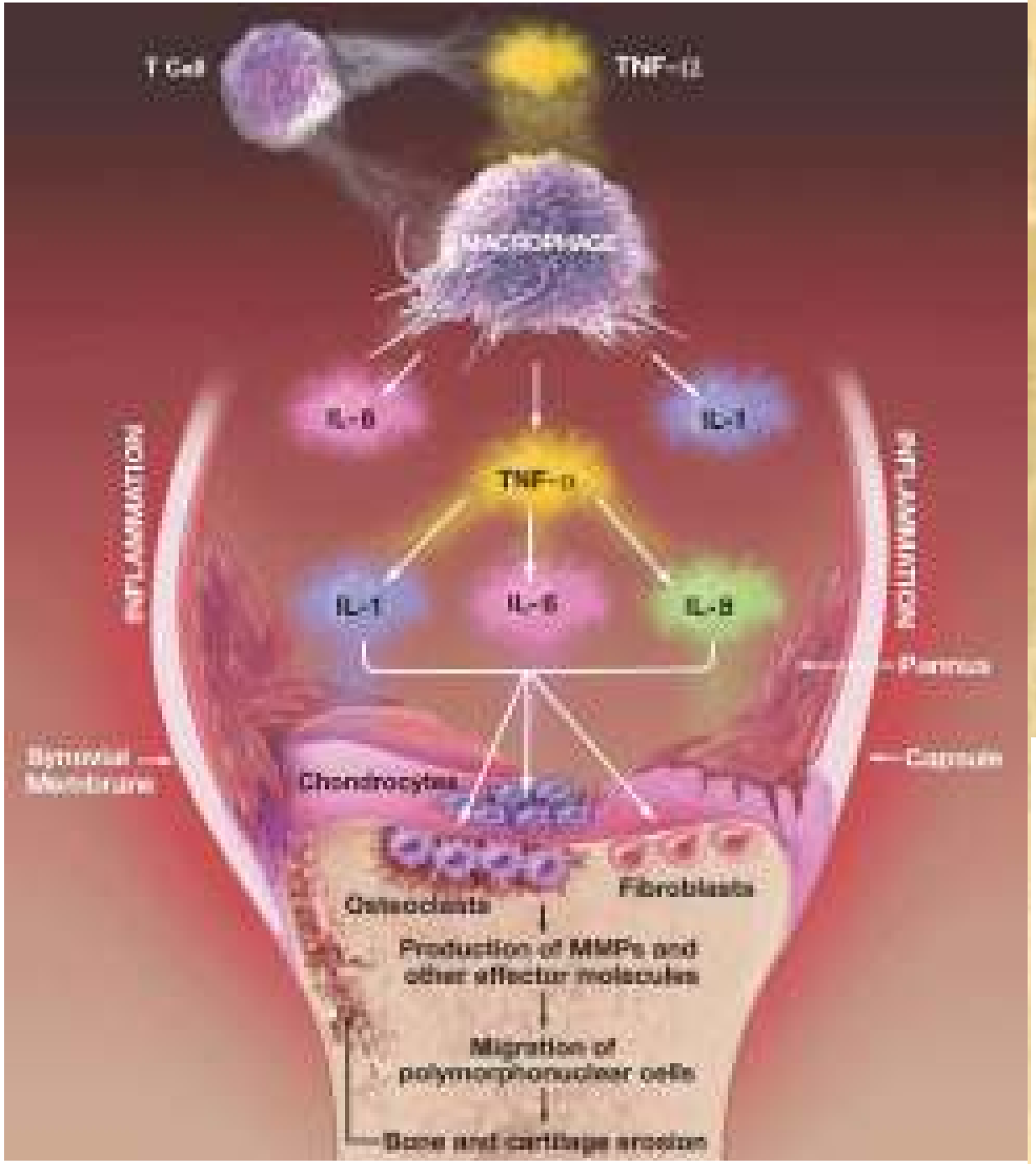
COSA CI HANNO INSEGNATO 10 ANNI DI JAK INIBIZIONE??

Dott L. Severino Martin

UOC di Medicina Interna

Ospedale di Velletri – ASL RM6



Trends in Biochemical Sciences

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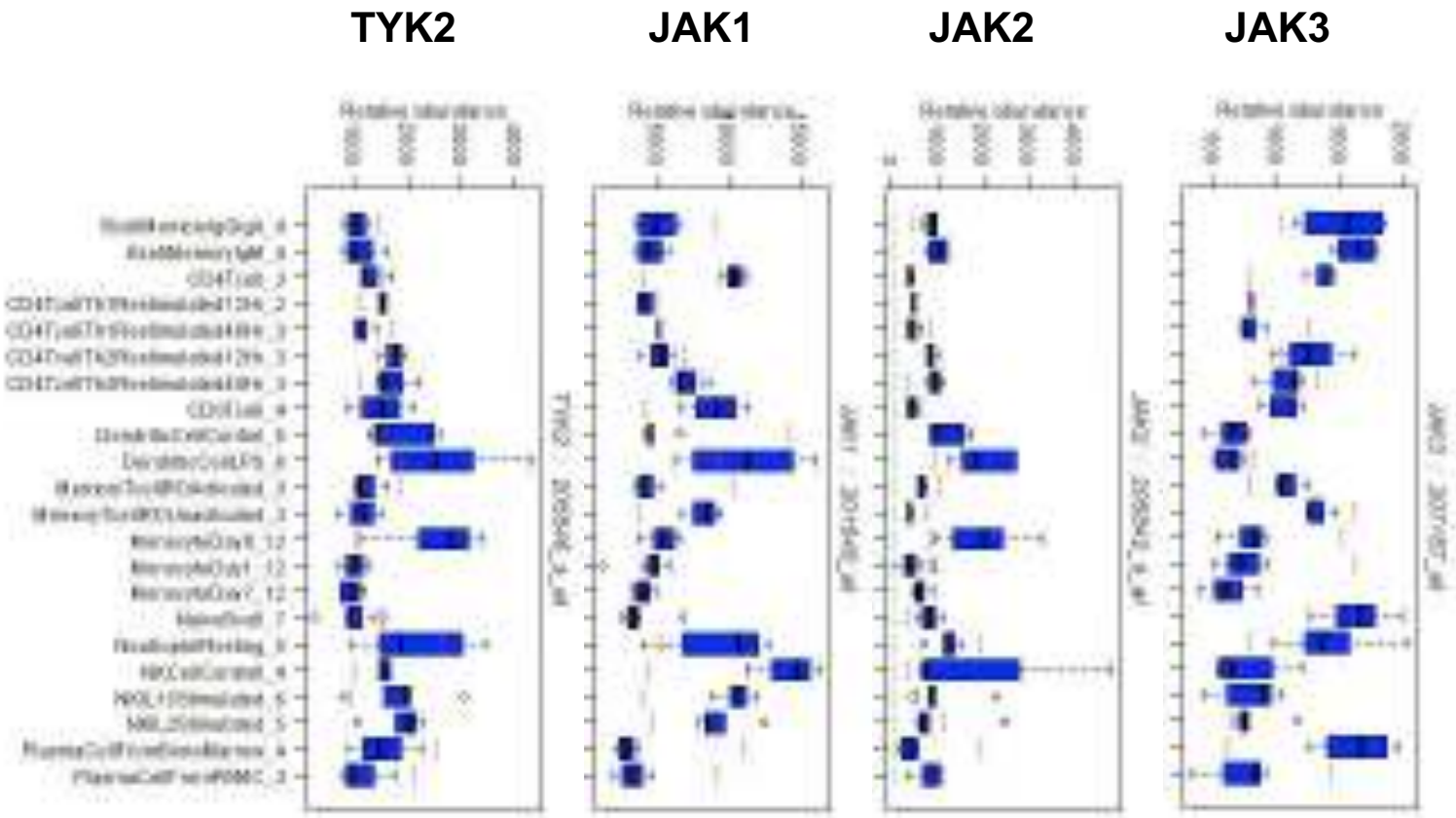
Welcome trends

Trends in brief

Signaling by the cytokine receptor superfamily: JAKs and STATs

James N. Ihle, Bruce A. Witthuhn, Frederick W. Quelle, Koh Yamamoto, William E. Thierfelder, Brent Kreider and Olli Silvennoinen

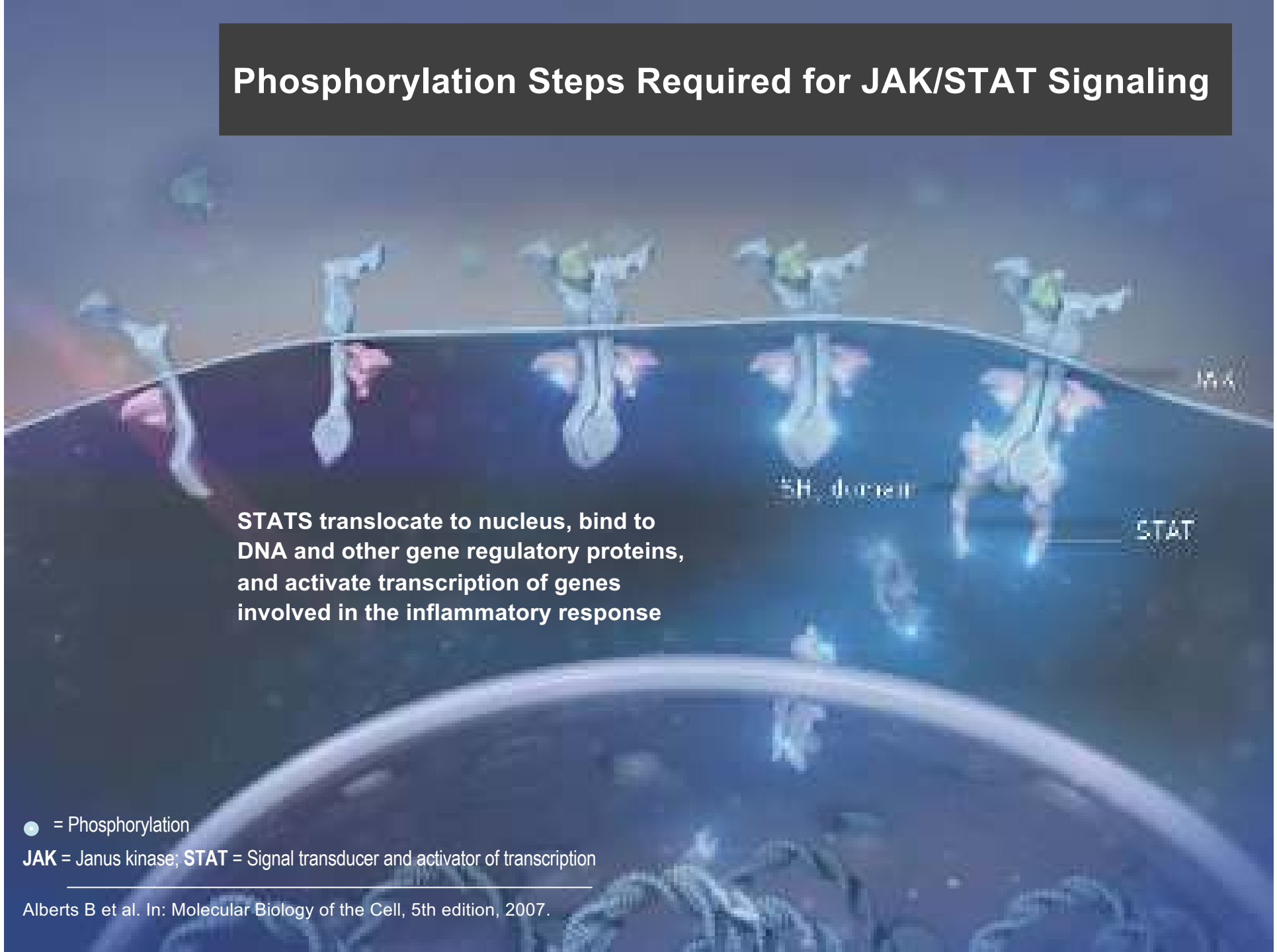
JAKs Are Ubiquitously Expressed in Immune Cells



Tao Wei TS&T June 2012

Data published by Abbas et al. *Genes Immun* 2005;6(4):319-31.

Phosphorylation Steps Required for JAK/STAT Signaling



STATS translocate to nucleus, bind to DNA and other gene regulatory proteins, and activate transcription of genes involved in the inflammatory response

● = Phosphorylation

JAK = Janus kinase; **STAT** = Signal transducer and activator of transcription

Alberts B et al. In: Molecular Biology of the Cell, 5th edition, 2007.

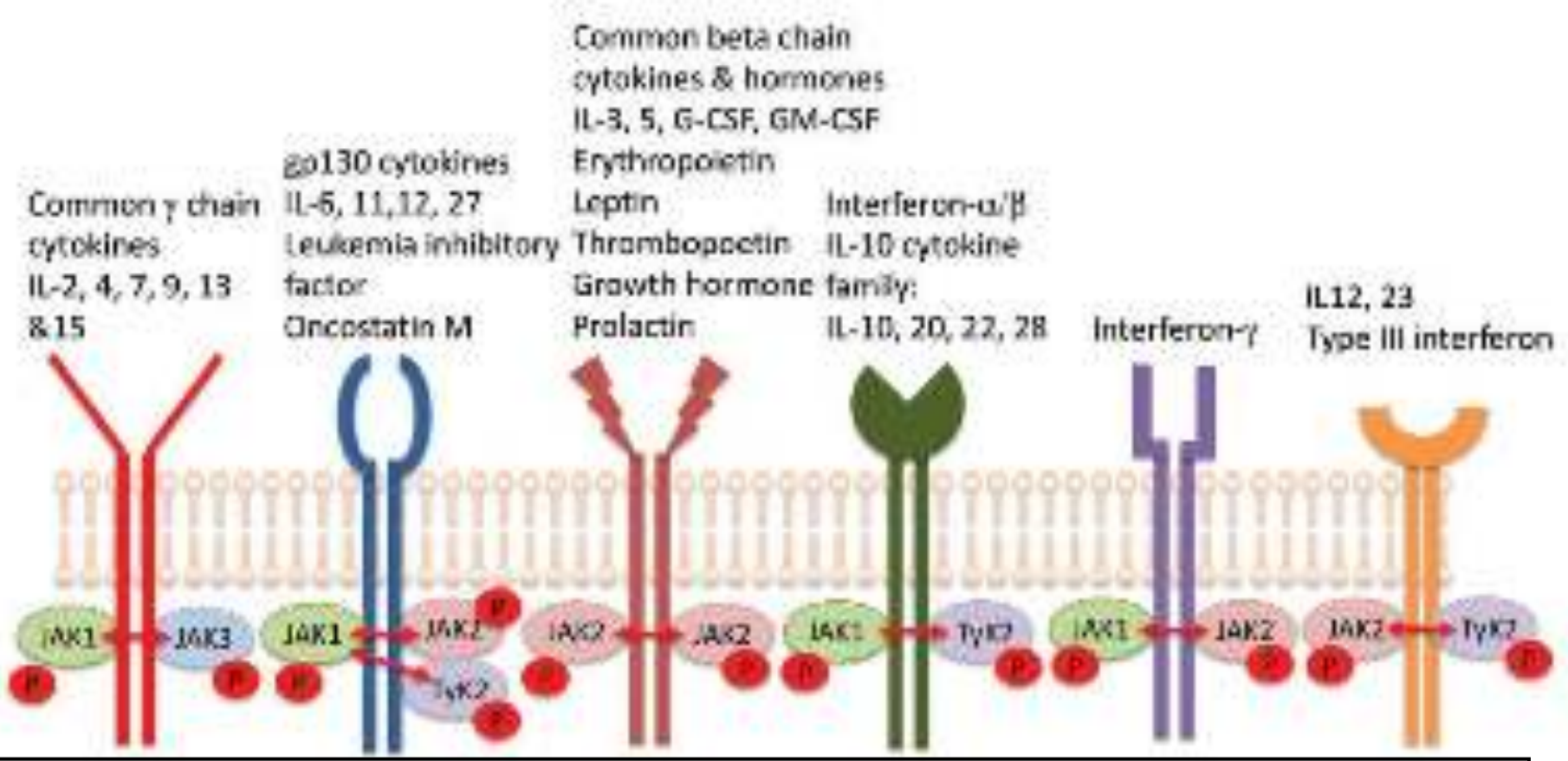
JAK and STAT Pairing Provides Specificity in Function

Based on the receptor subunits involved and the specific JAKs that are associated with the receptor, different STATs dock to the receptor and are phosphorylated by the JAKs. Dimerized STATs then move to the nucleus and stimulate gene transcription.

EPO = Erythropoietin; **GH** = Growth hormone; **GM-CSF** = Granulocyte-macrophage colony-stimulating factor; **INF** = Interferons; **IL** = Interleukin; **JAK** = Janus kinase; **RA** = Rheumatoid arthritis; **STAT** = Signal transducer and activator of transcription; **TPO** = Thrombopoietin; **TYK** = Nonreceptor tyrosine-protein kinase

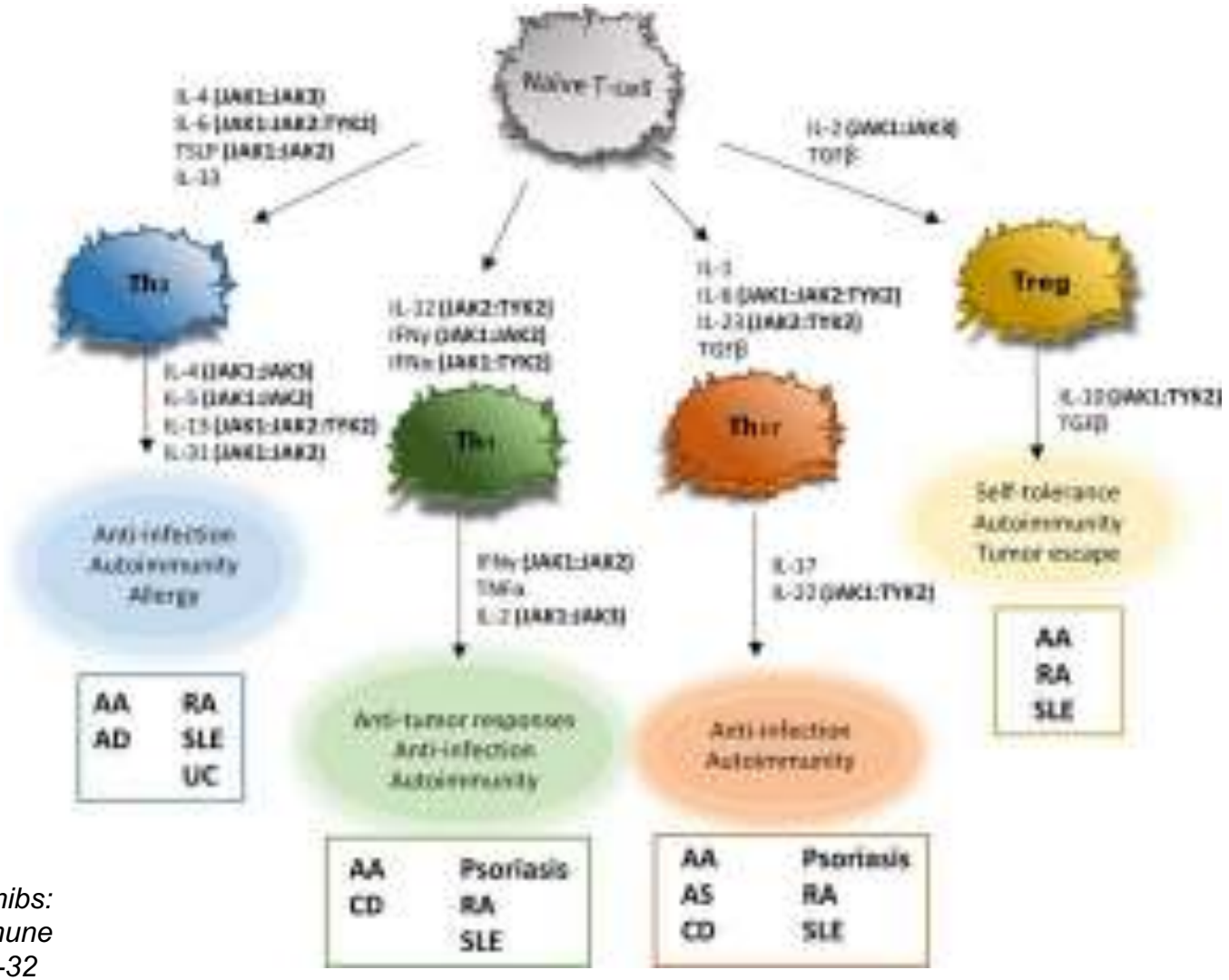
O'Shea JJ et al. *Annu Rev Med* 2015;66:311-28.

Signaling by Different Cytokines Requires Unique JAK Pairing



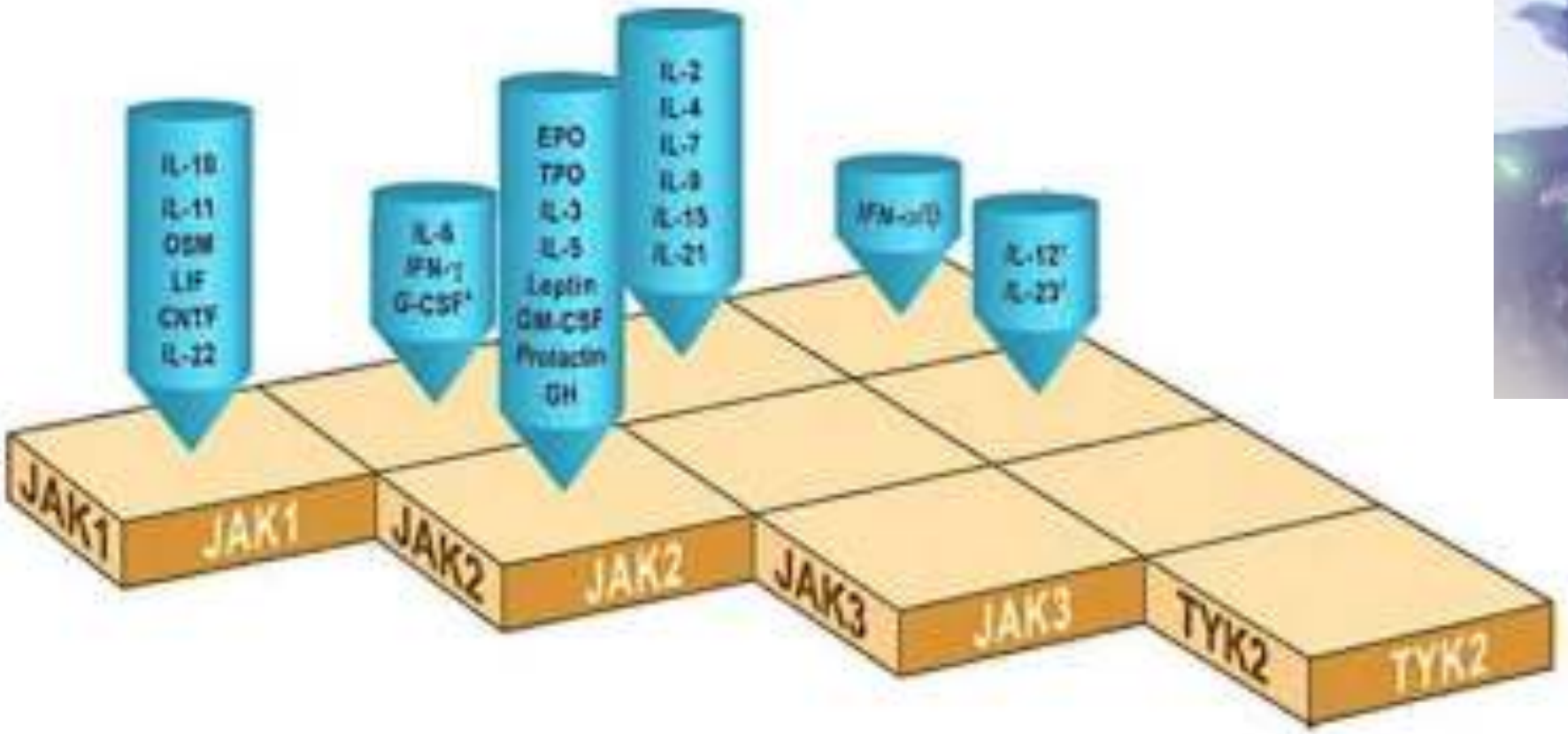
JAK1	+	+	-	+	+	-
JAK2	-	+	+	-	+	+
JAK3	+	-	-	-	-	-
TYK2	-	+	-	+	-	+

Cytokines play a central role in the pathogenesis of infammatory and autoimmune diseases



T Virtanen A, et al. Selective JAKinibs: Prospects in Inflammatory and Autoimmune Diseases. BioDrugs. 2019 Feb;33(1):15-32

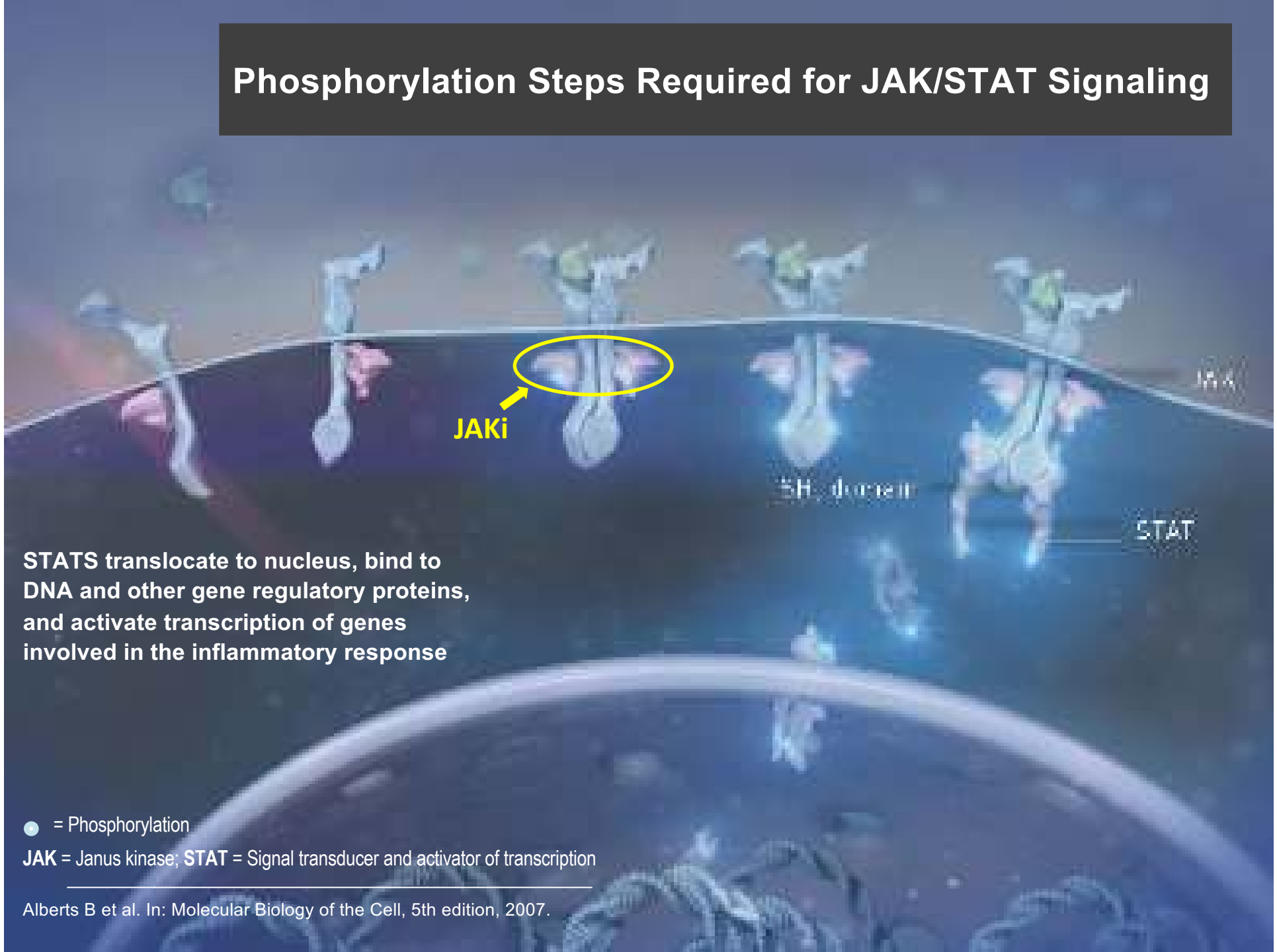
The JAK-STAT Signaling Pathway: Input and Output Integration



P.J. Murray: J Immunol 2007; 178:2623-2629.

Non sono stati mai descritti Recettori che utilizzano JAK2 e JAK3, JAK3 da solo, TYK2 da solo, o JAK3 e TYK2

Phosphorylation Steps Required for JAK/STAT Signaling



STATS translocate to nucleus, bind to DNA and other gene regulatory proteins, and activate transcription of genes involved in the inflammatory response

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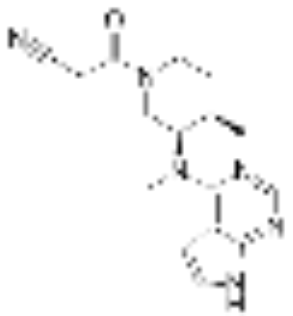
JAK = Janus kinase; **STAT** = Signal transducer and activator of transcription

Alberts B et al. In: Molecular Biology of the Cell, 5th edition, 2007.

Development of JAK Inhibitors for Autoimmune Diseases

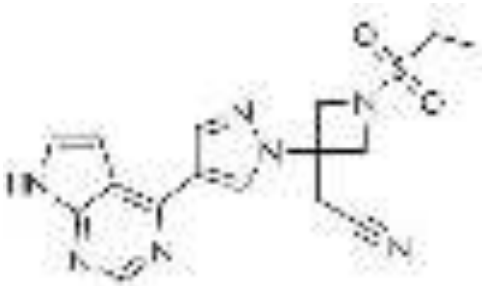


Tofacitinib

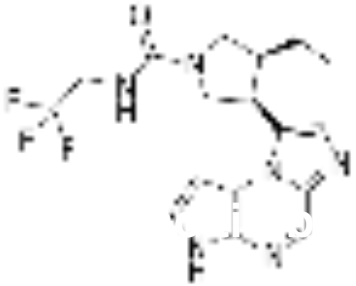
Table 1 Proposed nomenclature of disease-modifying antirheumatic drugs

Disease-modifying antirheumatic drugs (DMARDs)			
Synthetic DMARDs (sDMARDs)		Biological DMARDs (bDMARDs)	
Conventional synthetic DMARDs (csDMARDs)	Targeted synthetic DMARDs (tsDMARDs)	Biological originator DMARDs (boDMARDs)	Biosimilar DMARDs (bsDMARDs)

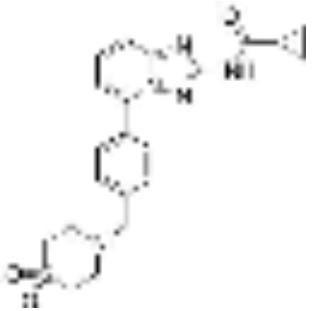
Smolen JS, et al. Ann Rheum Dis 2014;73:3–5.



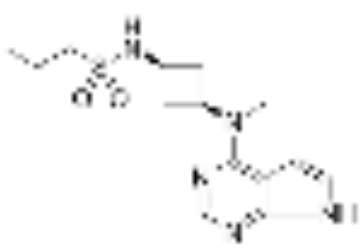
Baricitinib



Upadacitinib



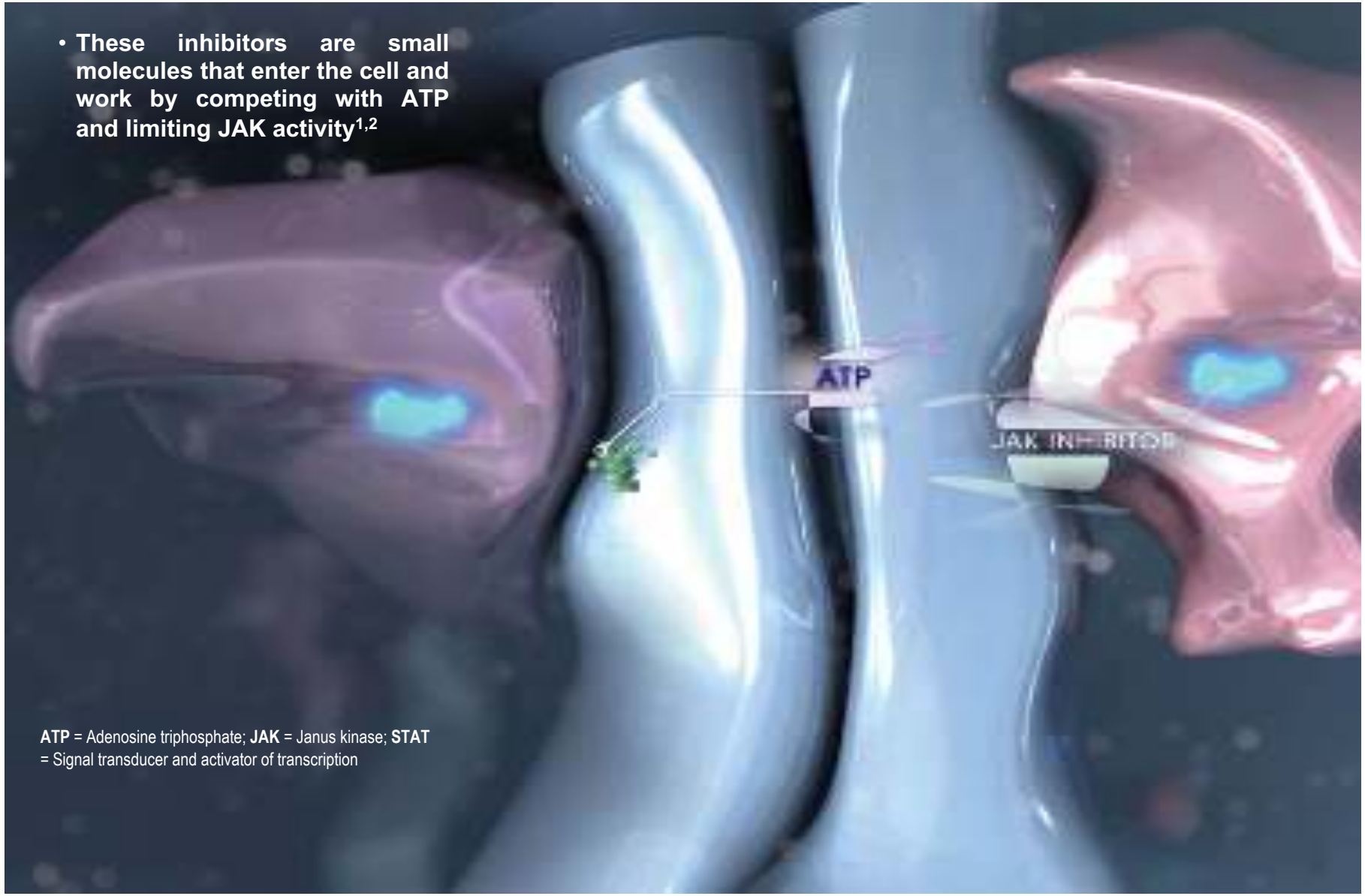
Filgotinib



Abrocitinib

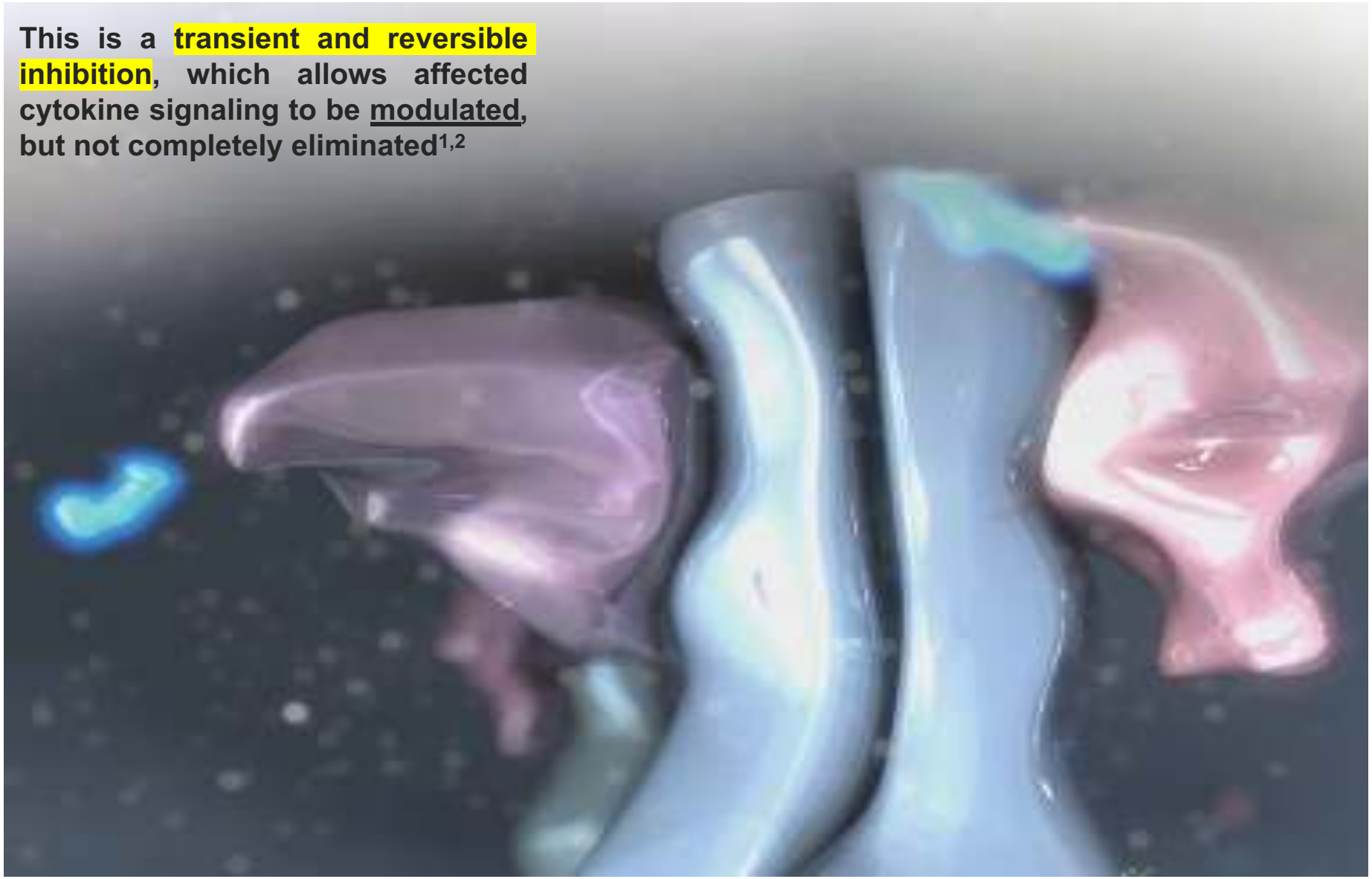
Ruxolitinib

Janus kinase inhibitors in autoimmune diseases



1. O'Shea JJ et al. *Ann Rheum Dis* 2013;72(Suppl 2):ii111-5. **2.** Meyer SC and Levine RL. *Clin Cancer Res* 2014;20:2051-9.

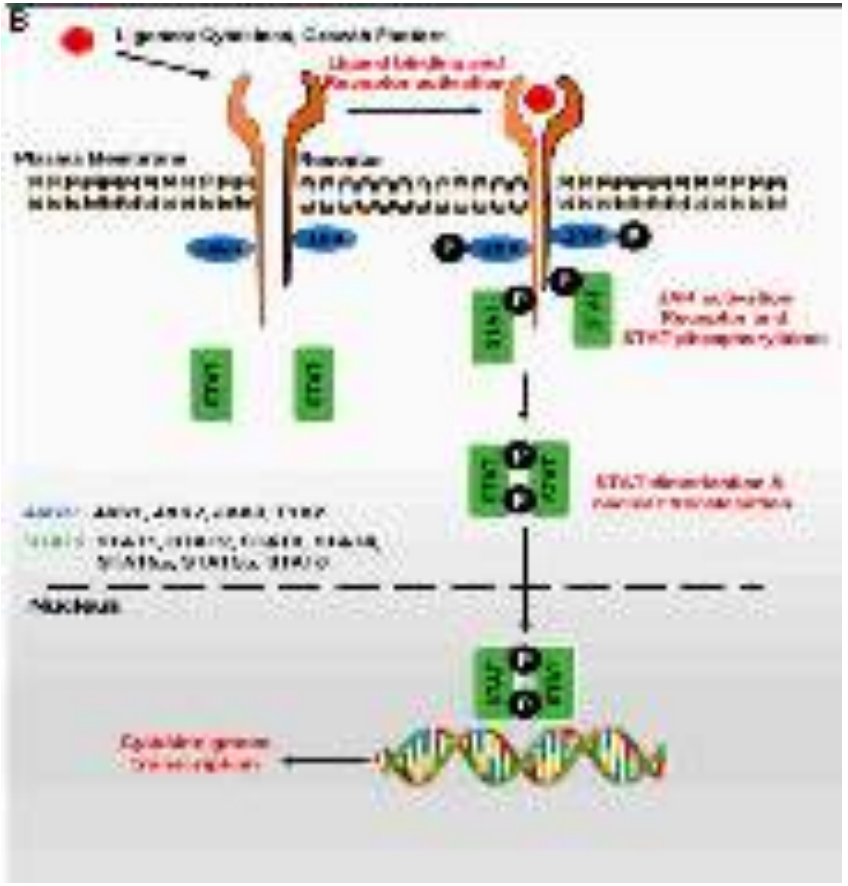
Janus kinase inhibitors in autoimmune diseases



1. O'Shea JJ et al. *Ann Rheum Dis* 2013;72(Suppl 2):ii111-5. **2.** Meyer SC and Levine RL. *Clin Cancer Res* 2014;20:2051-9.

Janus kinase-targeting therapies in rheumatology: a mechanisms-based approach

Yoshiya Tanaka 1, Yiming Luo2, John J. O'Shea3 and Shingo Nakayamada1



NATURE REVIEWS | RHEUMATOLOGY
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Fragoulis et al. The role for JAK inhibitors in the treatment of immune mediate disease

Diseases	GCA, IBD, PsO, RA, SSC, SLE, SS	GCA, RA, SSC, SS	GCA, PsO, RA, SSC, SLE	GCA, RA, SSC	GCA, PsO, RA, SSC, SLE, SpA, SS	GCA, IBD, PsO, RA, SSC, SLE, SS
Cytokines	IL-23 IL-12	EPO, TPO GM-CSF IL-3, IL-5	IL-2, IL-4, IL-7, IL-9, IL-15, IL-21	IL-6	IFN-α IFN-β IL-10	IFN-γ
JAKs						
JAK-inhibitors	Baricitinib Peficitinib Tofacitinib	Baricitinib Peficitinib Tofacitinib	Baricitinib Filgotinib Peficitinib Tofacitinib Upadacitinib	Baricitinib Filgotinib Peficitinib Tofacitinib Upadacitinib	Baricitinib Filgotinib Peficitinib Tofacitinib Upadacitinib	Baricitinib Filgotinib Peficitinib Tofacitinib Upadacitinib

Baricitinib restrains the immune dysregulation in patients with severe COVID-19

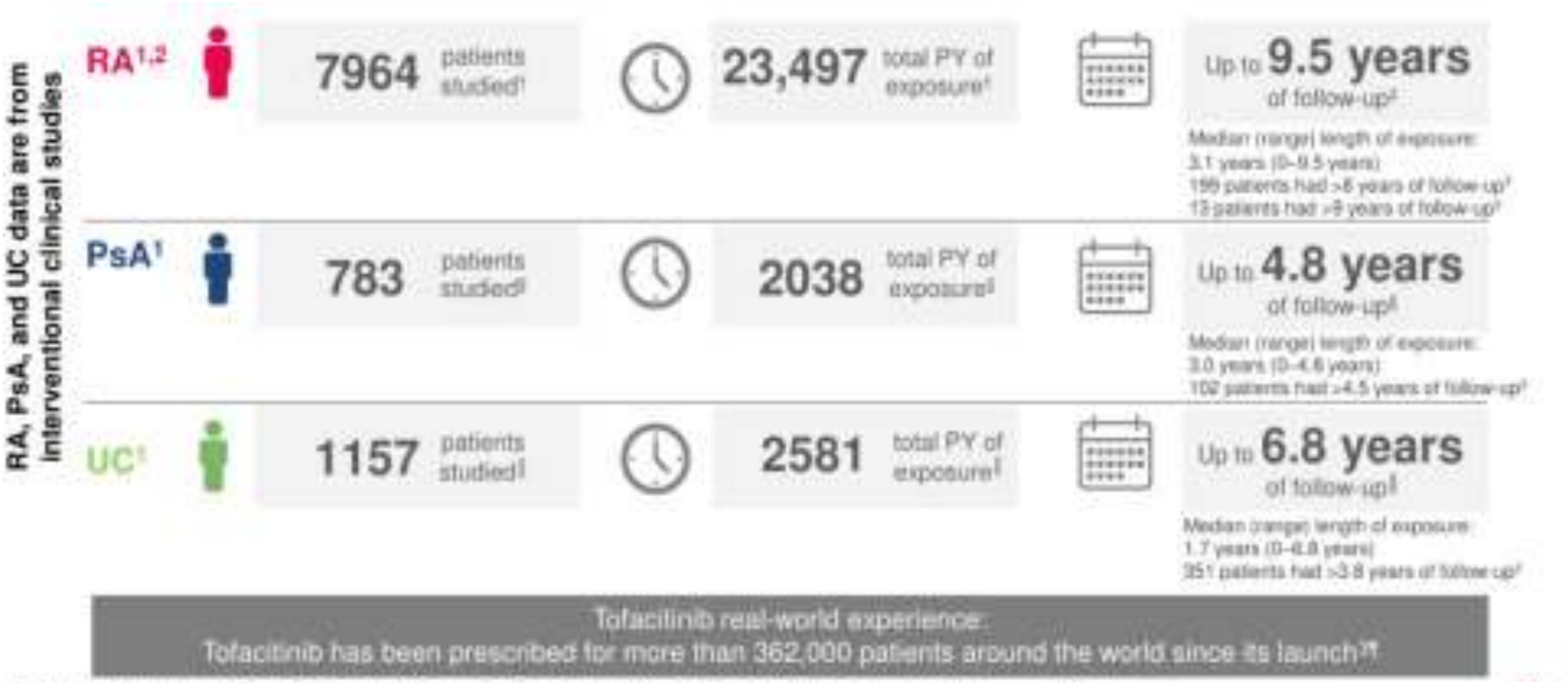
Vincenzo Bronte,[1] Stefano Ugel,[1] Elisa Tinazzi,[2] Antonio Vella,[1] Francesco De Sanctis,[1] Stefania Canè,[1] Veronica Batani,[1] Rosalinda Trovato,[1] Alessandra Fiore,[1] Varvara Petrova,[1] Francesca Hofer,[1] Roza Maria Barouni,[1] Chiara Musiu,[1] Simone Caligola,[1] Laura Pinton,[1] Lorena Torroni,[1] Enrico Polati,[4] Katia Donadello,[4] Simonetta Feiso,[2] Francesca Pizzolo,[2] Manuela Iezzi,[5] Federica Facciotti,[5] Pier Giuseppe Pelicci,[6] Daniela Righetti,[7] Paolo Bazzoni,[7] Mariaelisa Rampudda,[7] Andrea Comel,[7] Walter Mosaner,[7] Claudio Lunardi,[2] and Oliviero Olivieri[2]

[2] Immunology Section, Department of Medicine, Internal Medicine Section B, Department of Medicine, Unit of Epidemiology and Medical Statistics, Department of Diagnostics and Public Health, University and Hospital Trust of Verona, Verona, Italy. [3] Intensive Care Unit, Department of Surgery, Dentistry, Maternity and Infant, University and Hospital Trust of Verona, Verona, Italy. [4] Center for Advanced Studies and Technology (CAST), University of G. D'Annunzio of Chieti-Pescara, Chieti, Italy. [5] Department of Experimental Oncology, European Institute of Oncology, IRCCS, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Milan, Italy. [6] Federal Hospital, Resistero sul Garda, Italy.

RESULTS. ***We provide evidence that patients treated with baricitinib had a marked reduction in serum levels of IL-6, IL-1β, and TNF-α, a rapid recovery of circulating T and B cell frequencies, and increased antibody production against the SARS-CoV-2 spike protein, all of which were clinically associated with a reduction in the need for oxygen therapy and a progressive increase in the P/F (PaO_2, oxygen partial pressure/FiO_2, fraction of inspired oxygen) ratio.***

Bronte V, et al. J Clin Invest. 2020 Dec 1;130(12):6409-6416.

TOFACITINIB CLINICAL STUDIES AND REAL-WORLD EXPERIENCE



The approved dose of tofacitinib for RA and PsA is 5 mg BID. Per UC la dose raccomandata è di 10 mg somministrati per via orale due volte al giorno per l'induzione per 8 settimane. La dose raccomandata per il trattamento di mantenimento è tofacitinib 5 mg somministrato per via orale due volte al giorno (RCP Tofacitinib marzo 2023). †Data as of April 2019. ‡Data as of March 2017. ‖Data as of May 2019. ¶Estimate as of October 2020.

BID, twice daily; PsA, psoriatic arthritis; PY, patient-years; RA, rheumatoid arthritis; UC, ulcerative colitis.

1. Burmester GR, et al.RMD Open. 2021;7(2):e001595. **2.** Cohen SB, et al. RMD Open. 2020;6(3):e001395. 3. Tofacitinib. Riassunto delle Caratteristiche del Prodotto. Marzo 2023.

1° lezione: nuovi potenziali bersagli nella terapia delle malattie autoimmuni.

JAK INIBITORI IN AR

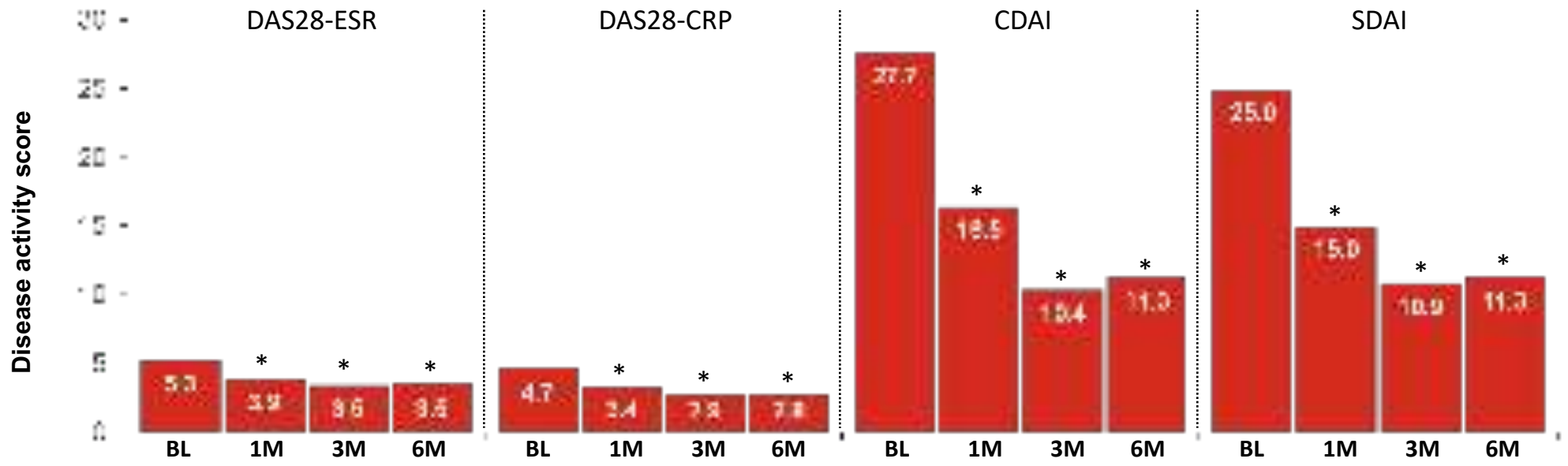
TOFACITINIB	bDMARDs-IR	STEP		**Studi ORAL 4277 pz**
	MTX-IR	SCAN STANDARD	Comparatore attivo (ADA)	
	cs-DMARDs-IR	SOLO, SYNC		
	MTX naive	START	off label	
BARICITINIB	bDMARDs-IR	BEACON		**Studi RA 3100 pz**
	MTX-IR	BEAM	Comparatore attivo (ADA)	
	cs-DMARDs-IR	BUILD		
	MTX naive	BEGIN	off label	
UPADACITINIB	bDMARDs-IR	BEYOND, CHOICE	Comparatore attivo (ABA)	**Studi SELECT 4284 pz**
	MTX-IR	COMPARE, MONOTHERAPY	Comparatore attivo (ADA)	
	cs-DMARDs-IR	NEXT		
	MTX naive	EARLY	off label	
FILGOTINIB	bDMARDs-IR	FINCH 2	Comparatore attivo (ADA)	**Studi FINCH 3460 pz**
	MTX-IR	FINCH 1		
	MTX naive	FINCH 3	off label	

Early Improvements in Disease Activity Scores

Treatment Response

- **Statistically significant improvements in all disease activity indexes** were observed as **early as the first month of baricitinib treatment (4 mg, N=43)** and continued through to Month 6 follow-up

Italian single-center experience



*p<0.0001 versus BL.

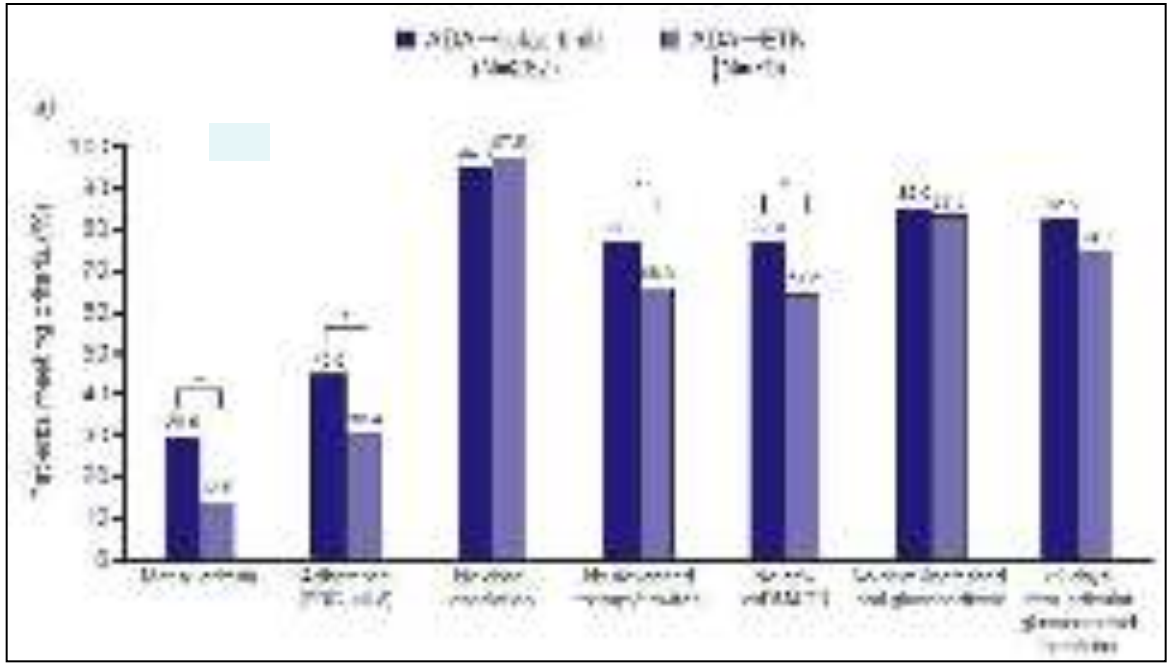
Tesei G, et al. Ther Adv Musculoskelet Dis. 2021;13:1759720X211014019.

EFFECTIVENESS OF TOFACITINIB AFTER SWITCHING FROM bDMARD

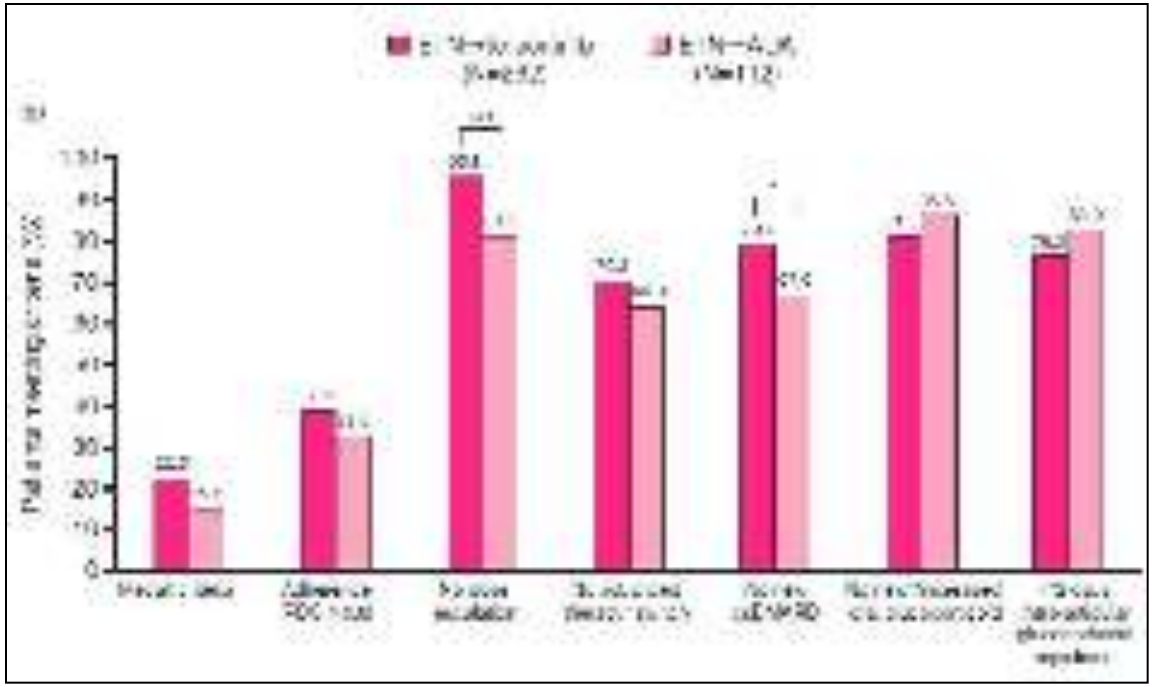
Results from a retrospective cohort study showed effectiveness was greater in patients who switched from ADA /ETN to tofacitinib vs patients who cycled between ADA and ETN

Tofa n=549

Switching from ADA→tofacitinib vs cycling from ADA→ETN



Switching from ETN→tofacitinib vs cycling from ETN→ADA



*P<0.05; ***P<0.0001. [a]Any biologic DMARD or JAK inhibitor (specifically, baricitinib or tofacitinib); [b]≤30 days of oral glucocorticoid between Months 3–12 post-index in patients with no glucocorticoid prescriptions for 6 months pre-index; [c]No increase in oral glucocorticoid dose ≥20% during Months 6–12 post-index (for those with claims for oral glucocorticoids for 6 months pre-index).

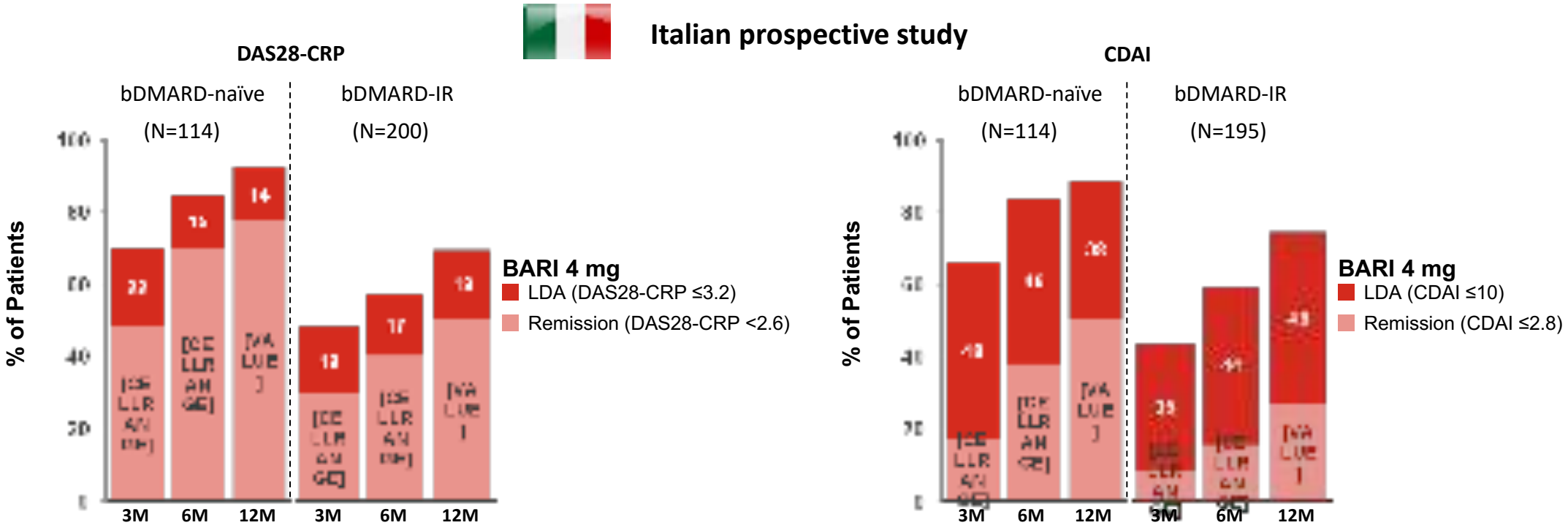
ADA, adalimumab; bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic DMARD; ETN, etanercept; IBM, international business machines; MOA, mechanism of action; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor; USA, United States of America.

Harnett J, et al. [abstract 1426]. Arthritis Rheumatol. 2019; 71 (suppl 10).

In Both bDMARD-naïve and bDMARD-IR Patients a High Proportion Achieved Remission or LDA as Early as 3 Months

Treatment Response

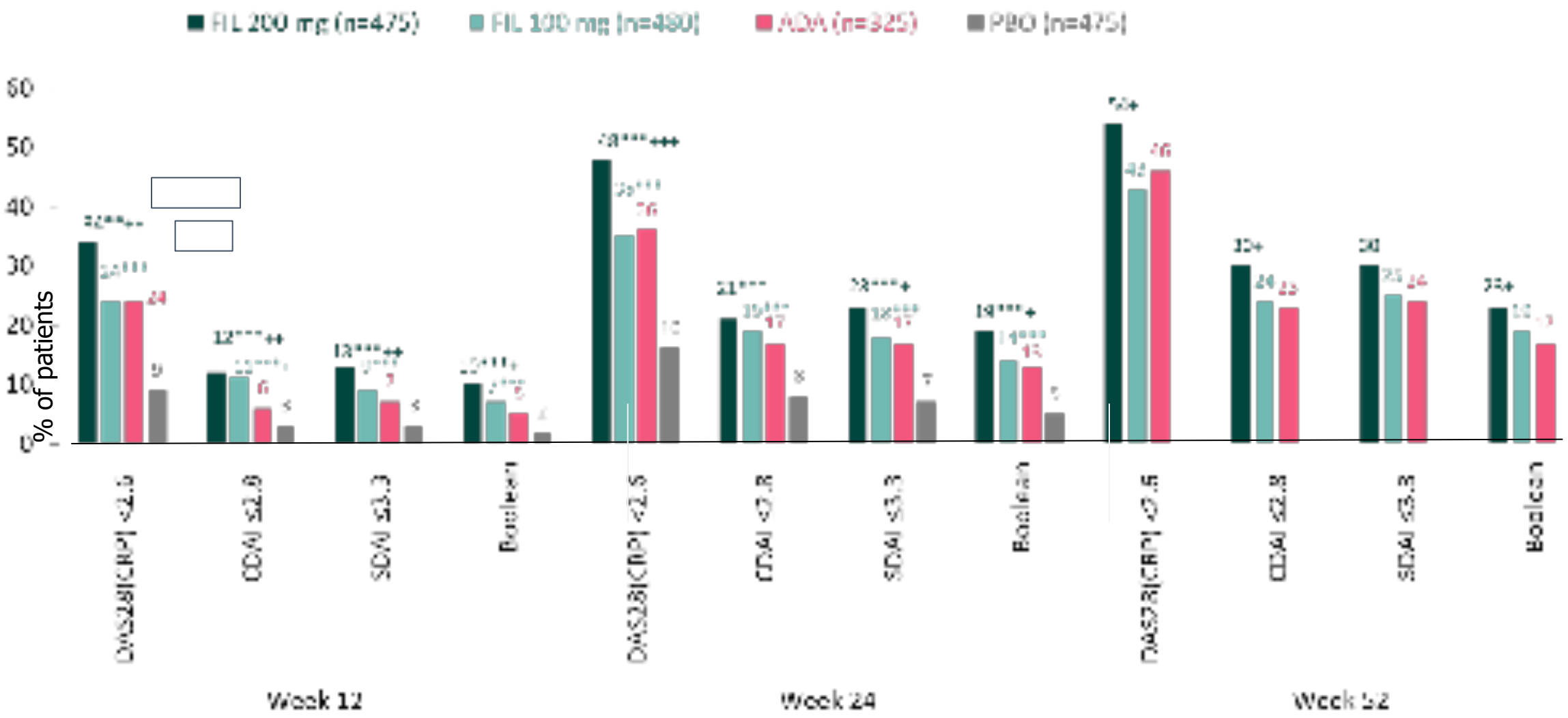
- Baricitinib was associated with a high frequency of remission or LDA as early as 3 months in both bDMARD-naïve and bDMARD-IR patients



BARI, Baricitinib; bDMARD-IR, biologic Disease-modifying Anti-rheumatic Drug-Inadequate Responder; CDAI, Clinical Disease Activity Index; DAS28-CRP, Disease Activity Score Based on 28 Joints-C-Reactive Protein; LDA, Low Disease Activity; M, Month; N, Number of Patients in the Analysis Population.

Guidelli GM, et al. Clin Exp Rheumatol. 2021;39(4):868–73 (Supplementary appendix).

Secondary endpoint: Remission



Comparisons significant in prespecified analyses controlled for multiplicity are boxed
**p<0.01, ***p<0.001 vs placebo, not adjusted for multiplicity and should be considered exploratory except for FIL200 and FIL100 versus placebo for DAS28 (CRP) <2.6 at Week 12; +p<0.05, ++p<0.01, +++p<0.001 vs ADA, not adjusted for multiplicity and should be considered exploratory.
ADA: adalimumab; CDAI: clinical disease activity index; DAS28 (CRP): Disease Activity Score in 28 joints with C-reactive protein; FIL: filgotinib; PBO: placebo; SDAI: simplified disease activity index. Combe B et al. Ann Rheum Dis 2021;80:848–858.

5-year UPA safety and efficacy data from SELECT-COMPARE

Objective

- To present safety and efficacy data through 5 years for UPA vs ADA in the SELECT-COMPARE LTE study

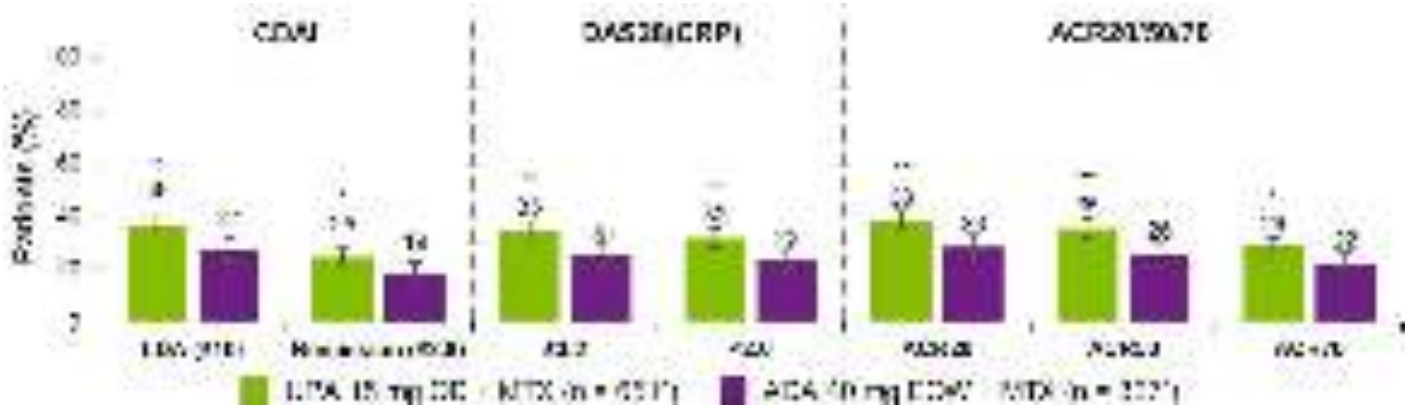
Methods

- Patients entering the open-label LTE could continue to receive UPA or ADA for up to 10 years in total
- Rates of TEAEs and TEAEs of special interest are presented as E/100 PY through 5 years for all patients who received ≥1 dose of UPA or ADA
- Efficacy assessments at 5 years were performed by both original randomized group (NRI) and treatment sequence (AO) for CDAI LDA (≤10) and remission (≤2.8), DAS28-CRP ≤3.2 and <2.6, and ACR20/50/70
- Radiographic progression and the proportion of patients with no radiographic progression were assessed at Week 192 (latest available timepoint) by treatment sequence

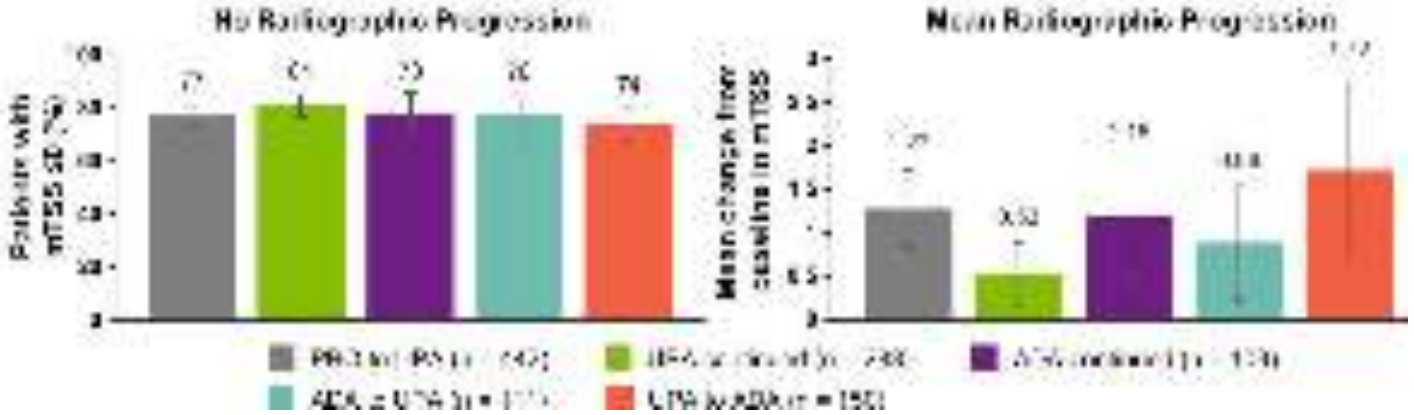
Key results

- At Week 48, 1402 patients entered the LTE study (PBO to UPA: n = 565; UPA continued: n = 342; ADA continued: n = 126; ADA to UPA: n = 141; UPA to ADA: n = 228)
- There were numerically greater proportions of patients randomized to UPA vs ADA (NRI) who achieved clinical responses as assessed by CDAI, DAS28-CRP, and ACR20/50/70 at 5 years
- Similar proportions of patients across treatment sequences showed no radiographic progression (mTSS <=0) at Week 192
- Mean radiographic progression (mean change from baseline in mTSS) was lowest for continuous UPA (0.53)

Clinical responses at Year 5 (NRI)[a]

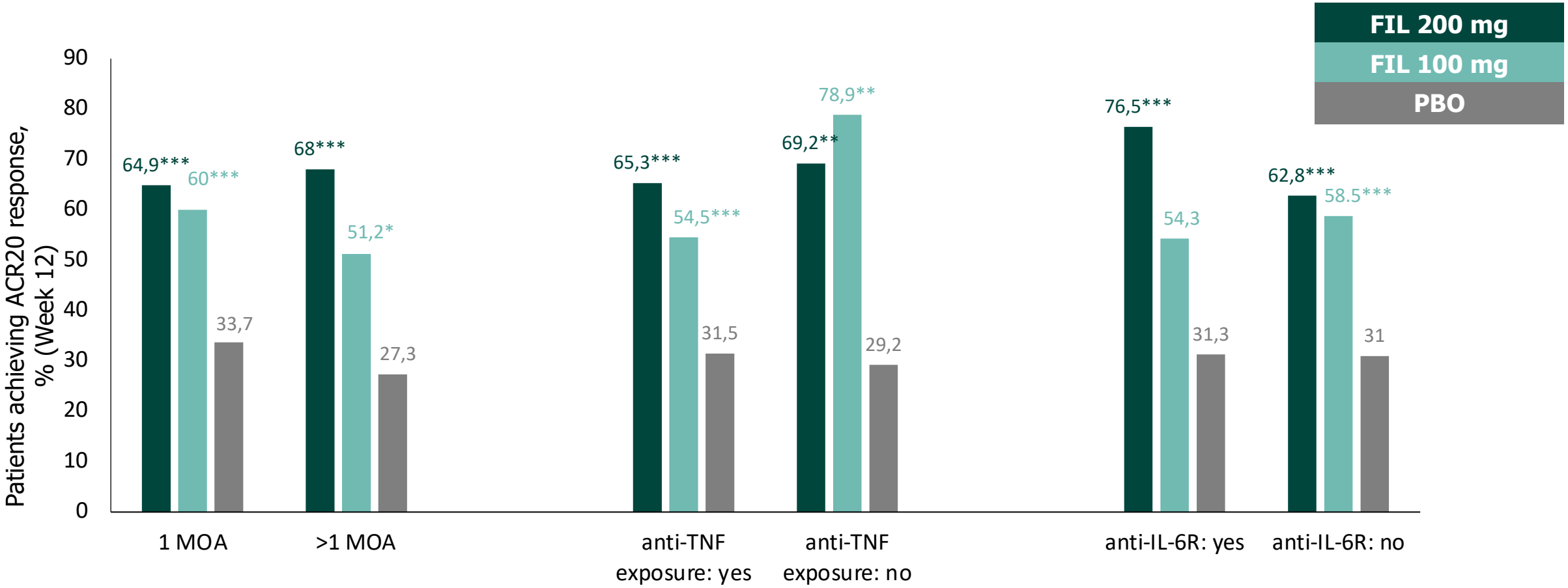


Radiographic progression at Week 192 (AO)[d]



[a]Treatment groups are by initial randomization. *P<.05, **P<.01 for UPA + MTX vs ADA + MTX. All P-values are nominal. Treatment comparisons were made using Cochran–Mantel–Haenszel test adjusting for the stratification factor of prior biologic DMARD use. [b]252 patients were rescued to ADA. [c]159 patients were rescued to UPA. [d]Groups are by treatment sequence, without imputation for missing data.

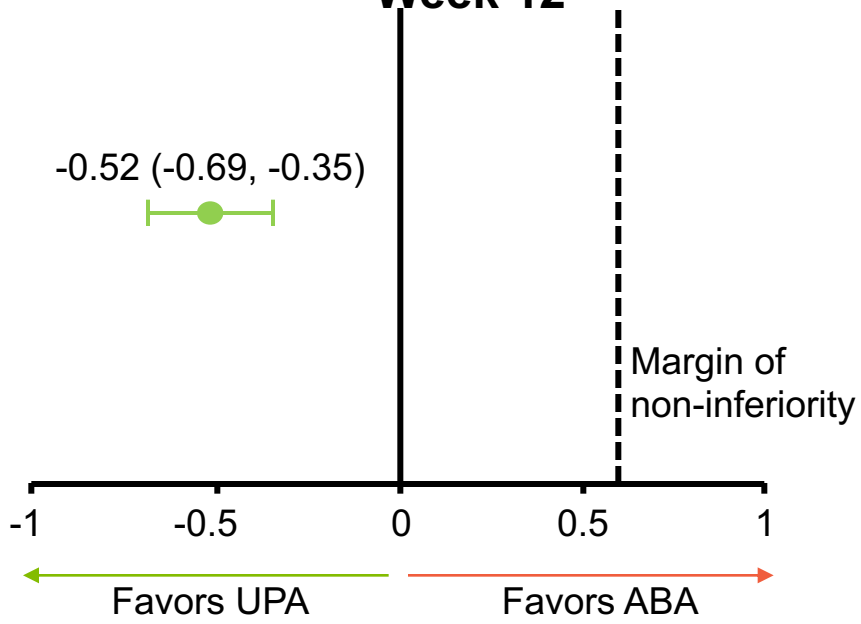
Subgroup analysis: ACR20 for patients with prior exposure to TNF- or IL-6R inhibitors (Week 12)



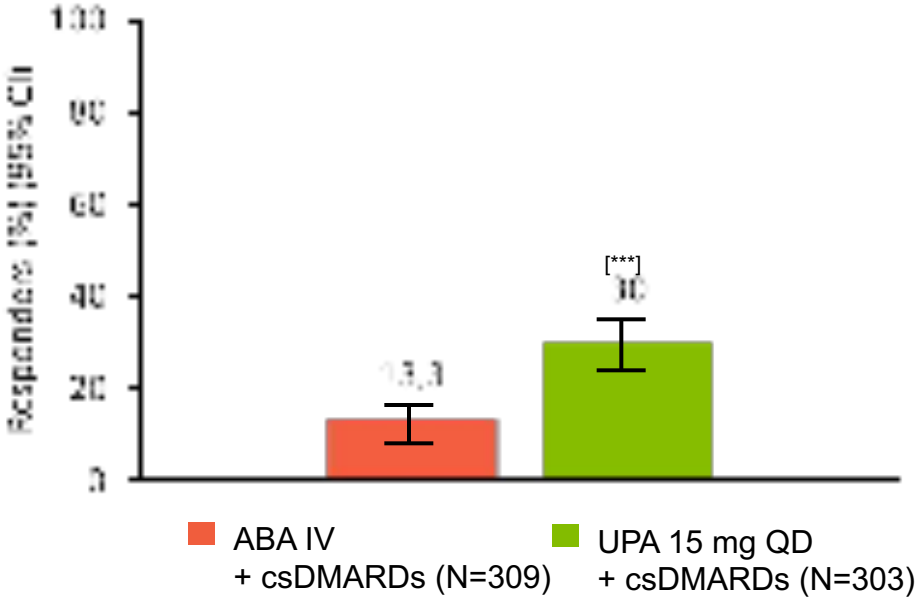
ACR20: American College of Rheumatology 20% improvement; FIL: filgotinib; IL-6R: interleukin-6 receptor; MOA: mechanism of action; PBO: placebo; TNF: tumour necrosis factor.
Genovese MC et al. JAMA 2019;322:315–325 (Suppl. 10).

SELECT CHOICE

Treatment difference in Δ DAS28-CRP at Week 12



DAS28-CRP <2.6 at Week 12 (superiority)



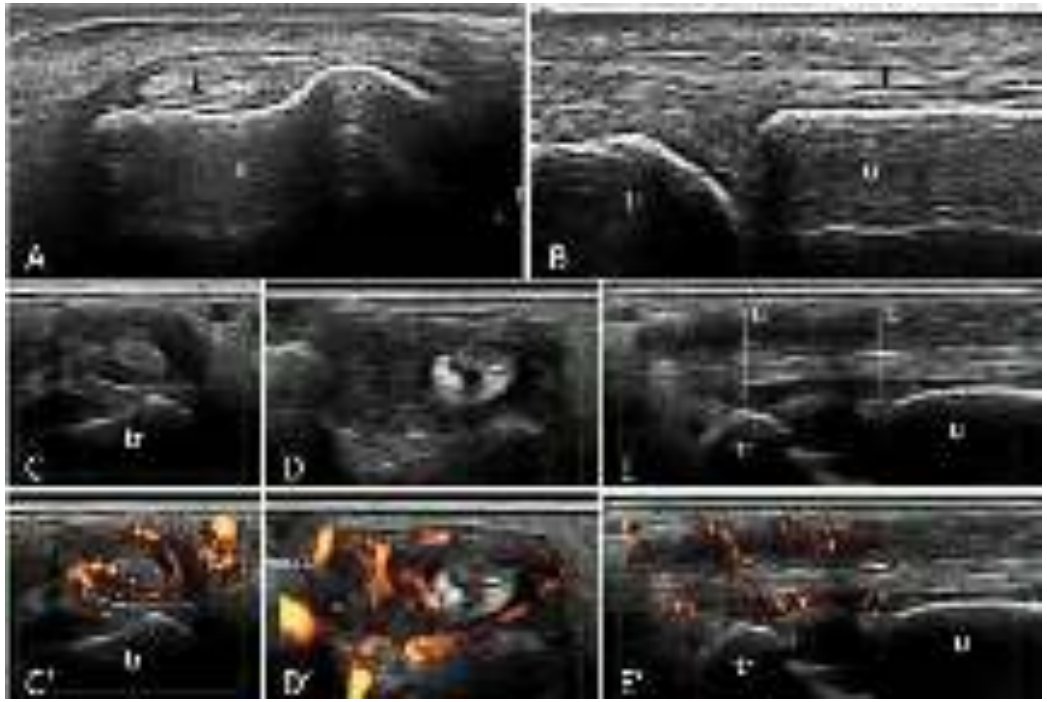
UPA met the primary endpoint of non-inferiority for Δ DAS28-CRP at Week 12 (p<0.001) and ranked secondary endpoints of superiority vs ABA for Δ DAS28-CRP and DAS28-CRP <2.6 at Week 12 (p<0.001)

MI analysis for ΔDAS28-CRP; NRI analysis for DAS28-CRP <2.6
Comparisons adjusted for multiplicity: [***]p≤0.001 vs ABA (superiority)

Rubbert-Roth A, et al. N engl j med 383;16 nejm.org October 15, 2020cal

Effect of Baricitinib on Ultrasound-Assessed Inflammation

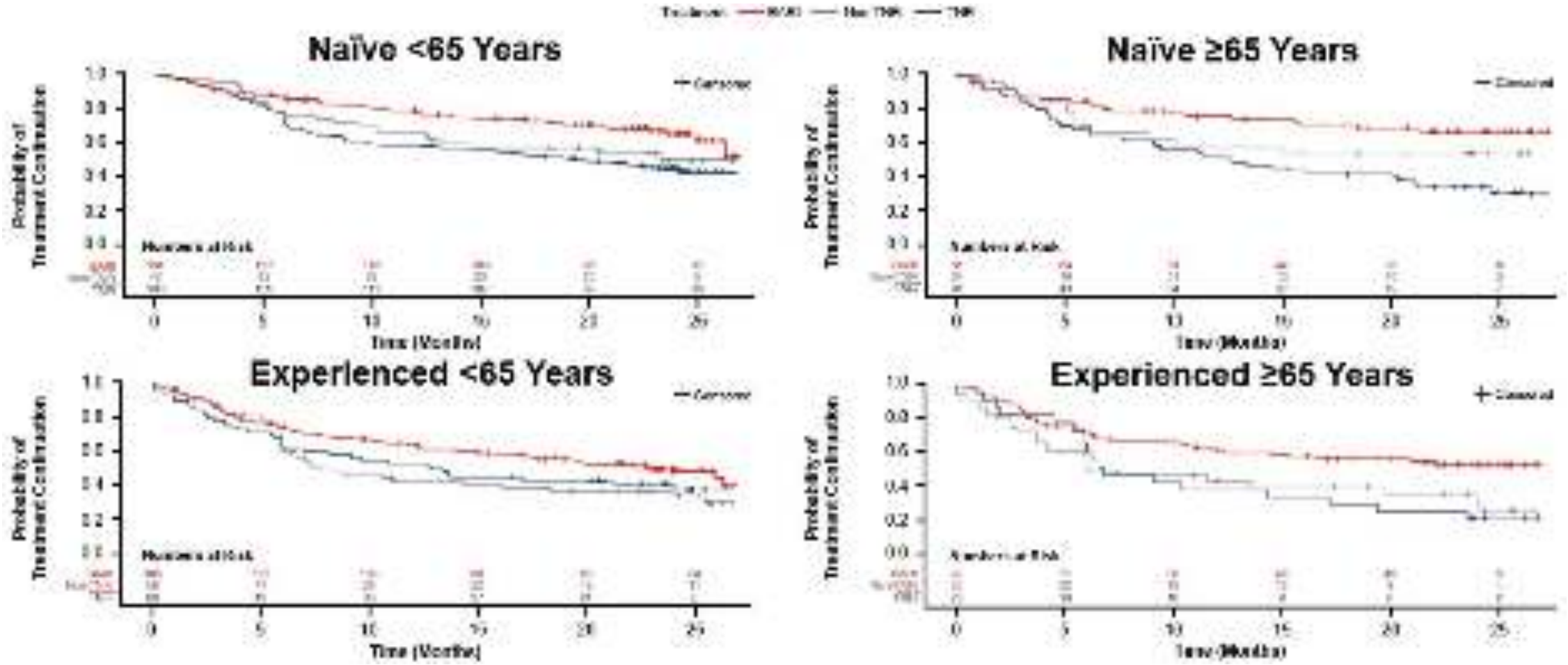
- **Tesei** and colleagues (2021) reported that **synovitis and tenosynovitis** analyzed with greyscale or with power Doppler were **significantly improved** as early as at one month of treatment, while erosion scores remained unchanged throughout the follow-up.
- **Spinelli and colleagues** (2021) reported **reductions in US inflammatory scores**, reflecting the joint inflammatory status, as early as at one month of treatment.
- These observations were confirmed in another monocentric study, in **Daegu, Republic of Korea** , and are in line with the observed decrease in inflammatory biomarkers associated with joint destruction in RCTs of baricitinib



Taylor PC, Laedermann C, Alten R, Feist E, Choy E, Haladyj E, De La Torre I, Richette P, Finckh A, Tanaka Y. A JAK Inhibitor for Treatment of Rheumatoid Arthritis: The Baricitinib Experience. J Clin Med. 2023 Jul 6;12(13):4527. doi: 10.3390/jcm12134527. PMID: 37445562; PMCID: PMC10342289.

RA-BE-REAL study

Time to discontinuation rates at 2 Years in b/tsDMARD Naïve and Experienced Patients Aged <65 and ≥65 Years



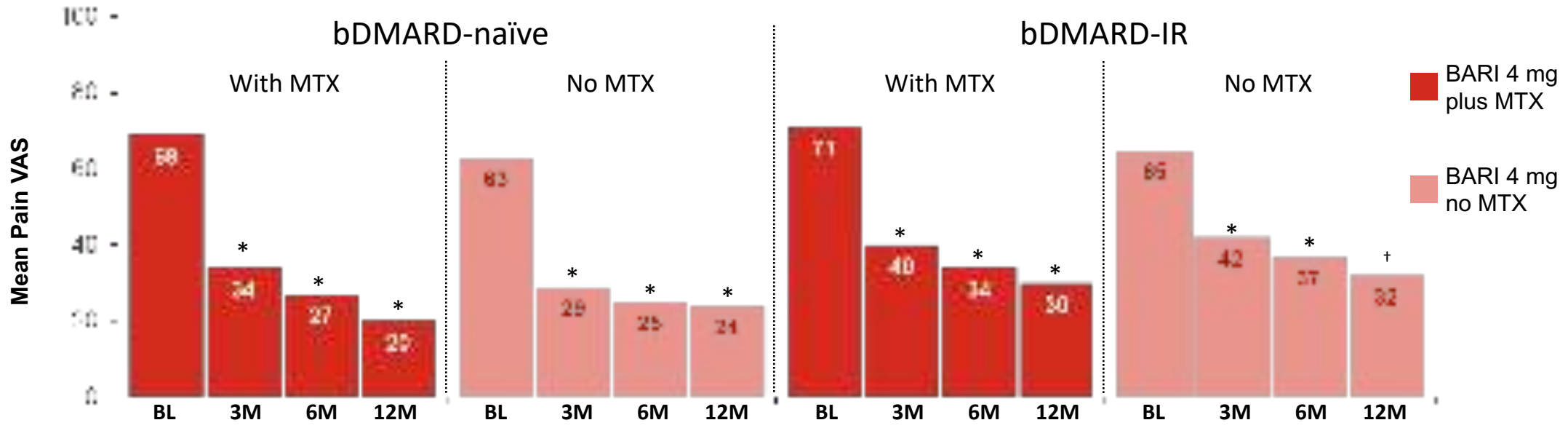
Alten R et al EULAR 2023 Milan Italy POS0848

Baricitinib Significantly Reduces Pain in Real-world Patients

Treatment Response

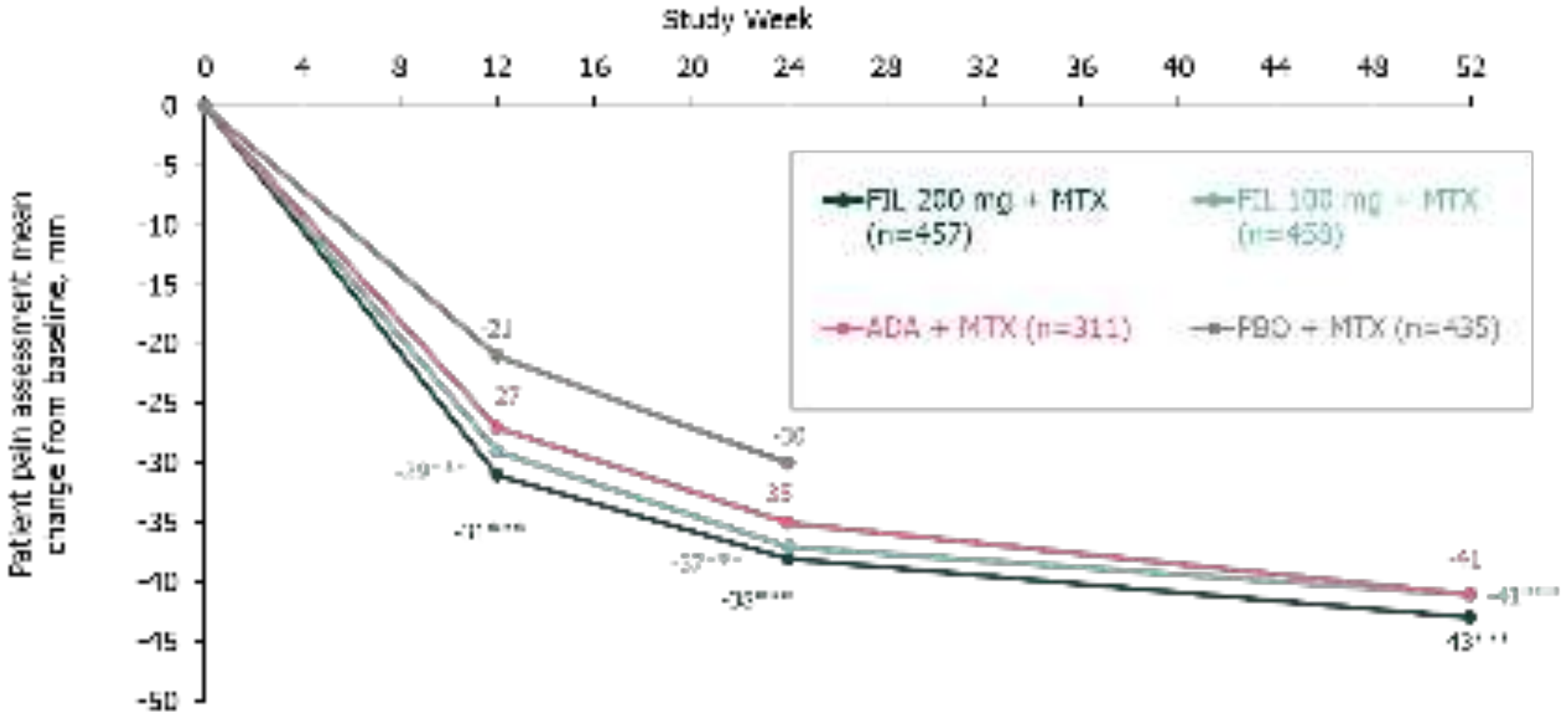
- Patients treated with baricitinib reported **significant reductions in pain VAS at 12 months, regardless of prior bDMARD experience or concomitant MTX**
- Most patients had a **significant reduction in pain VAS as early as 3 months**

Italian prospective study: Pain VAS over Time



*p<0.0001 versus BL; †p<0.01 versus BL.
bDMARD, biologic Disease-modifying Anti-rheumatic Drug; BL, Baseline; IR, Inadequate Responder; M, Month; MTX, Methotrexate; VAS, Visual Analog Scale.
Guidelli GM, et al. Clin Exp Rheumatol. 2021;39(4):868–73.

Patient pain assessment



***p<0.001 vs placebo.
ADA: adalimumab; FIL: filgotinib; MTX: methotrexate; PBO: placebo.
Combe B et al. Ann Rheum Dis 2021;80:848–858 (incl supplement).

CM-CSF


frontiers in Immunology

Roles of GM-CSF in the Pathogenesis of Autoimmune Diseases: An Update


ImmunoTargets and Therapy

REVIEW

GM-CSF: A Promising Target in Inflammation and Autoimmunity

Kevin HC Lee
Adrian A Achuthan
John A Hamilton

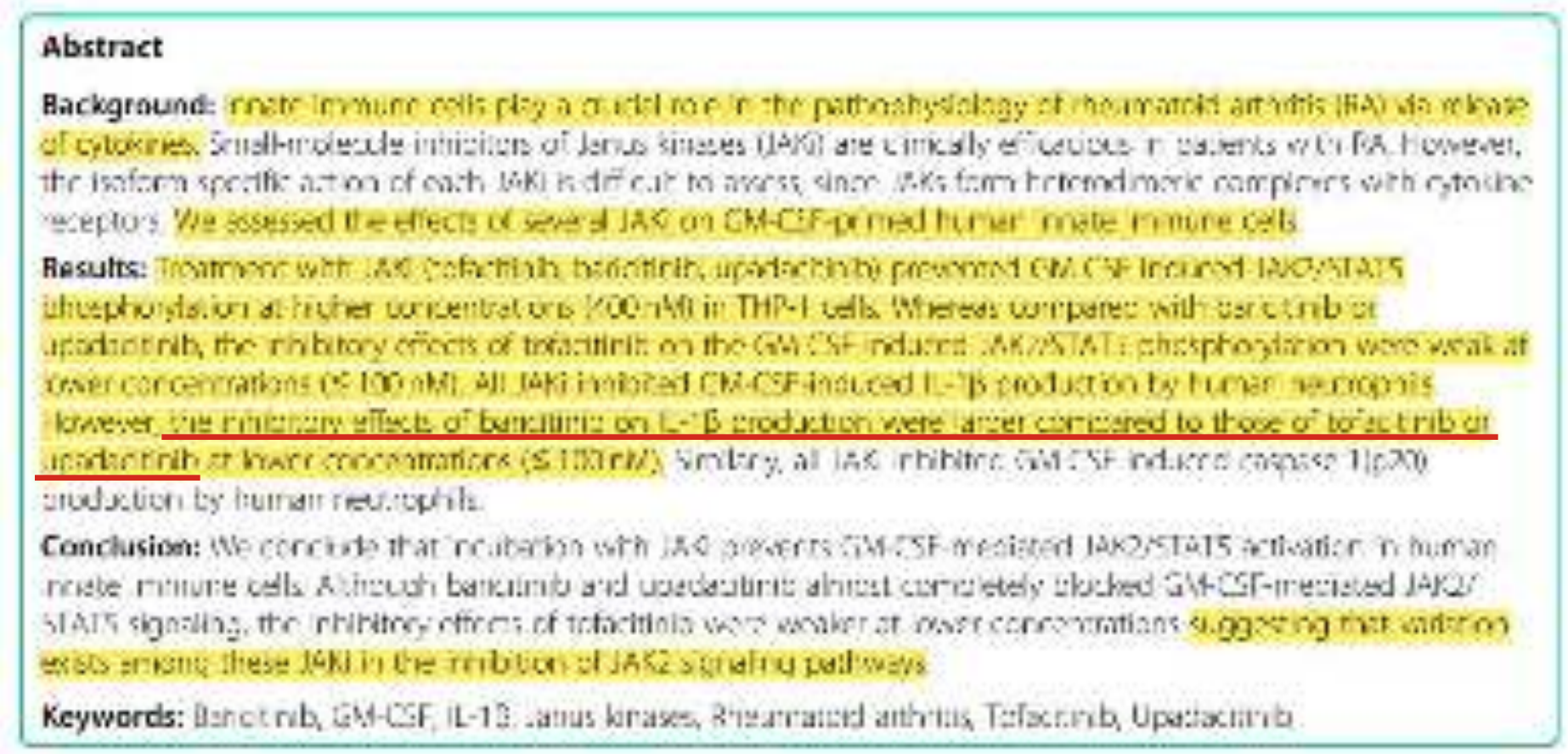

JEM

GM-CSF in Inflammation


RESEARCH ARTICLE | SEPTEMBER

GM-CSF Regulates Fusion of Mononuclear Osteoclasts into Bone-Resorbing Osteoclasts by Activating the Ras/ERK Pathway

JAK inhibitors impair GM-CSF-mediated signaling in innate immune cell



Abstract

Background: Innate immune cells play a crucial role in the pathophysiology of rheumatoid arthritis (RA) via release of cytokines. Small-molecule inhibition of Janus kinases (JAK) are clinically efficacious in patients with RA. However, the isoform specific action of each JAKi is difficult to assess since JAKs form heterodimeric complexes with cytokine receptors. We assessed the effects of several JAKi on GM-CSF-primed human innate immune cells.

Results: Treatment with JAKi (tofacitinib, baricitinib, upadacitinib) prevented GM-CSF-induced JAK2/STAT5 phosphorylation at higher concentrations (≥100 nM) in THP-1 cells. Whereas compared with baricitinib or upadacitinib, the inhibitory effects of tofacitinib on the GM-CSF-induced JAK2/STAT5 phosphorylation were weak at lower concentrations (≤ 100 nM). All JAKi inhibited GM-CSF-induced IL-1β production by human neutrophils. However, the inhibitory effects of baricitinib on IL-1β production were larger compared to those of tofacitinib or upadacitinib at lower concentrations (≤ 100 nM). Similarly, all JAKi inhibited GM-CSF-induced caspase-1(p20) production by human neutrophils.

Conclusion: We conclude that incubation with JAKi prevents GM-CSF-mediated JAK2/STAT5 activation in human innate immune cells. Although baricitinib and upadacitinib almost completely blocked GM-CSF-mediated JAK2/STAT5 signaling, the inhibitory effects of tofacitinib were weaker at lower concentrations suggesting that selectivity exists among these JAKi in the inhibition of JAK2 signaling pathways.

Keywords: Baricitinib, GM-CSF, IL-1β, Janus kinases, Rheumatoid arthritis, Tofacitinib, Upadacitinib

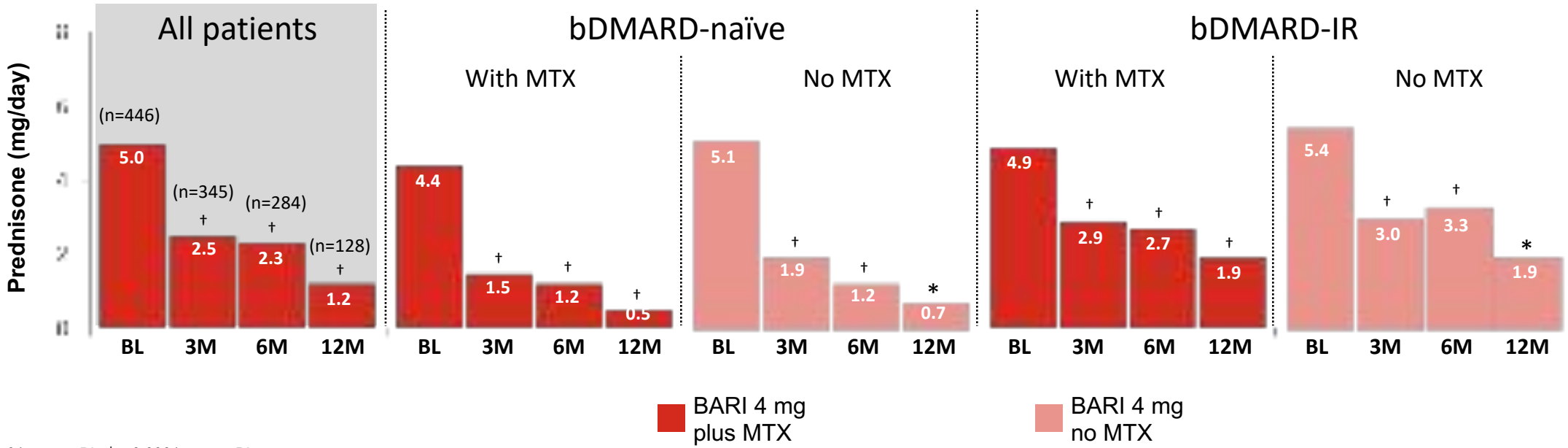
Fujita Y, Matsuoka N, Temmoku J, Furuya-Yashiro M, Asano T, Sato S, Matsumoto H, Watanabe H, Kozuru H, Yatsuhashi H, Kawakami A, Migita K. JAK inhibitors impair GM-CSF-mediated signaling in innate immune cells. BMC Immunol. 2020 Jun 15;21(1):35. doi: 10.1186/s12865-020-00365-w.

Baricitinib is Associated With Reduction in Steroid Use in a Real-world Setting

Treatment Response

- A **significant reduction in oral steroid dose** was observed as **early as at 3 months in patients receiving baricitinib,** regardless of prior bDMARD experience, and with or without concomitant MTX

Italian prospective study: Prednisolone daily dose



*p<0.01 versus BL; †p<0.0001 versus BL.
BARI, baricitinib; bDMARD, biologic Disease-modifying Anti-rheumatic Drug; BL, Baseline; IR, Inadequate Responder; M, Month; MTX, Methotrexate; n, number of patients within specified category.
Guidelli GM, et al. Clin Exp Rheumatol. 2021;39(4):868–73.

Simon David (Orcid ID: 0000-0001-8310-7820)
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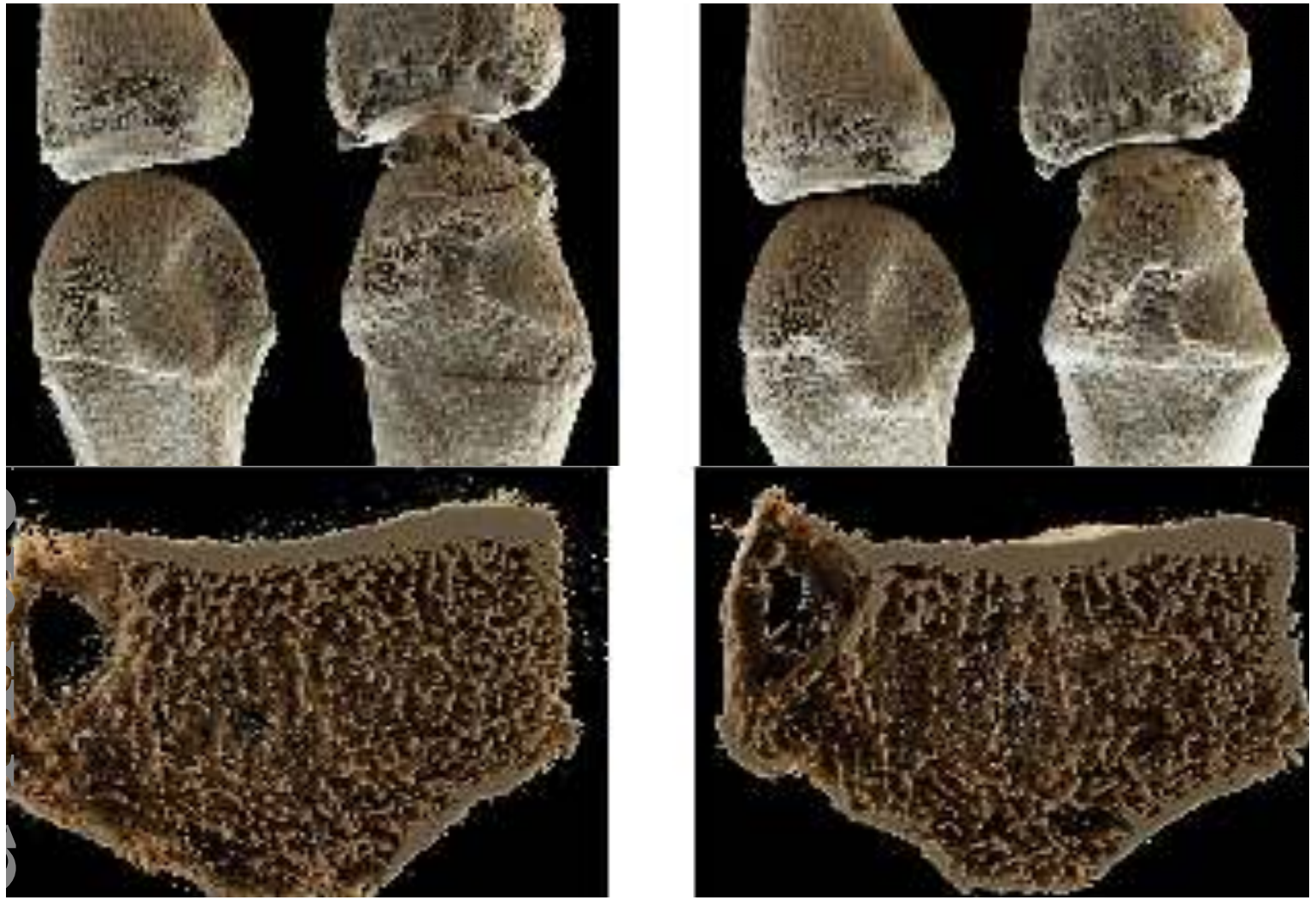
Baricitinib improves bone properties and biomechanics in patients with rheumatoid arthritis – results of the prospective interventional BARE BONE trial

Simon D, et al. Arthritis Rheumatol 2023. doi: 10.1002/art.42617.

Change in cortical bone structure and erosions at the metacarpophalangeal joints after 52 weeks of treatment visualized by high-resolution CT

Change of trabecular vBMD of the radius is clearly evident

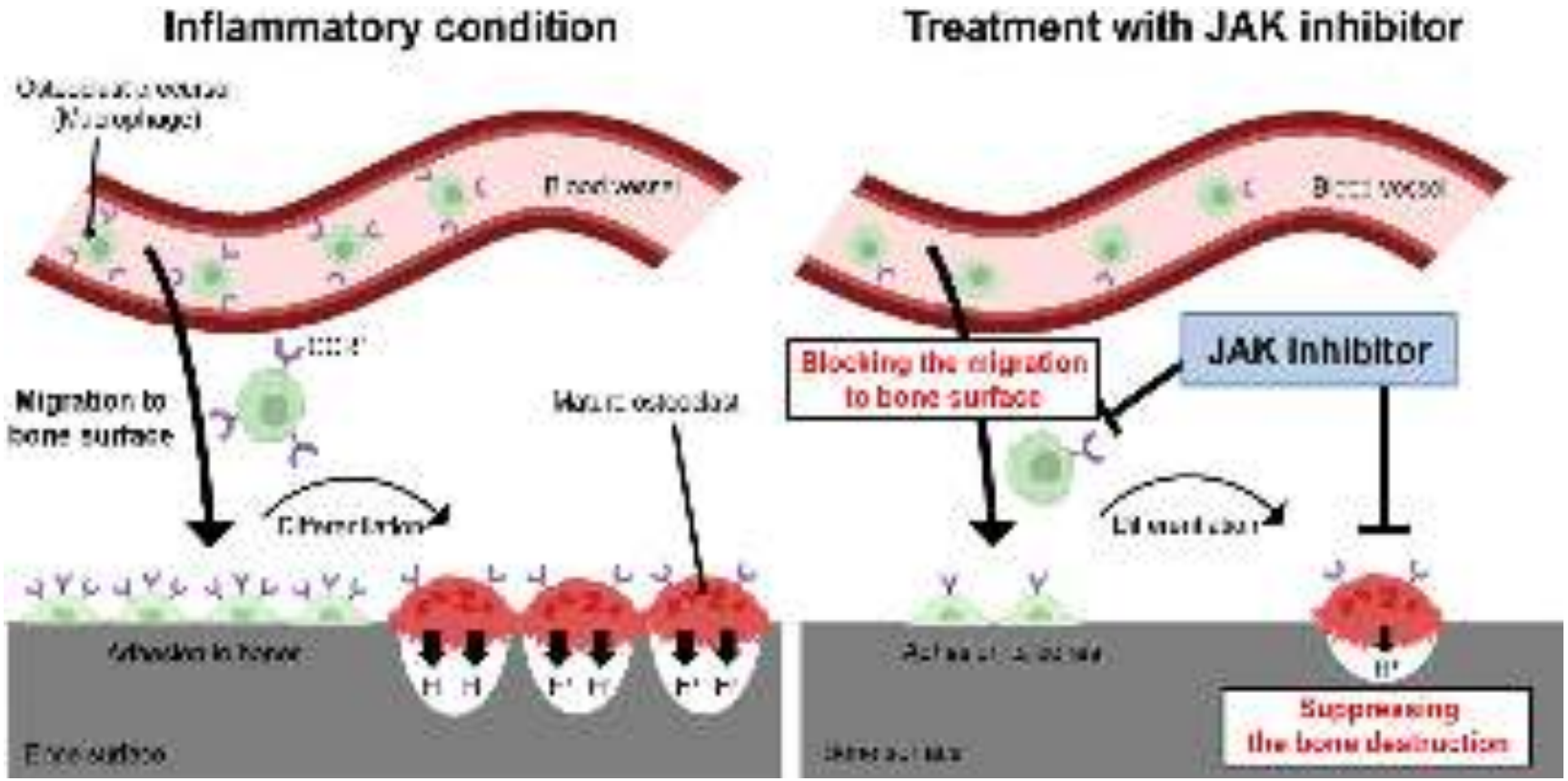


Yari et al. Inflammation and Regeneration (2023) 43:18
https://doi.org/10.1186/s41232-023-00268-4

RESEARCH ARTICLE Open Access

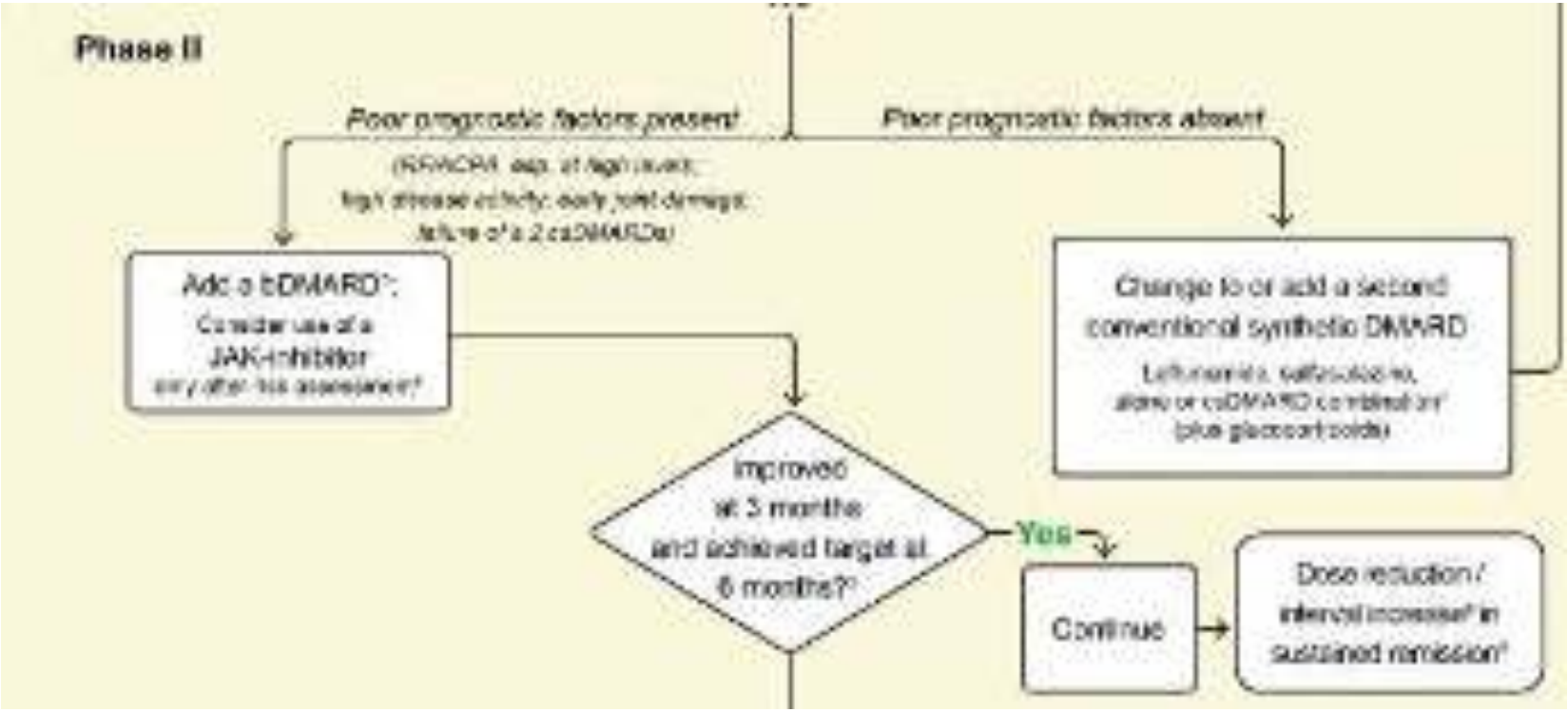
JAK inhibition ameliorates bone destruction by simultaneously targeting mature osteoclasts and their precursors

Shinya Yari[1,2], Junichi Kikuta[1,2,3*], Hotaka Shigyo[1], Yu Miyamoto[1,2], Daisuke Okuzaki[2,4], Yuki Furusawa[5], Masafumi Minoshima[6], Kazuya Kikuchi[2,6] and Masaru Ishii[1,2,3*]



2° lezione: Abbiamo una classe di farmaci estremamente efficaci, rapidi, semplici da somministrare (orali) e particolarmente utili nei pazienti con intenso dolore.

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update



Se l'obiettivo del trattamento non viene raggiunto con la prima strategia csDMARD, quando sono presenti fattori prognostici sfavorevoli, dovrebbe essere aggiunto un bDMARD; Possono essere presi in considerazione anche gli inibitori JAK, ma devono essere presi in considerazione i fattori di rischio pertinenti.*

Josef S Smolen et al. Ann Rheum Dis 2023;82:3-18

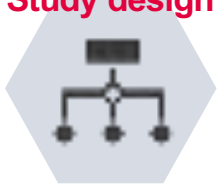
EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update

I seguenti fattori di rischio per eventi cardiovascolari e tumori maligni devono essere considerati quando si intende prescrivere un inibitore JAK:

- **Età superiore a 65 anni.**
- **Anamnesi di fumo, altri fattori di rischio cardiovascolare (come diabete, obesità, ipertensione),**
- **Altri fattori di rischio per malignità (anamnesi attuale o pregressa di malignità altri rispetto NMSC trattato con successo).**
- **Fattori di rischio per eventi tromboembolici (storia di infarto del miocardio o insufficienza cardiaca, cancro, trombofilia ereditaria, trombosi o una storia di trombosi).**
- **Contraccettivi ormonali combinati o terapia ormonale sostitutiva.**
- **Interventi di chirurgia maggiore o immobilita'.**

Josef S Smolen et al. Ann Rheum Dis 2023;82:3-18

KEY DIFFERENCES BETWEEN RCTS AND RWE

	RCTs	RWE
Patient population 	• Controlled, narrowly **defined patient population**[1,2] • **Randomized** treatment assignment[3]	•More varied medical settings and more **diverse patient populations**[3] •Treatment assignment based on **physician judgement**, rather than random assignment[5]
Methodology 	• **Robust methodology, reducing confounding factors**[3] • Trial protocol may force uncommon clinical scenarios, and comparison group may not represent current SoC[1] • **Smaller sample sizes limit the ability to detect minor treatment effects** or rare AEs[1]	• Statistical approaches reduce selection bias[4,6] • Observational studies are more representative of clinical practice[6] • **Larger sample sizes** may minimize bias[6]
Study design 	• Experimental/interventional/prospective[4] • **Short follow-up period**[4] • Blinded, controlled trials and other interventional studies[3,4]	• Retrospective/prospective/observational[4] • **Long follow-up period**[4] • Varied and blended sources[3,6]

AE=adverse event; RCT=randomized controlled trial; RWE=real-world evidence; SoC=standard of care.

1. Nallamothu BK, et al. *Circulation.* 2008;118:1294-1303. **2.** Nikiphorou E, et al. *Nat Rev Rheumatol.* 2017;13:503-510. **3.** Katkade VB, et al. *J Multidiscip Healthc.* 2018;11:295-304.
4. Blonde L, et al. *Adv Ther.* 2018;35:1763-1774. **5.** FDA. Framework for FDAs real world evidence program. https://www.fda.gov/media/120060/download. Accessed Apr 08, 2022.
6. Garrison LP, et al. *Value Health.* 2007;10:326-335.

Real-world Studies in RA Versus RCTs

General characteristics of patients with RA in observational studies vs RCTs[1]

	Real-world		RCTs
	11.5 years	**3.1 years longer** disease duration p<0.001	8.4 years
	55.5 years	**3.0 years** older p<0.001	52.5 years
	3.6	**1.6 more** prior DMARD p=0.001	2.0

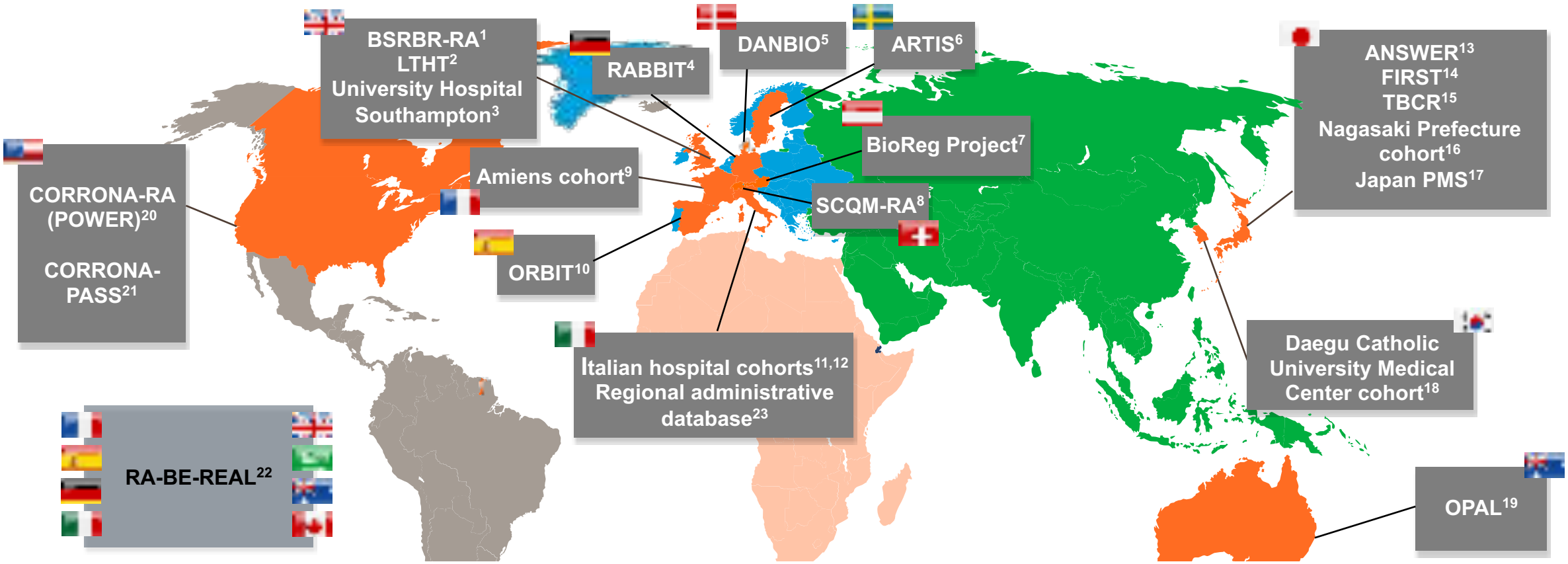
>90%

of patients in observational clinical cohorts **do not meet inclusion criteria** for RCTs for targeted agents[2]

	Real-world	RCT
Mean DAS28 at enrolment[2]	3.65 to 3.87	6.59

1. Kilcher G, et al. Rheumatology (Oxford). 2018;57(2):354–69. 2. Vashisht P, et al. Arthritis Care Res (Hoboken). 2016;68(10):1478–88.

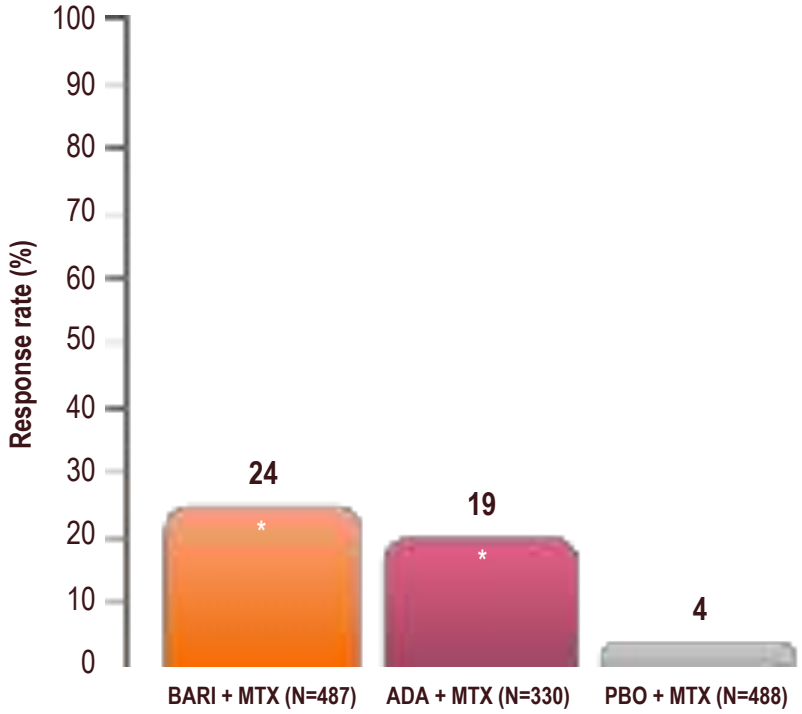
The Global Baricitinib Experience in RA



RA, Rheumatoid Arthritis.
1. Edwards CJ, et al. Rheumatology. 2021;60(Supplement_1):Abstract O33. 2. Fitton J, et al. Rheumatology. 2021;60(9):4048–54. 3. Lwin MN, et al. Rheumatology. 2021;60(Supplement_1):Abstract O10. 4. Schäfer M, et al. RMD Open. 2020;6(3):e001290. 5. Egeberg A, et al. Semin Arthritis Rheum. 2022;53:151979. 6. Barbulescu A, et al. Rheumatology. 2022; doi:10.1093/rheumatology/keac068 (Ahead of print). 7. Leeb BF, et al. Rheumatology (Sunnyvale). 2021;11:1–7. 8. Gilbert B, et al. Ann Rheum Dis. 2021;80(Suppl 1):577–8. 9. Deprez V, et al. J Clin Med. 2020;9(10):3319. 10. Hernández-Cruz B, et al. Rheumatol Ther. 2022;9:589–608. 11. Guidelli GM, et al. Clin Exp Rheumatol. 2021;39(4) 868–73. 12. Tesei G, et al. Ther Adv Musculoskelet Dis. 2021; doi:13:1759720X211014019. 13. Ebina K, et al. Clin Rheumatol. 2021;40(7):2673–80. 14. Miyazaki Y, et al. Ann Rheum Dis. 2021;80(9):1130–6. 15. Asai S, et al. Clin Rheumatol. 2021;40(8):3143–51. 16. Iwamoto N, et al. Arthritis Res Ther. 2021;23(1):197. 17. Takagi M, et al. Mod Rheumatol. 2022;roac089. doi:10.1093/mr/roac089. Online ahead of print. 18. Kim S-K, et al. Medicine (Baltimore). 2021;100(30):e26739. 19. Ciciriello S, et al. Ann Rheum Dis. 2021;80:330–1. 20. Patient Outcomes: Real World Evidence in Rheumatoid Arthritis (POWER) https://clinicaltrials.gov/ct2/show/NCT04512573 (Accessed September 2022). 21. Olumiant Summary of Risk Management Plan. EMA 2021. 22. Alten R, et al. Poster presented at EULAR 2022. Poster POS0666. 23. Perrone V, et al. Rheumatol Ther. 2020;7(3):657–65.

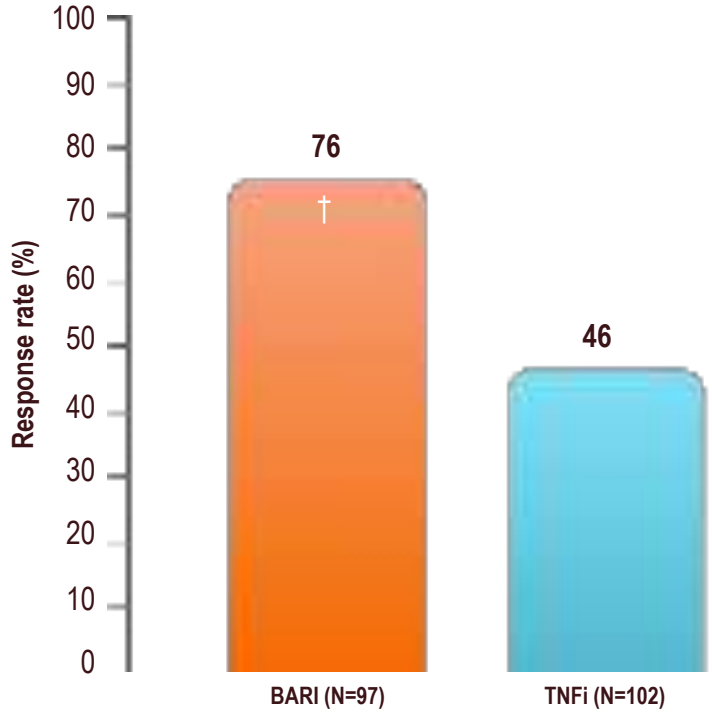
BARI demonstrated superior outcomes vs TNFi in both RCT and real-world setting

RA-BEAM: Proportion of patients achieving DAS28 remission (DAS28-CRP <2.6) at 12 weeks[1]



Patients who were MTX-IR and had a mean disease duration 10 years[1]

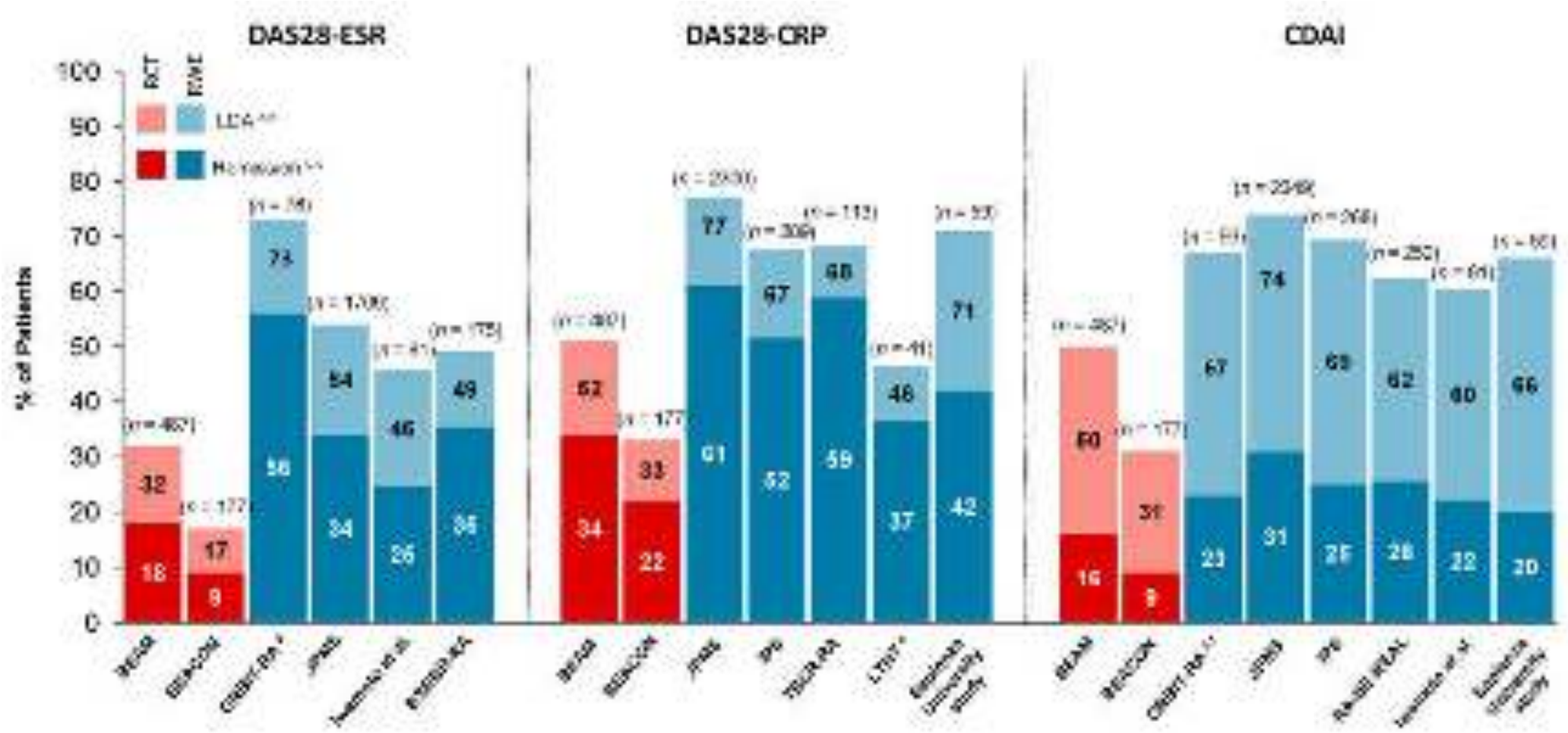
PERFECT: Proportion of patients achieving DAS28 remission (DAS28-CRP <2.6) at 12 weeks[2]



Patients who were csDMARD-IR previously treated according to treat-to-target principles with disease duration <5 years and no contraindications for b/tsDMARDs[2]

*p≤0.001 BARI or ADA vs PBO. †p<0.001 BARI vs TNFi.
ADA, adalimumab; BARI, baricitinib; b/cs/tsDMARD-IR, biologic/conventional synthetic/targeted synthetic disease-modifying antirheumatic drug; DAS28-CRP, Disease Activity Score 28 C-reactive protein; IR, inadequate response; MTX, methotrexate; PBO, placebo; RCT, randomised controlled trial; TNFi, tumour necrosis factor inhibitor.
1. Taylor PC, et al. N Engl J Med 2017;376:652–62 (SUPPL APPENDIX). 2. Oude Voshaar MAH, et al. Abstract to be presented at EULAR 2023, 31 May–3 June, Milan, Italy.

Treatment Outcomes for Baricitinib in Real-Life Settings



Taylor PC, Laedermann C, Alten R, Feist E, Choy E, Haladyj E, De La Torre I, Richette P, Finckh A, Tanaka Y. A JAK Inhibitor for Treatment of Rheumatoid Arthritis: The Baricitinib Experience. J Clin Med. 2023 Jul 6;12(13):4527. doi: 10.3390/jcm12134527. PMID: 37445562; PMCID: PMC10342289.

CLINICAL SCIENCE

Safety profile of upadacitinib in patients at risk of cardiovascular disease: integrated post hoc analysis of the SELECT phase III rheumatoid arthritis clinical programme

Roy Fleischmann,[1] Jeffrey R Curtis,[2] Christina Charles-Schoeman ,[3] Eduardo Mysler,[4] Kunihiro Yamaoka,[5] Christophe Richez ,[6] Hannah Palac,[7] Deanne Dilley,[7] Jianzhong Liu,[7] Sander Strengholt,[7] Gerd Burmester [8]

ABSTRACT

Objective Increased risk of serious adverse events (AEs) was reported for tofacitinib relative to tumour necrosis factor inhibitor therapy in patients with rheumatoid arthritis (RA) aged ≥50 years enriched for cardiovascular (CV) risk (ORAL Surveillance). We assessed post hoc the potential risk of upadacitinib in a similar RA population.

Fleischmann R, *et al*. Ann Rheum Dis 2023;0:1–12. doi:10.1136/ard-2023-223916

Methodology

Populations analyzed from a pooled safety analysis from 6 phase 3 trials in patients receiving 15mg QD UPA (with or without csDMARD[s]), 40mg ADA EOW (in combination with MTX), or MTX monotherapy

1 Overall RA population (UPA-ADA-MTX)

2 Overall higher CV risk population: patients aged ≥50 years with ≥1 CV risk factor

3 SELECT-COMPARE higher CV risk population (assessed UPA 15 mg vs ADA 40mg EOW): patients aged ≥50 years with ≥1 CV risk factor

Patients are excluded in case of (based on original protocol of the pivotal trials):

- Previous malignancies (except for successfully treated NMSC or localized carcinoma in situ of the cervix)
- Moderate to severe congestive heart failure sc
- Uncontrolled hypertension
- Recent (within past 6 months) myocardial infarction or stroke, and some other CV conditions

- ADA, ADA; AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; MTX, methotrexate; PY, patient-years; TEAE, treatment-emergent adverse event

Fleischmann R, et al. Ann Rheum Dis 2023;0:1–12. doi: 10.1136/ard-2023-223916

Methodology Cont'd

CV risk factors were selected based on the ORAL Surveillance inclusion criteria (when collected)*:

1. Prior CV event (defined as any medical history event with a system organ class of "cardiac disorders" per MedDRA version 25.0)
2. Hypertension as recorded in the past medical history but not based on measured BP values in the trial
3. Diabetes mellitus
4. Current or former tobacco/nicotine use
5. Baseline HDL-C levels <40 mg/dL.

*family history of premature coronary heart disease and presence of extra-articular RA were not available within the UPA RA program

Fleischmann R, et al. Ann Rheum Dis 2023;0:1–12. doi: 10.1136/ard-2023-223916

Conclusioni dello studio

- In this integrated post-hoc analysis from 6 UPA phase III trials, the incidence of MACE, malignancy (excluding NMSC), VTE, and mortality were typically higher in patients at increased CV risk compared to the overall RA population, but the **rates remained generally similar between UPA, ADA and MTX monotherapy**
- In the SELECT-COMPARE higher-risk population, UPA did not appear to be associated with increased risk of any examined TEAEs, except for HZ, NMSC, and SIE in patients aged ≥65 years.
- In the higher CV risk population, patients with MACE and VTE events had worse disease control than those without these events
- These findings in patients with RA at risk of potential CV events may help to clinically contextualize the overall risk profile of UPA

3° lezione: La realtà non è sempre come ce la dipingono

REGIONE LAZIO

REGIONE LAZIO

DETERMINAZIONE - GSA

C) Effetti collaterali e sospette reazioni avverse

Per eventuali effetti collaterali ed interazioni farmacologiche si rimanda alle schede tecniche di ciascun farmaco e si ricorda l'importanza della segnalazione delle sospette reazioni avverse da parte dei clinici e dei pazienti stessi.

La legislazione vigente definisce la reazione avversa come un effetto nocivo e non voluto conseguente all'uso di un medicinale (art. 1 comma 2a D.M. Salute 30/04/2015). La normativa richiede a tutti gli operatori sanitari e ai cittadini di segnalare qualsiasi sospetta reazione avversa (grave e non grave, nota e non nota) derivanti da errore terapeutico, abuso, misuso, uso off-label, sovradosaggio ed esposizione professionale nonché la mancata efficacia. In relazione al significato di uso off-label si precisa che questa condizione riguarda l'uso del medicinale non in accordo con le condizioni di autorizzazione non solo nelle indicazioni terapeutiche, ma anche nella via di somministrazione e nella posologia. A partire dal 20 giugno 2022, una sospetta reazione avversa può essere segnalata attraverso una delle seguenti modalità:

- compilando la scheda di segnalazione e inviandola via e-mail al Responsabile di farmacovigilanza della

REGIONE LAZIO

Accedi con le tue credenziali

[redacted]

Autenticazione a due fattori

QRcode | SMS

Perché l'autenticazione a due fattori?

Per una maggiore sicurezza del tuo account. L'autenticazione si svolge in due passaggi

Il primo è quello di inserire il tuo nome utente e la tua password e il secondo è quello di inserire un codice che sarà generato e ti sarà

ALLEGATO

Centro prescrittore _____

Medico prescrittore (cognome, nome) _____

Tel. _____ e-mail _____

Paziente (cognome, nome) _____

Data di nascita _____ sesso M ☐ F ☐ _____ peso (Kg) _____

Codice fiscale |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_| Tel._____

ASL di residenza_____ Regione _____ Prov._____

Medico di Medicina Generale _____ recapito Tel. _____

+

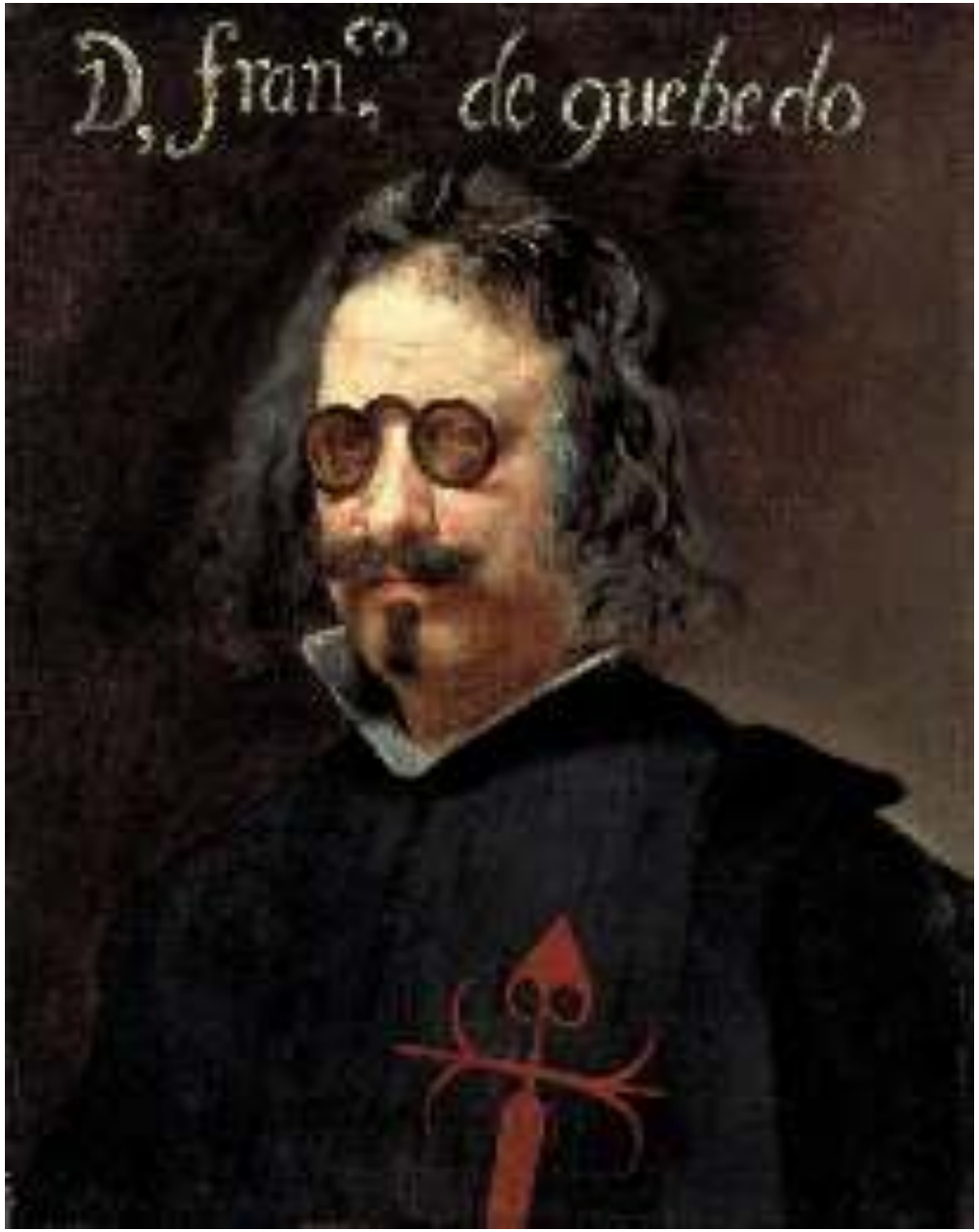
= SOLUZIONE

RA-BE-REAL study

Patient Baseline Characteristics

	BARI (n=510)	b/tsDMARDs (n=583)
Age, years, mean (SD)	59.1 (13.2)	57.0 (13.9)
Duration of RA, years, mean (SD)	10.1 (9.1)	8.9 (9.7)
b/tsDMARD treatment any time before enrollment, n (%)		
Naïve	245 (48.0)	344 (59.1)
1 b/tsDMARD	68 (13.3)	55 (9.8)
2 b/tsDMARDs	111 (21.8)	79 (14.0)
>2 b/tsDMARDs	86 (16.9)	85 (15.1)
Oral GCCs at time of enrollment, n (%)		
Yes	219 (42.9)	247 (43.9)
No	291 (57.1)	316 (56.1)
Concomitant use of csDMARDs, n (%)		
With any csDMARD	250 (49.0)	387 (68.7)
Monotherapy	260 (51.0)	176 (31.3)

Alten R et al EULAR 2023 Milan Italy POS0848



4° lezione: Poderoso caballero es Don Dinero.

JAK-STAT Signaling Overview: many “Actors”

- More than 40 different cytokines and their receptors (Type I and II)
- 4 NRTKs (JAK1, JAK2, JAK3, and TYK2)
- 7 STAT members (STAT 1, -2, -3, -4, -5a, -5b, and -6)
- Phosphatases, including SHP1, are also involved in feedback inhibition
- 8 SOCS feedback inhibitors (SOCS 1-7, CISH)
- 7 PIAS (PIAS1, PIASxα, PIASxβ, PIAS3, PIAS3L, PIASy, PIASyE6)

JAK = Janus kinase; **NRTK** = Nonreceptor tyrosine kinase; **SHP** = SH2 domain containing protein; **SOCS** = Suppressor of cytokine signaling; **STAT** = Signal transducer and activator of transcription; **PIAS** = protein inhibitors of activated STAT **TYK** = Nonreceptor tyrosine-protein kinase

1. O'Shea JJ and Murray PJ. *Immunity* 2008;28:477-87. **2.** Farabegoli F et al. *J Clin Pathol* 2005;58:1046-50. **3.** Constantinescu SN et al. *Trends Endocrinol Metab* 1999;10:18-23. **4.** O’Shea JJ et al. *Annu Rev Med* 2015;66:311-28. **5.** Kaminska B and Swiatek-Machado K. *Expert Rev Clin Immunol* 2008;4:93-112. **6.** O'Shea JJ et al. *Ann Rheum Dis* 2013;72(Suppl 2):ii111-5. **7.** Seif F. Cell Commun Signal. 2017 Jun 21;15(1):23.. Hodge JA. Clin Exp Rheumatol. 2016 Mar-Apr;34(2):318-28

GRAZIE