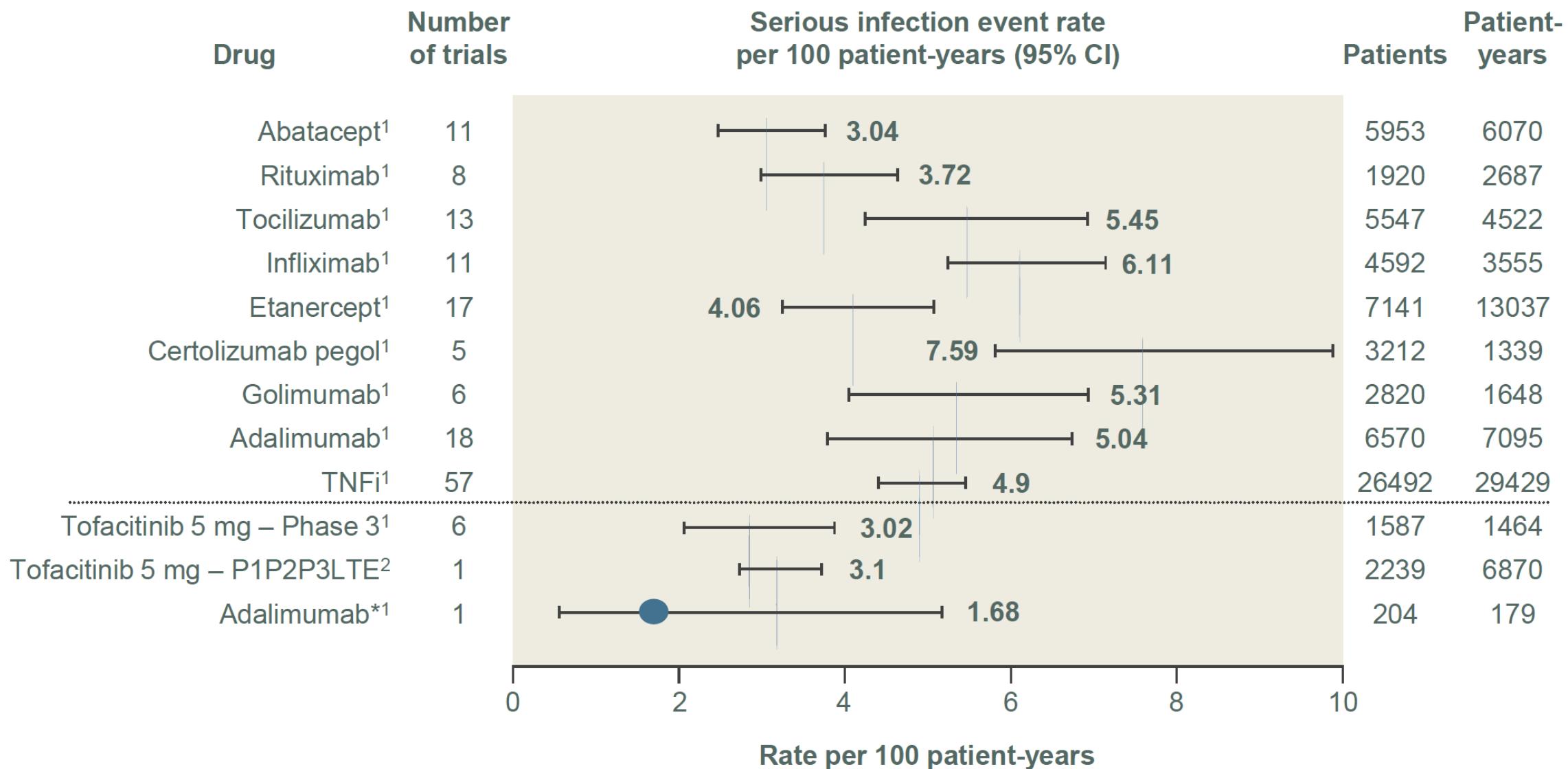
Vaccination recommendation^{31,32}

Administer live zoster vaccine prior to treatment with tofacitinib, preferably 4 weeks before start

The approved dose of tofacitinib is 5 mg twice daily

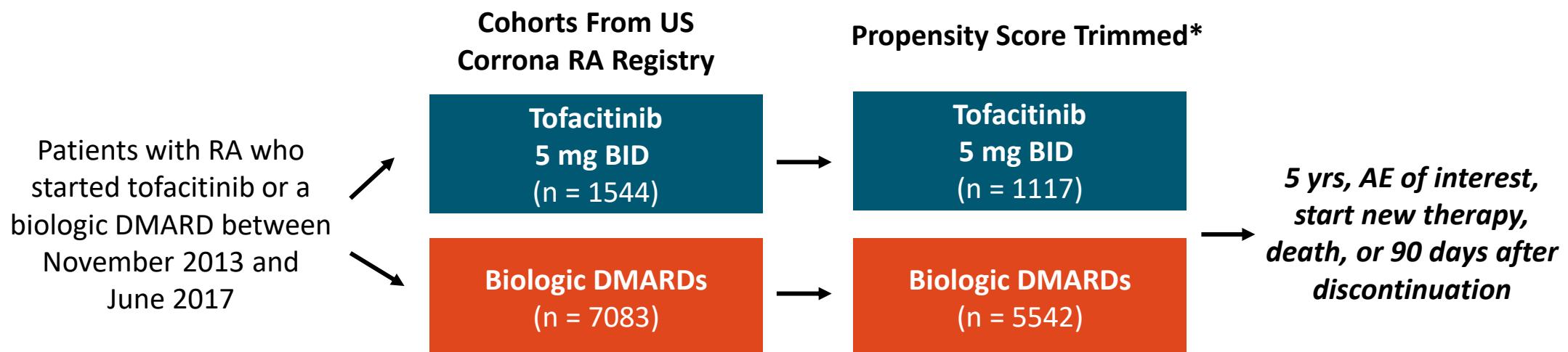
- Cohen SB et al. Ann Rheum Dis. 2017;76(7):1253-1262. Supplement to: Cohen SB et al. Ann Rheum Dis. 2017;76(7):1253-1262. Winthrop KL et al. Ann Rheum Dis. 2016;75(6):1133-1138. Mariette X et al. Arthritis Care Res (Hoboken). 2017 Sep 21. doi: 10.1002/acr.23421. [Epub ahead of print]. Winthrop KL et al. Arthritis Rheumatol. 2017. DOI: 10.1002/art.40189 Strand V et al. Arthritis Res Ther. 2015;17:362. Vieira MC et al. Clin Ther. 2016;38(12):2628-2641. Yamaoka K. Drug Saf. 2016;39(9):823-840. Curtis JR et al. Ann Rheum Dis. 2016;75(10):1843-1847. Weinblatt ME et al. J Rheumatol. 2013;40(6):787-797. Keystone EC et al. J Rheumatol. 2013;40(9):1487-1497. Bykerk VP et al. Ann Rheum Dis. 2015;74(1):96-103. Burmester GR et al. Ann Rheum Dis. 2013;72(4):517-524. Kay J et al. J Rheumatol. 2016;43(12):2120-2130. Schiff MH et al. Arthritis Res Ther. 2011;13(5):R141. Gomez-Reino JJ et al. Presented at: EULAR Annual Congress of Rheumatology; June 14-17, 2017; Madrid, Spain. Poster THU0196. Maneiro JR et al. Semin Arthritis Rheum. 2017. In press. [http://www.seminarthritisrheumatism.com/article/S0049-0172\(16\)30306-7/fulltext](http://www.seminarthritisrheumatism.com/article/S0049-0172(16)30306-7/fulltext). Accessed May 17, 2017. Gottlieb AB et al. J Drugs Dermatol. 2011;10(3):289-300. Centocor. Remicade® (infliximab). Presentation to the Food and Drug Administration Arthritis Advisory Committee. URL: <https://www.fda.gov/ohrms/dockets/ac/03/slides/3930s1.htm>. Accessed October 10, 2014. Charles-Schoeman C et al. Semin Arthritis Rheum. 2016;46(3):261-271. Alten R et al. Arthritis Rheumatol. 2014;66(8):1987-1997. van Vollenbroek RF et al. J Rheumatol. 2015;42(10):1761-1766. Wolfe F et al. Arthritis Rheum. 2004;50(2):372-379.
- Brassard P et al. Clin Infect Dis. 2006;43(6):717-722. Asling J et al. Arthritis Rheum. 2005;52(7):1986-1992. Dixon WG et al. Arthritis Rheum. 2006;54(8):2368-2376. Seong SS et al. J Rheumatol. 2007;34(4):706-711. Jung SM et al. Int J Rheum Dis. 2015;18(3):323-330. Ke WM et al. Int J Tuberc Lung Dis. 2013;17(12):1590-1595. Chiu YM et al. Int J Rheum Dis. 2014;17(suppl 3):9-19. Singh JA et al. Arthritis Care Res (Hoboken). 2016;68(1):1-25. Singh JA et al. Arthritis Care Res (Hoboken). 2016;68(1):1-252. Harpaz R et al. MMWR Morb Mortal Wkly Rep. 2008;57(RR-5):1-30; quiz CE2-4.

Systematic review and meta-analysis of serious infections with tofacitinib and bDMARDs in RA clinical trials



Corrona: Real-World Safety Study of Tofacitinib vs Biologic DMARDs in RA patients

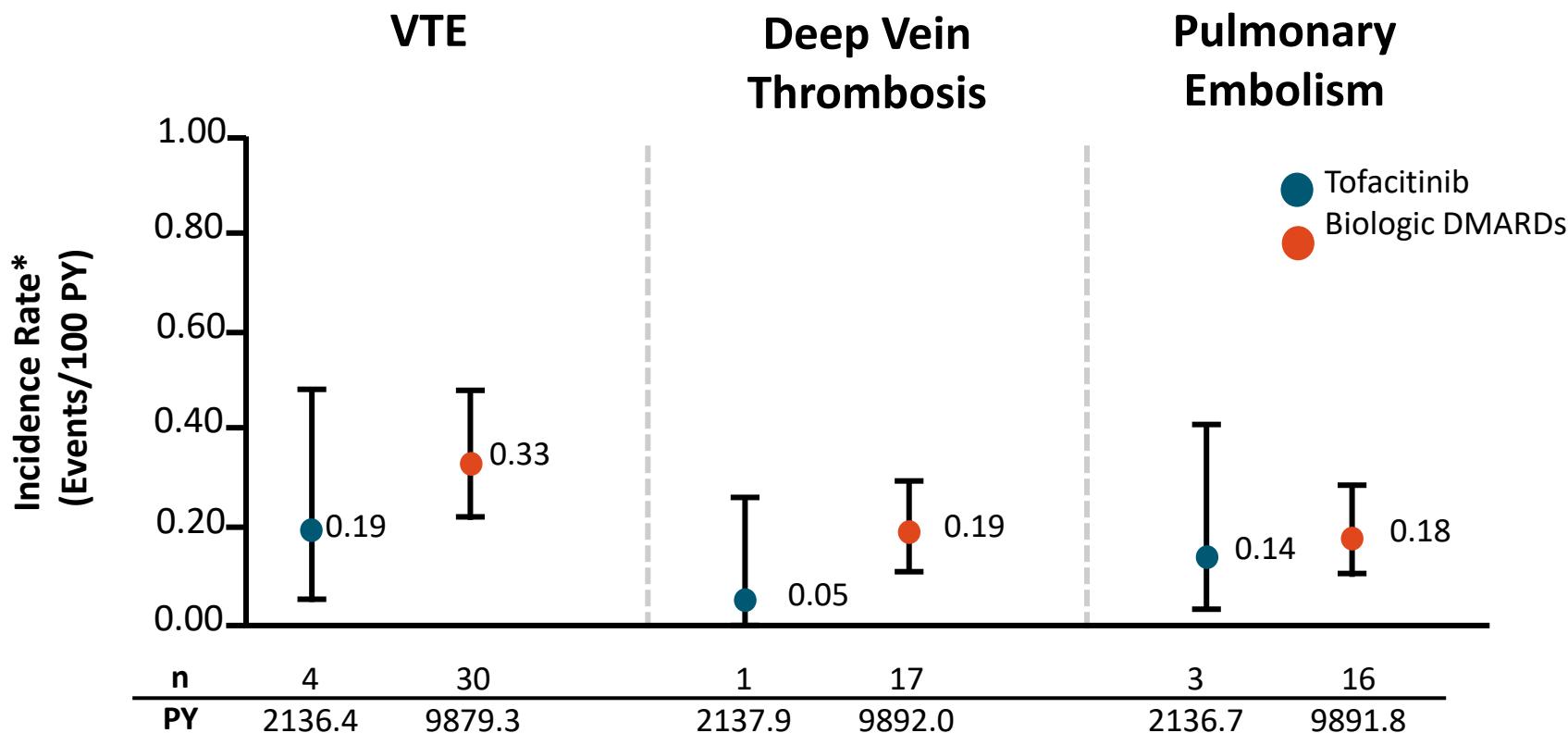
- Prospective, observational, 5-yr safety study using **propensity score methods**



Kremer. EULAR 2019. Abstr OP0028.

Kremer J, et al. Arthritis Rheumatol. 2019; 71 (suppl 10): Abstract # 2372

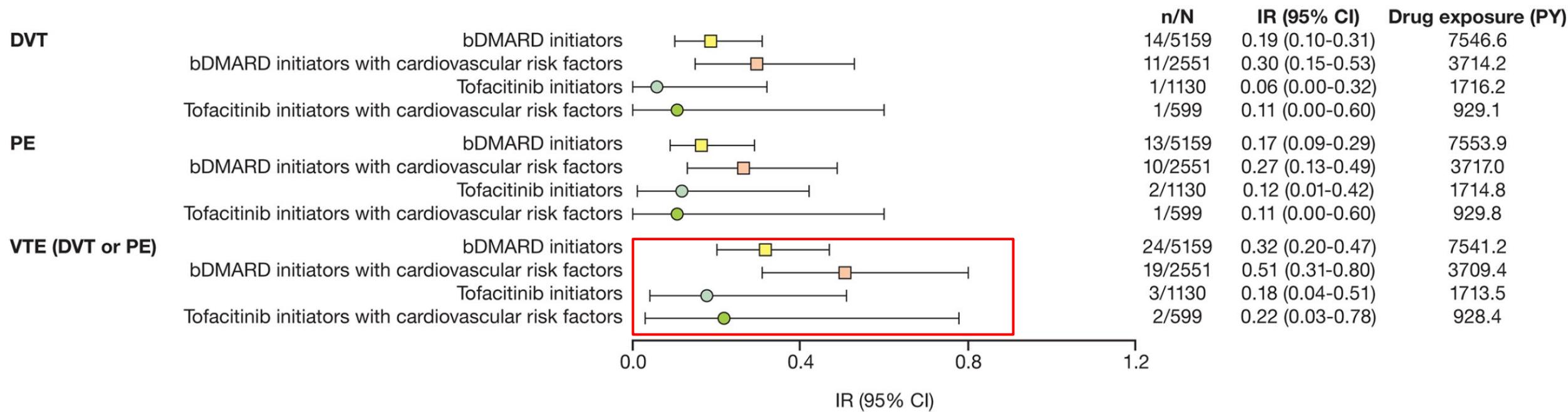
Corrona: Venous Thromboembolic Events



Kremer. EULAR 2019. Abstr OP0028.

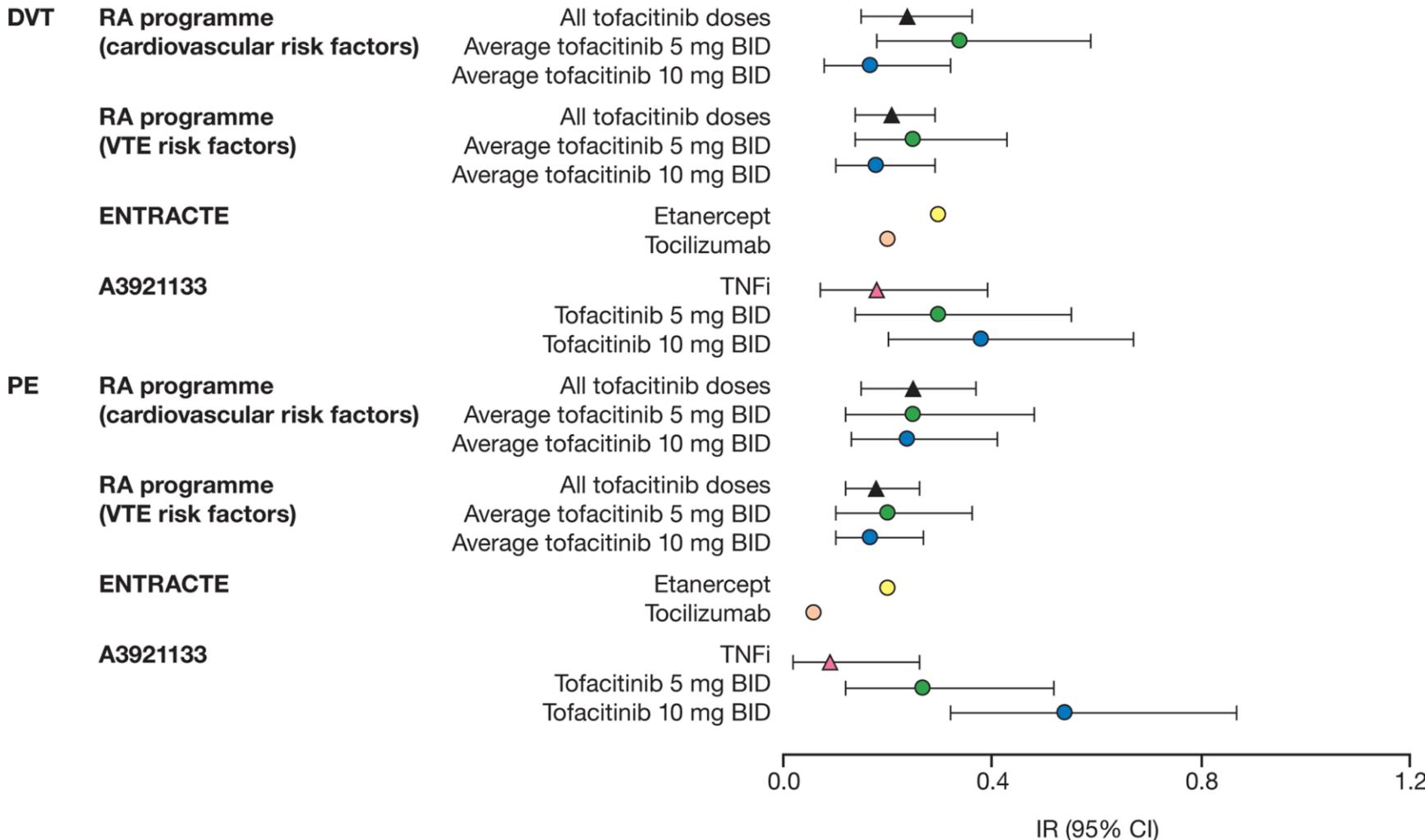
Kremer J, et al. Arthritis Rheumatol. 2019; 71 (suppl 10): Abstract # 2372

Incidence of venous and arterial thromboembolic events reported in the tofacitinib rheumatoid arthritis, Development programmes and from real-world data



IRs of DVT, PE, VTE were higher in patients with defined baseline cardiovascular CV or VTE risk factors vs those without, in both tofacitinib- and bDMARD-treated patients.

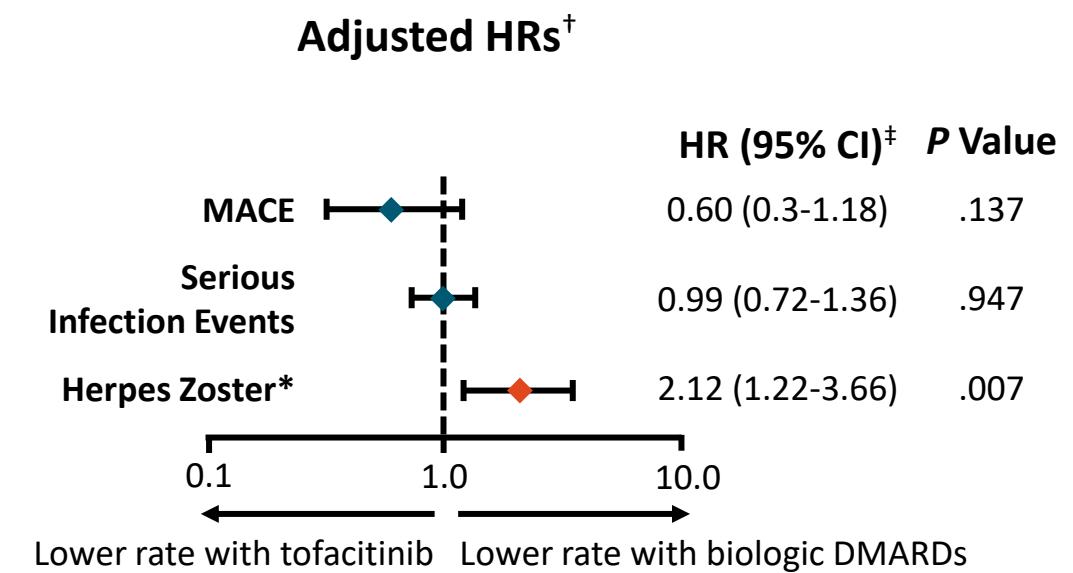
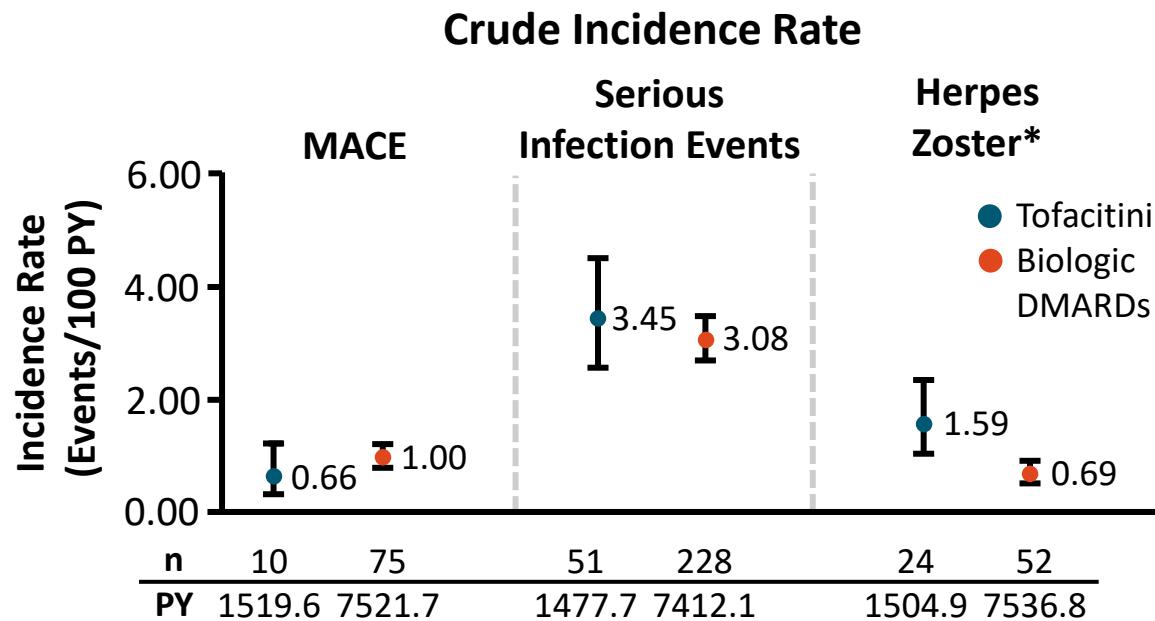
Incidence of venous and arterial thromboembolic events reported in the tofacitinib rheumatoid arthritis, Development programmes and from real-world data



ONLY 5mg BID is the approved dose of tofacitinib in RA and PsA

Mease P. et al. ARD 2020

Corrona: MACE, Serious Infection Events, Herpes Zoster

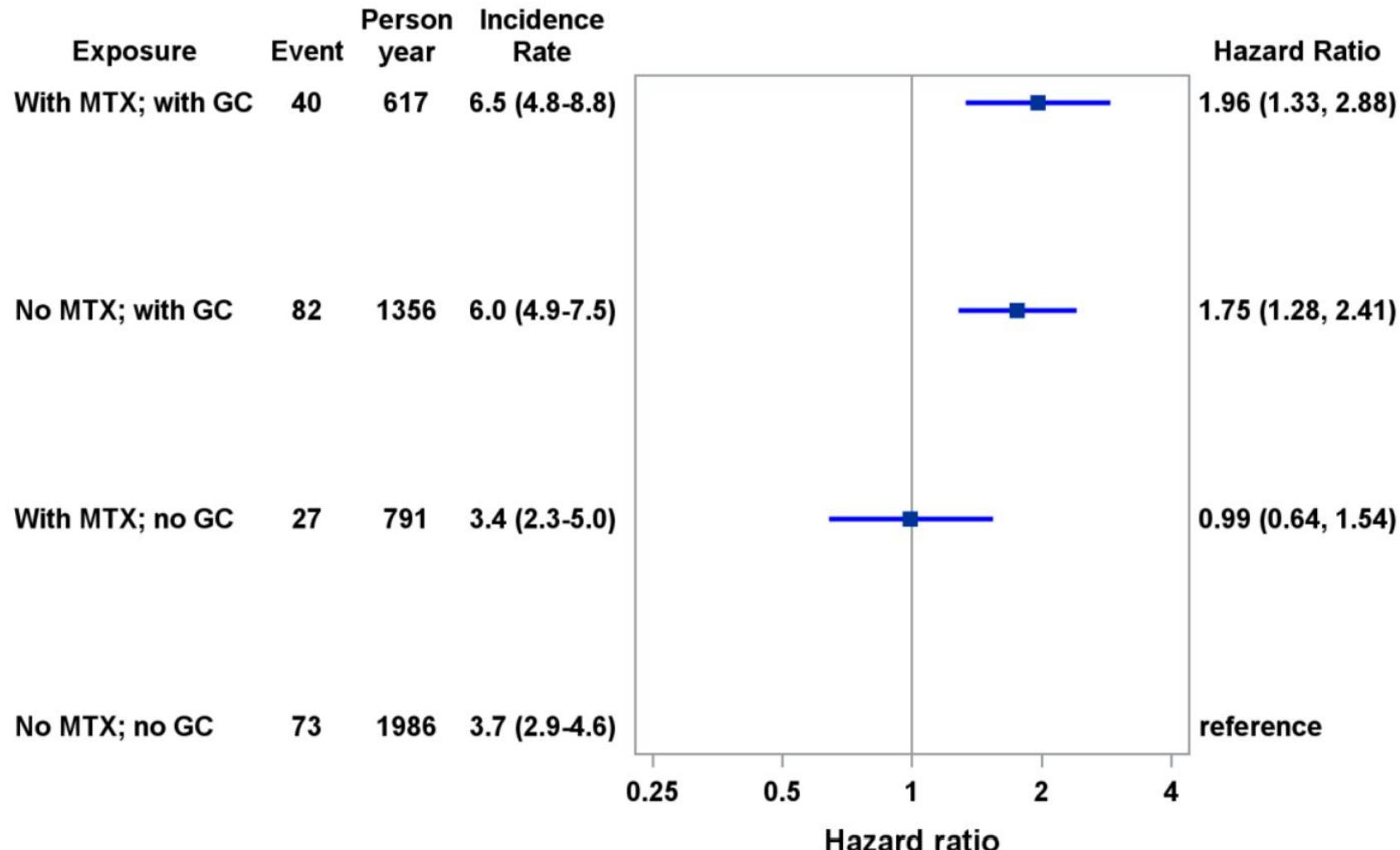


Kremer. EULAR 2019. Abstr OP0028.

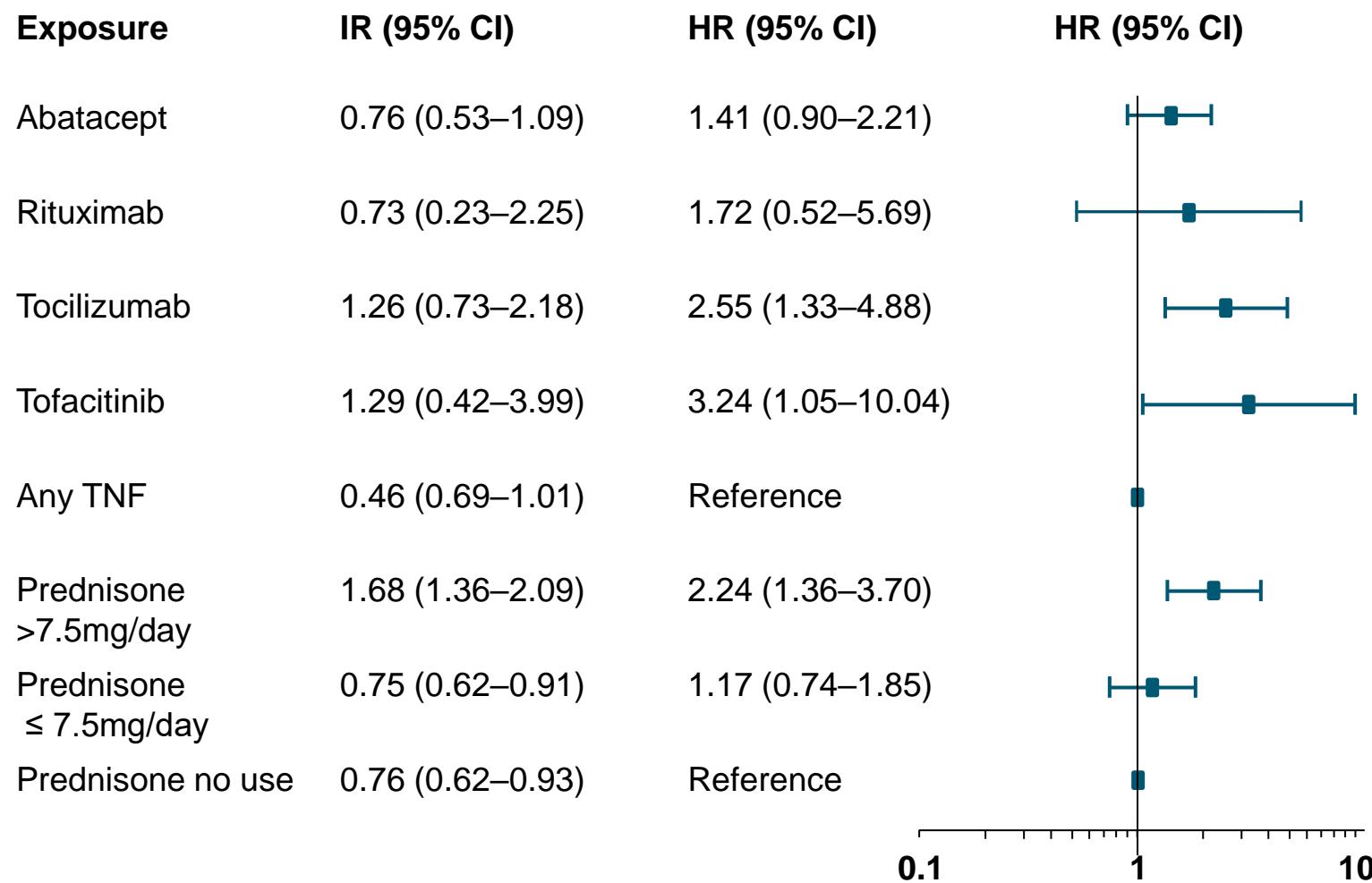
Kremer J, et al. Arthritis Rheumatol. 2019; 71 (suppl 10): Abstract # 2372

In TOF users, exposure to GC approximately doubled the HR for HZ.
No increased risk associated with MTX.

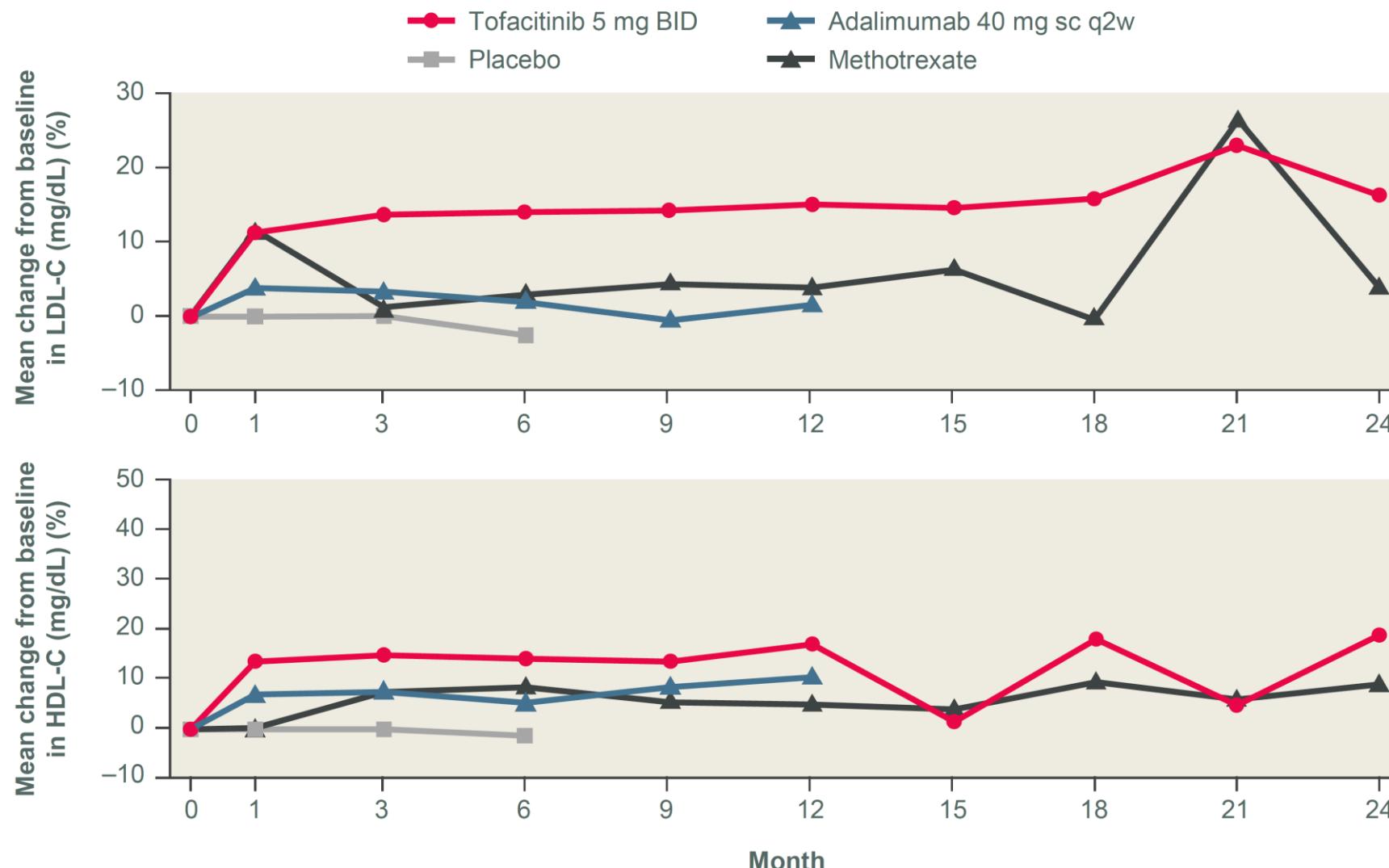
8030 pts (Medicare and MarketScan 2011-2016)



Lower tract GIP associated with RA therapies



Increases in serum lipids have been seen in the first 3 months, with stable levels thereafter.

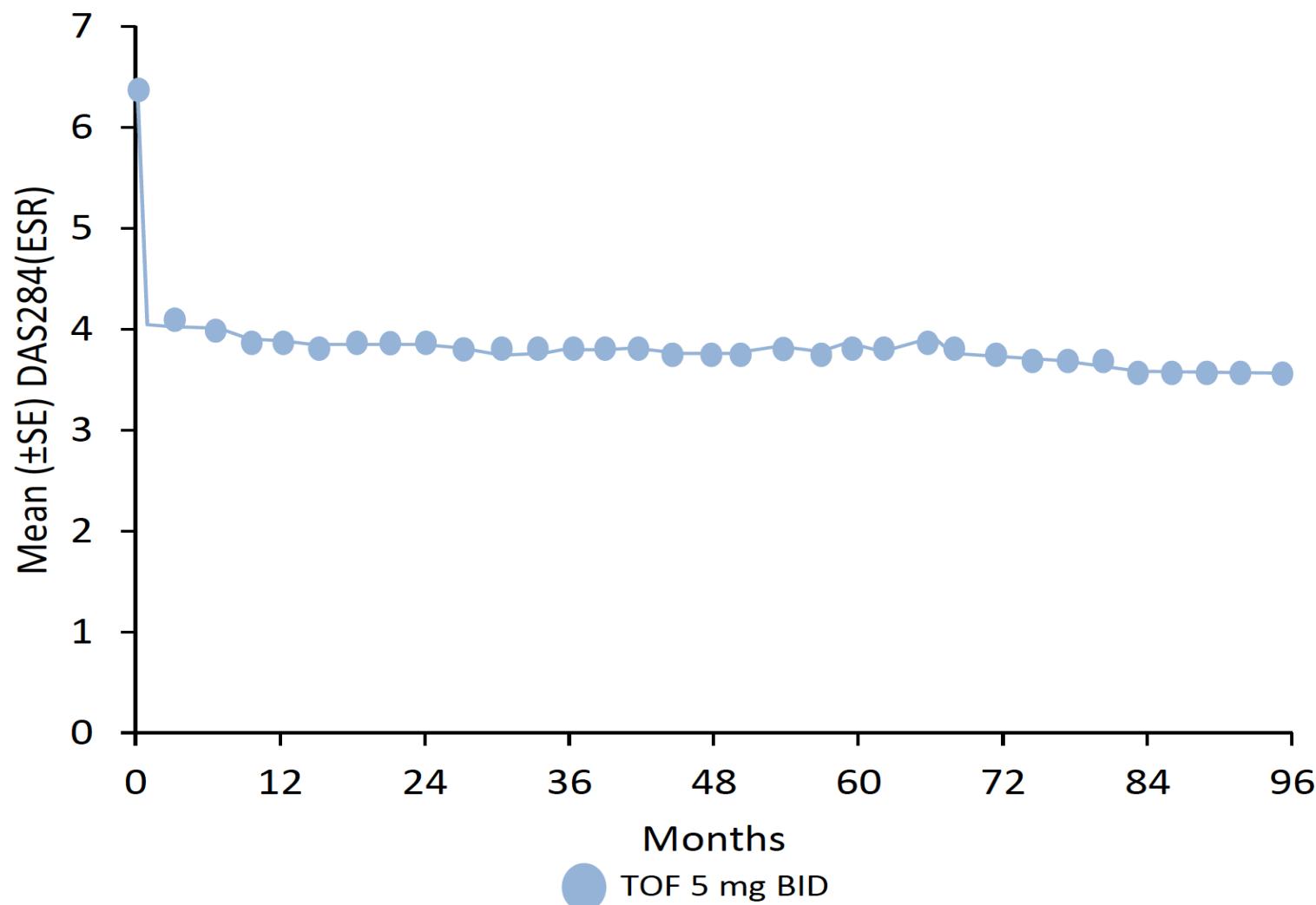


Safety and Efficacy of Tofacitinib For Up to 9.5 Years in The Treatment of Rheumatoid Arthritis: Final Results of a Global, Open-Label, Long-Term Extension Study (4.481 pts)

Wollenhaupt J, Lee EB, Curtis JR, Silverfield J, Terry K, Soma K, Mojck C, DeMasi R, Strenghold S, Kwok K, Lazariciu I, Wang L, Cohen S

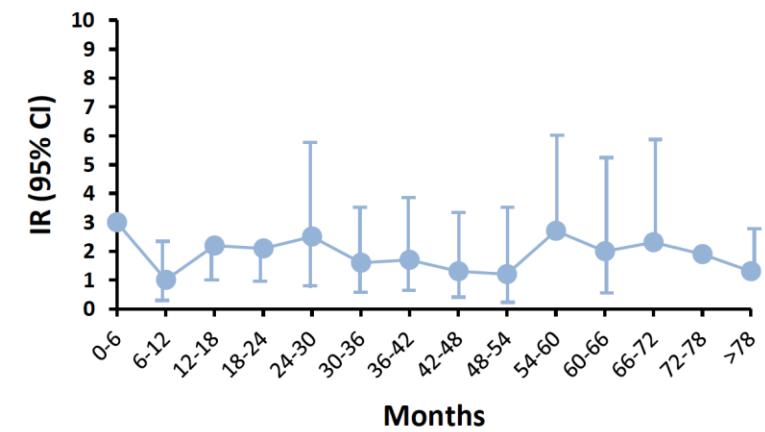
Arthritis Res Ther. 2019 Apr 5;21(1):89.

**Mean DAS28-4(ESR) decreased at Month 1 but remained consistent over time
Remission was observed in 24.7% of patients with all TOF at Month 96**

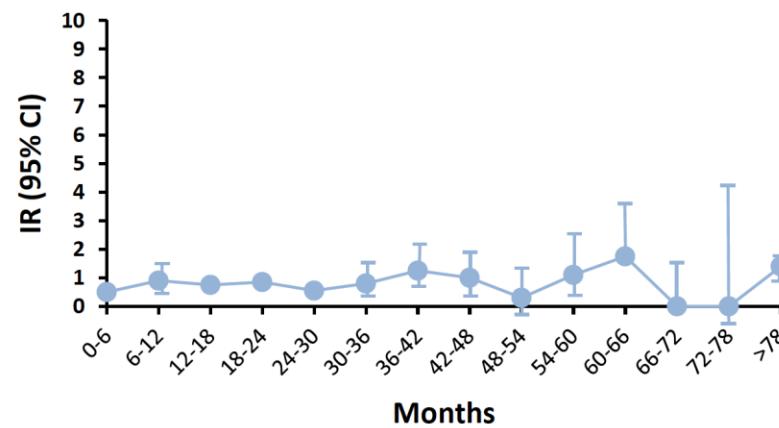


Serious infections, malignancies excluding NMSC and herpes zoster over time have showed to remain generally stable.

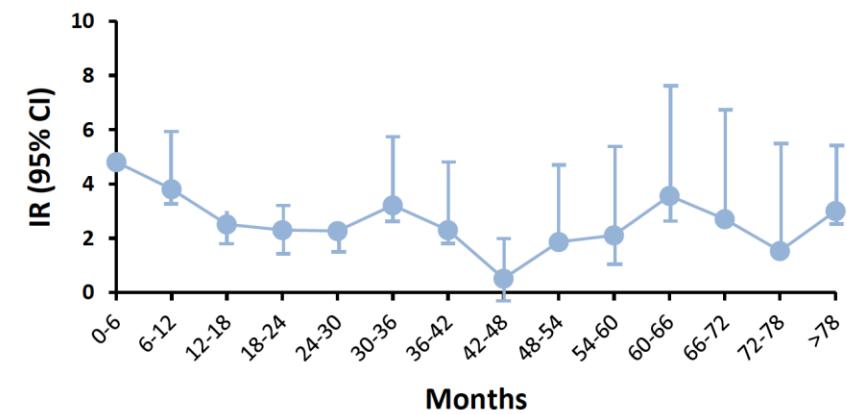
Serious Infection



Malignancies (Excluding NMSC)



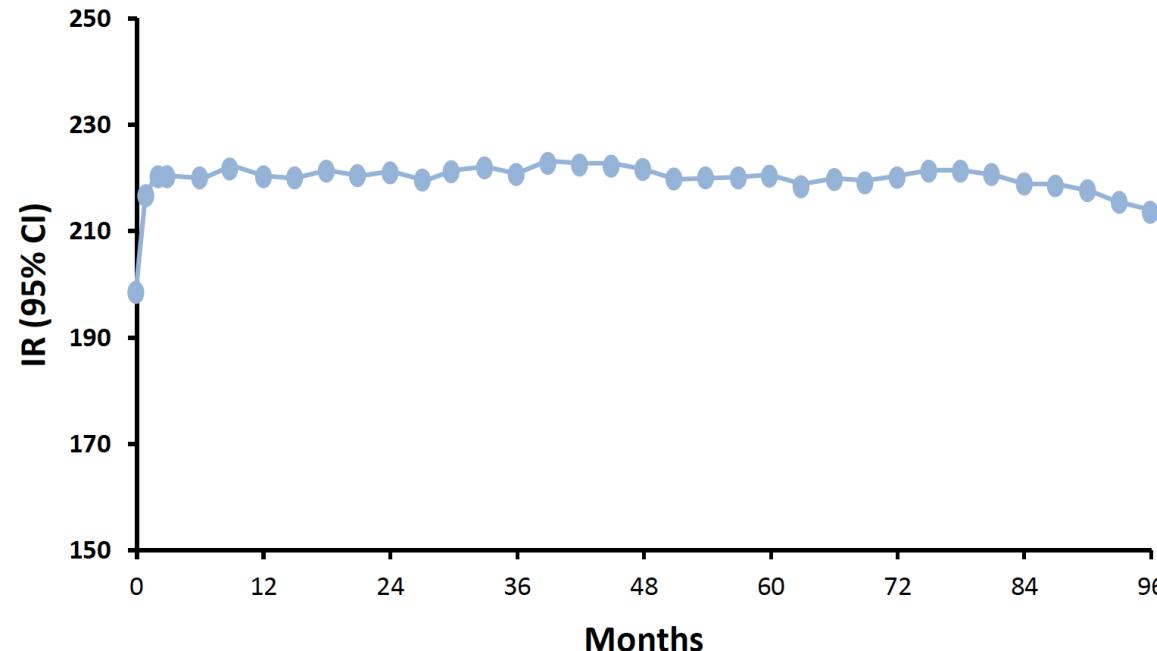
Herpes Zoster



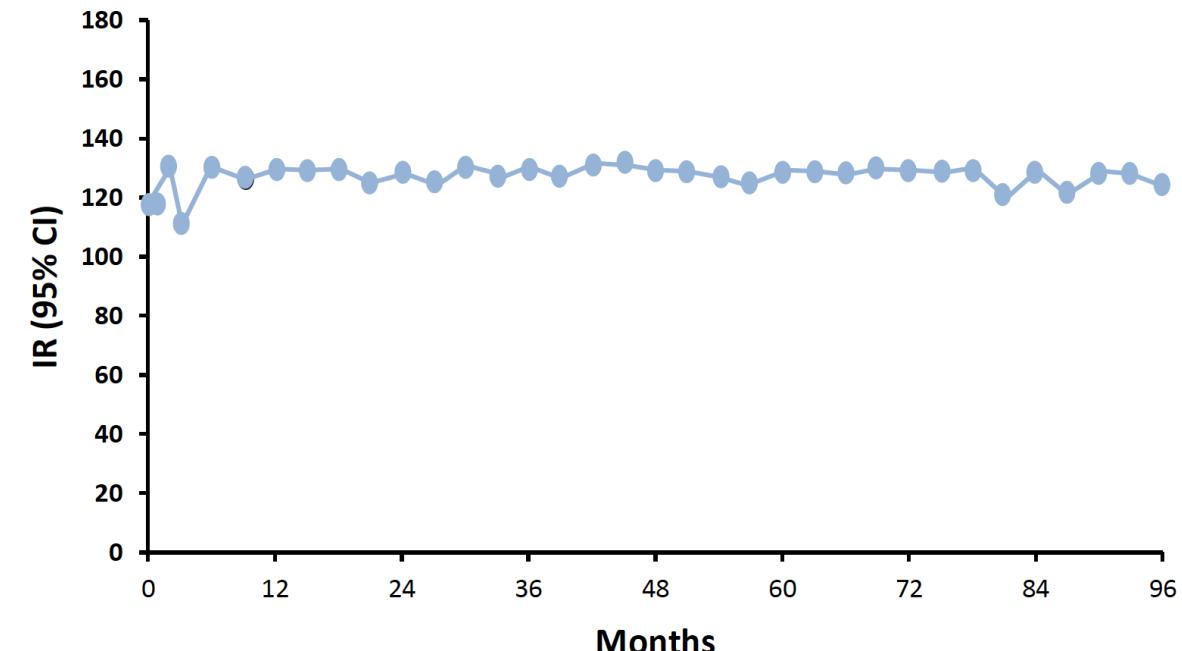
TOF 5 mg BID

Total cholesterol and LDL remained generally stable over time

Total Cholesterol

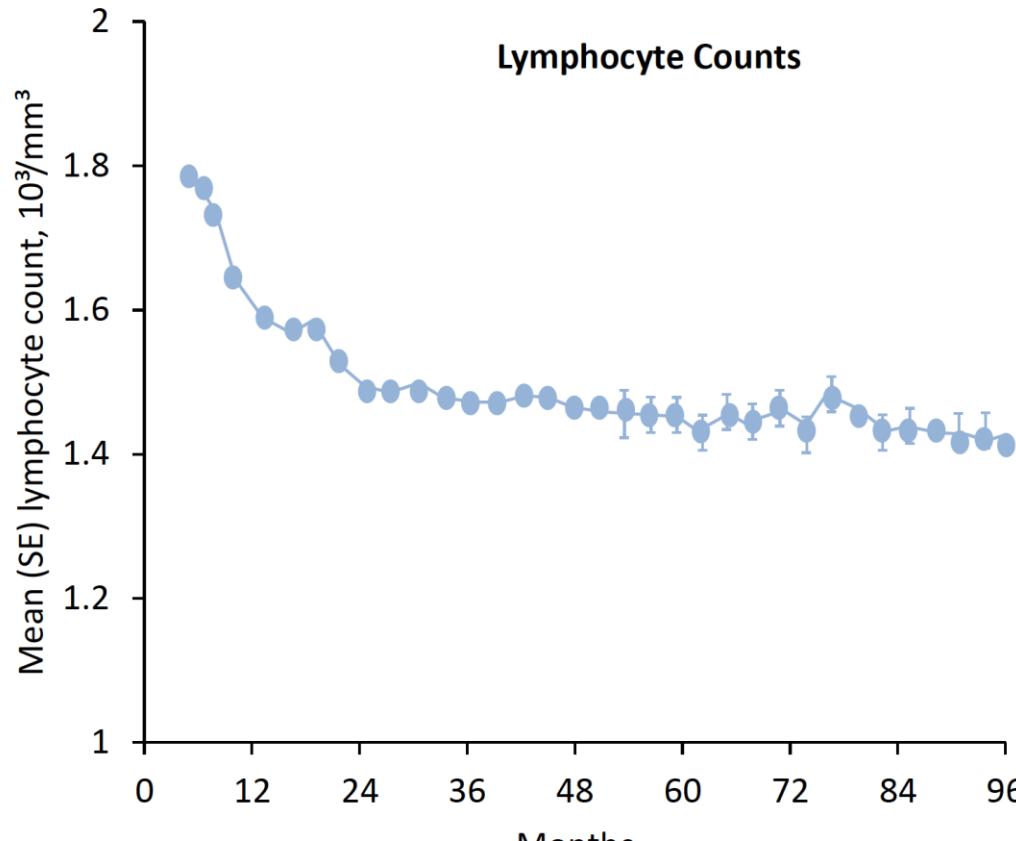


LDL

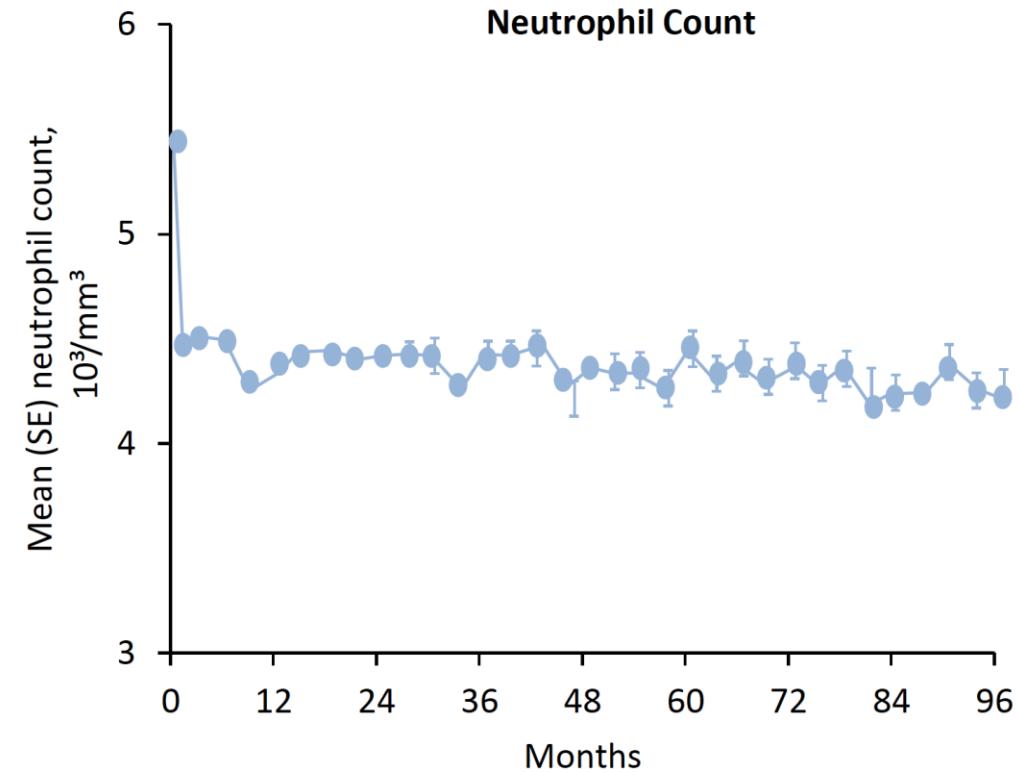


TOF 5 mg BID

Absolute lymphocyte count levels gradually declined until month 48, thereafter the levels stabilized. Changes over time were observed in neutrophils.



TOF 5 mg BID



Συμπερασματικά
Διαχείριση Αυτοάνοσων νοσημάτων το 2020. Τι αλλάζει;
Ρευματοειδής αρθρίτιδα
Jakinibs

- Η αποτελεσματικότητα δεν προσδιορίζεται από την εκλεκτικότητα
- >20 Jakinibs σε >60 κλινικές μελέτες φλεγμονωδών νοσημάτων
- Συγχορήγηση με βιολογικούς;
- Η δράση ποιων κυτταροκινών επηρεάζεται σε κάθε νόσο;
- Βιοδείκτες;

Συμπερασματικά

Tofacitinib

- Υψηλές ACR αποκρίσεις και ποσοστά ύφεσης με διατήρηση στον χρόνο
- Υπεροχή έναντι της MTX σε πρωτο-θεραπευόμενους ασθενείς
- Γρήγορη δράση (ημέρες – 6 εβδομάδες)
- Θεραπεία χορηγούμενη από το στόμα
- Αποδεκτό προφίλ ασφάλειας - παρόμοιο με bDMARDs



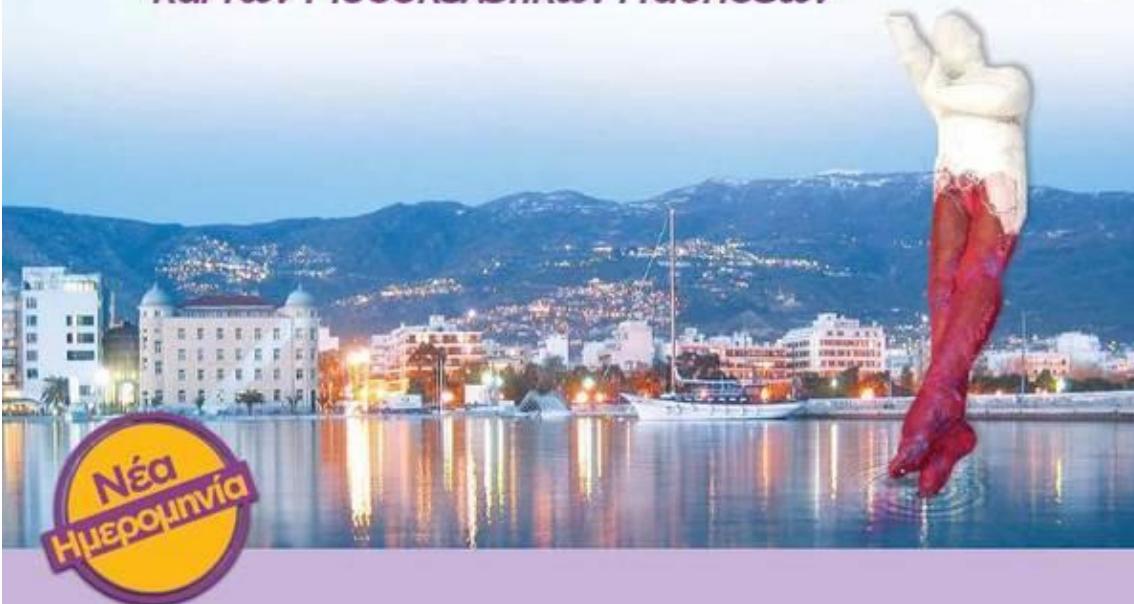
ΕΠΕΜΥ

Επιστημονική Εταιρεία
για τη Μυοσκελετική Υγεία

12^ο

Πανελλήνιο Συνέδριο

Ολοκληρωμένη διαχείριση των Φλεγμονώδων
και των Μυοσκελετικών Παθήσεων



29 Οκτωβρίου - **01** Νοεμβρίου 2020

Ξενοδοχείο Valis

Βόλος

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