Nuove prospettive nel trattamento dell'artrite reumatoide

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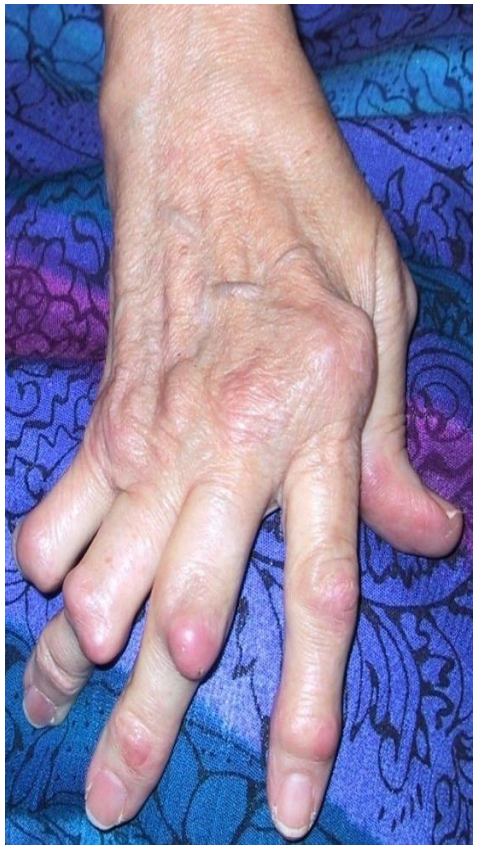
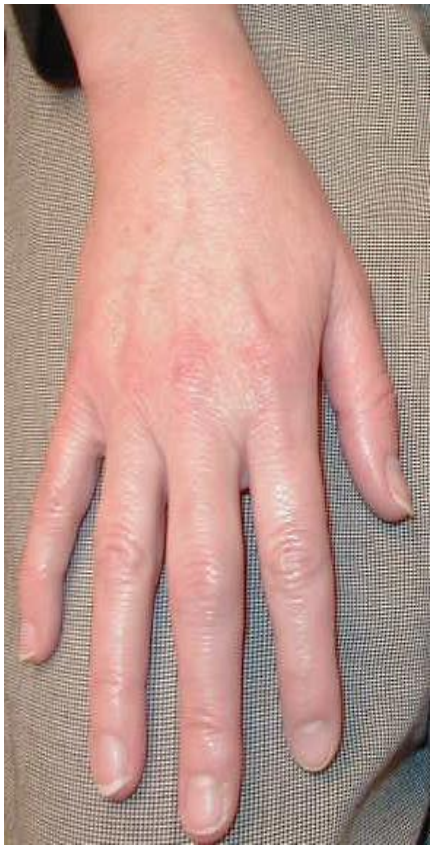
Mano del pz con AR 30 anni fa e mano pz ad oggi





Terapie attualmente disponibili per AR

- Several therapy options exist for the treatment of RA:

Non-steroidal anti-inflammatory drugs (NSAIDs) Therapies given to manage chronic pain, inflammation, and swelling associated with RA	**Glucocorticoids (GCs)** Used to reduce inflammation and disease activity in RA
csDMARDs A class of drugs used to slow progression of RA • Methotrexate (MTX) • Leflunomide (LEF) • Hydroxychloroquine (HCQ) • Sulfasalazine	**TNF biologics** bDMARDs targeting tumor necrosis factor α (TNF-α)
Non-TNF biologics bDMARDs targeting non-TNF-α elements of the immune system Sarilumab/Tocilizumab • Abatacept • Rituximab	**Targeted synthetic DMARDs (tsDMARDs)** Synthetic drugs with a specific target • Tofacitinib • Baricitinib

Le maggiori limitazioni delle terapie disponibili per AR

- **Pazienti con scarsa risposta**
- Pazienti che sviluppano effetti collaterali
- Via di somministrazione parenterale
- Costo della terapia
- Potenziale immunogenico con possibile perdita di risposta nel tempo

Dolore, fatigue, stress e umore sono strettamente correlati nel paziente con AR[1]

- Il dolore è il fattore principalmente responsabile della comparsa e del grado della fatigue[2]
- Il dolore si intensifica all'aumentare della fatigue[1]

Analisi di **>60** articoli scientifici

Dolore e fatigue permangono nonostante il raggiungimento della remissione o di una bassa attività di malattia[3]

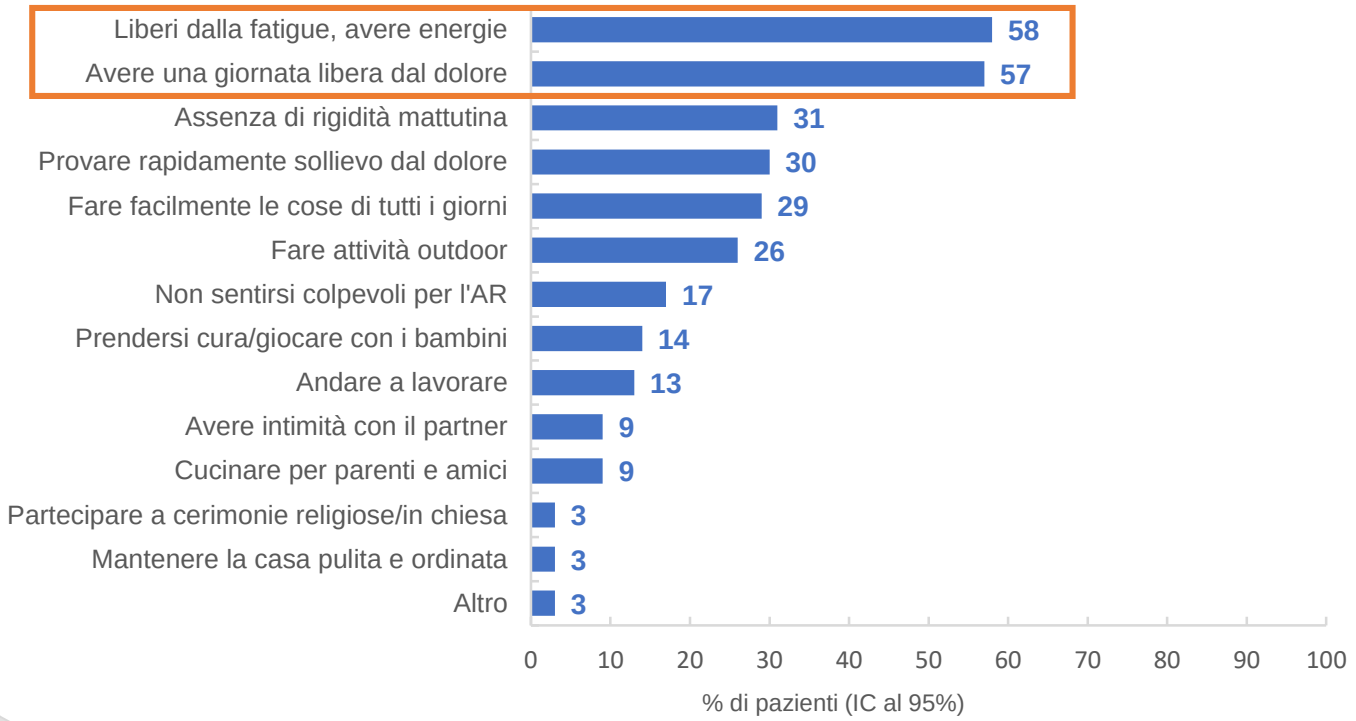
Revisione sistematica della letteratura che ha incluso 68 articoli scientifici e che ha valutato i sintomi residui e il loro impatto su pazienti adulti con AR in remissione o con bassa attività di malattia.[3]

Nonostante l'ampia gamma di trattamenti disponibili per l'AR, **le esigenze del paziente in termini di dolore, funzione fisica, funzione mentale e fatigue rimangono ancora insoddisfatte**[4]

1. Ahlstrand I. et al.; Disabil Rehabil 2012; 34 (15):1245-53.
2. Groth Madsen S. et al.; Scand J Rheumatol 2016; 45 (4): 255–261.
3. Ishida M. et al.; Mod Rheumatol 2018; 11:1-11.
4. Taylor P.C. et al.; Rheumatol Int 2016; 36 (5): 685-95.

Riduzione del dolore e della fatigue nel paziente con AR: una sfida quotidiana[1]

Essere liberi dal dolore e dalla fatigue è considerato uno degli **indicatori più rilevanti di "una giornata positiva"** per il paziente con AR[1]



Definizione di una «giornata positiva». Dati provenienti da 1 *survey* internazionale condotta su pazienti donne affette da AR (n=1.958).
Dati da Figura 5 di 1.

1. Strand V. et al.; J Rheumatol 2015; 42 (11): 2046-54.

Quanto sarebbe importante essere efficaci su dolore e fatigue al fine di raggiungere il “Good Day”?

L’efficacia sulla fatigue (oltre che sul dolore) garantisce un trattamento “completo”, patient-oriented e non solo disease-oriented

Smith SM, Wallace E, O'Dowd T, Fortin M. Cochrane Database Syst Rev. 2016 Mar 14;3:CD006560.

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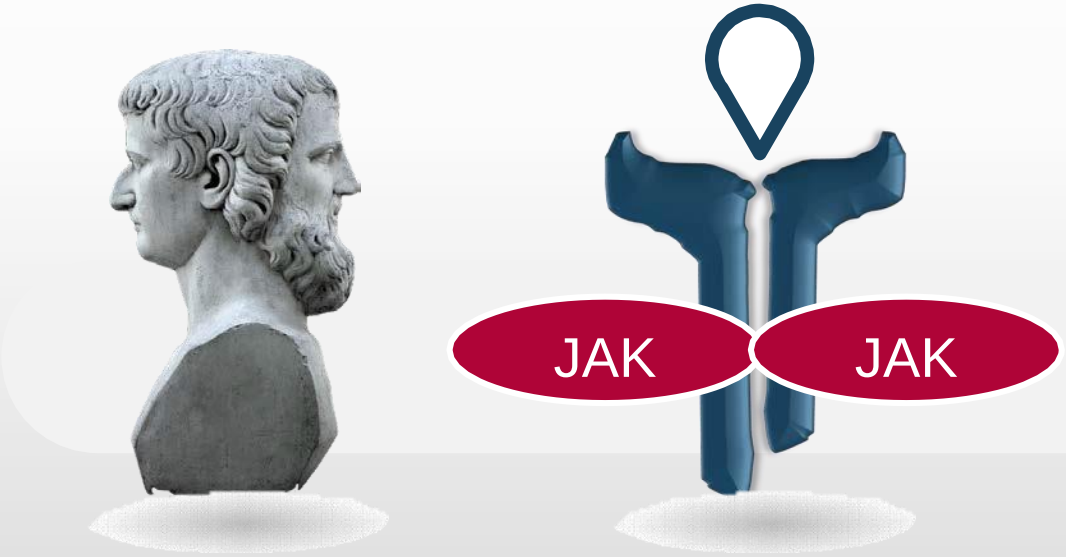
La famiglia JAK

I JAK sono proteine intracellulari, tirosin chinasi non recettoriali, che trasducono segnali mediati da citochine attraverso il percorso JAK-STAT1

- Four JAK family members: JAK1, JAK2, JAK3 and TYK2[2]
- Seven STAT family members: STAT1, 2, 3, 4, 5a, 5b and 6 activate transcription[3]



JAK, janus kinase: STAT, signal transducers and activators of transcription; TYK, tyrosine kinase;

Figure adapted from Shuai K & Lui B. Nat Rev Immunol 2003;3:900–911.
Image source: Shutterstock.

1. Roskoski R Jr. Pharmacol Res 2016;111:784–803; 2. Ghoreschi K et al. Immunol Rev 2009;228:273–287: 3. O'Sullivan LA et al. Molec Immunol 2007;44:2497–2506.

Development of JAK Inhibitors for Autoimmune Diseases

- Questi inibitori sono piccole molecole che entrano nella cellula e funzionano competendo con l'ATP e limitando l'attività JAK1,2,JAK3 o TYK2
- ,

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

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.

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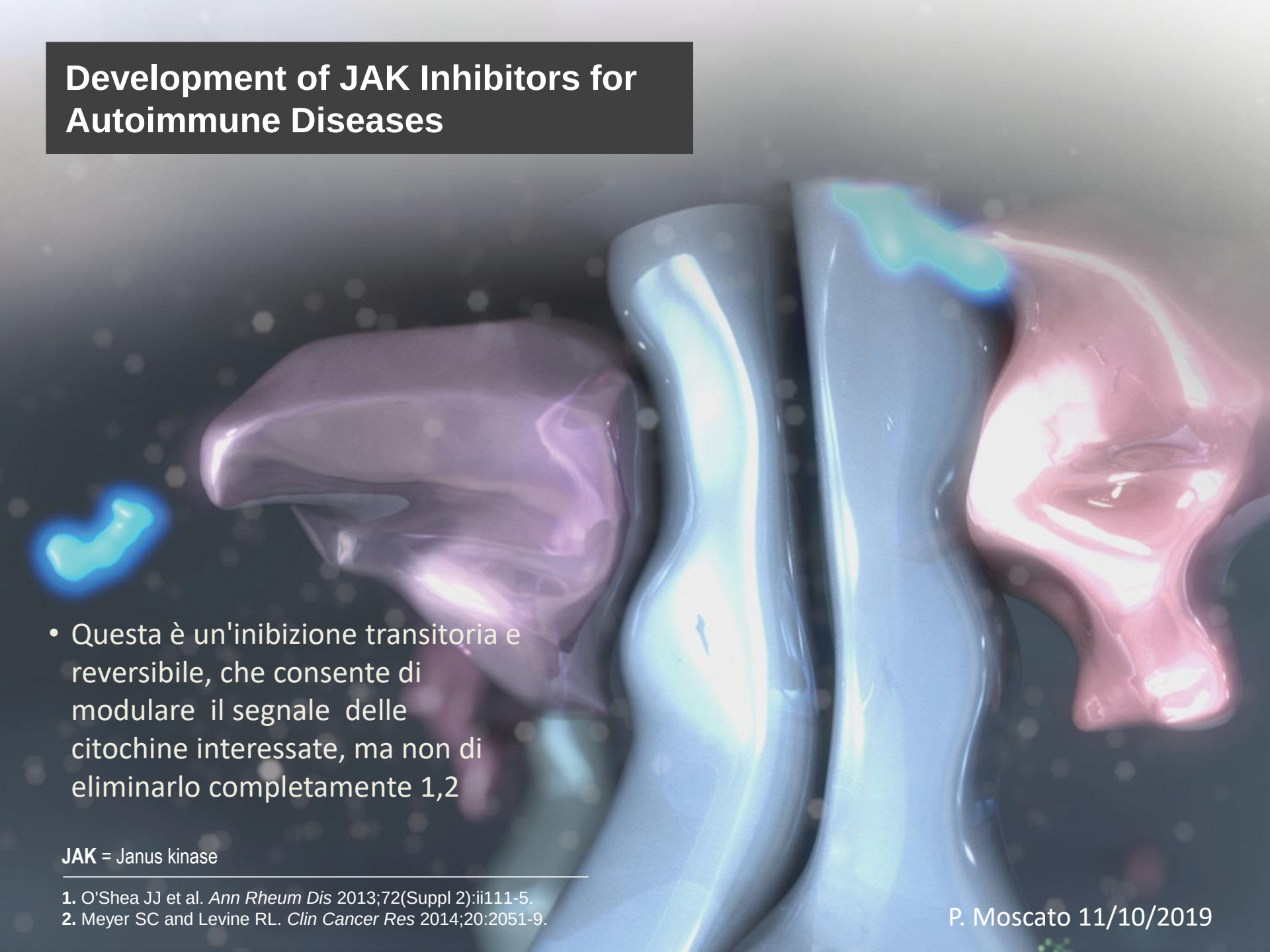
Development of JAK Inhibitors for Autoimmune Diseases



- Questa è un'inibizione transitoria e reversibile, che consente di modulare il segnale delle citochine interessate, ma non di eliminarlo completamente 1,2

JAK = Janus kinase

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.

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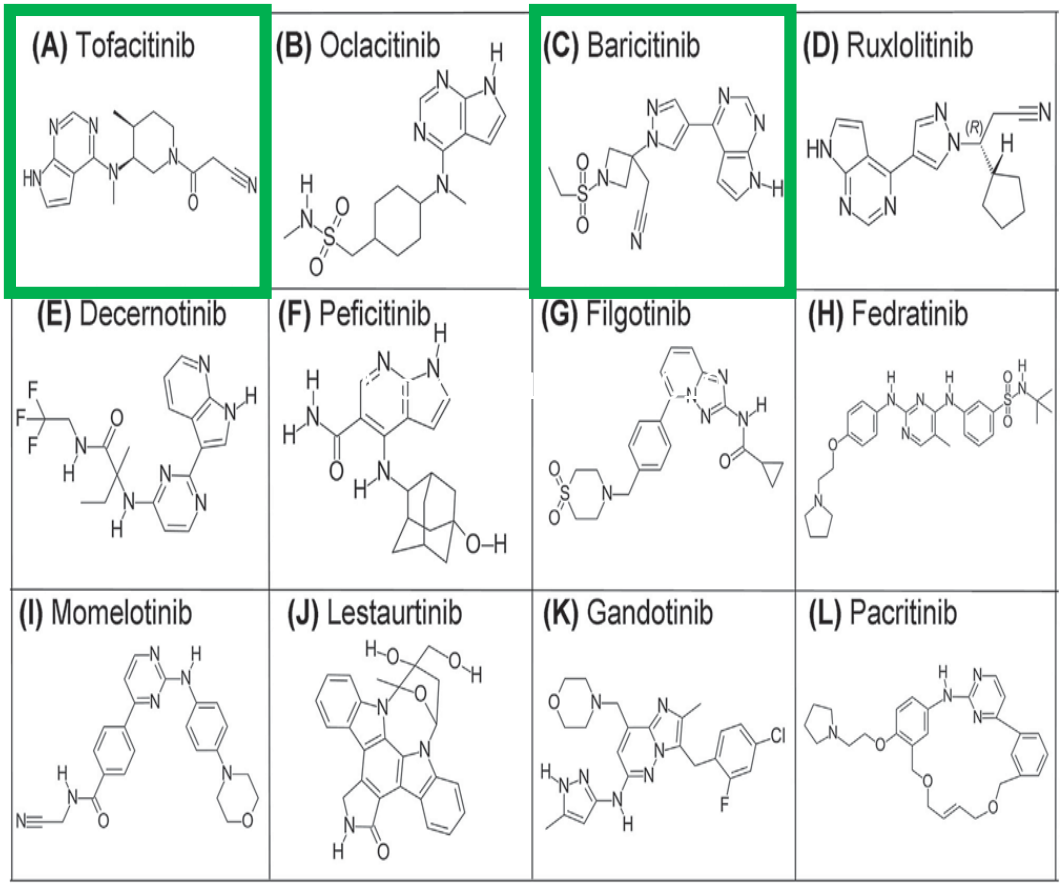
Quali JAK inhibitors?

Attualmente disponibili

- **Tofacitinib**
- **Baricitinib**



In sviluppo:

- Upadacitinib
- Decernotinib
- Filgotinib
- Peficitinib

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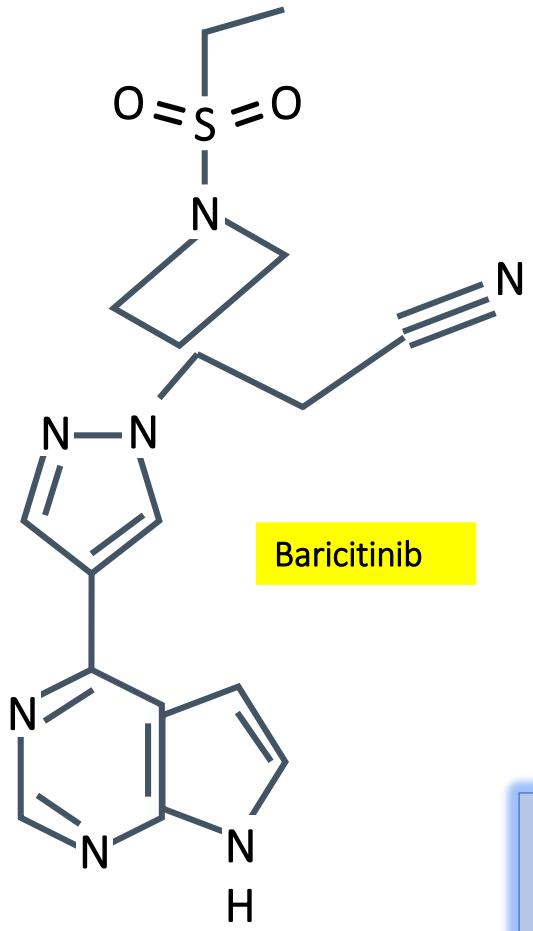
Smolen JS, et al. Ann Rheum Dis 2014;73:3–5.

Baricitinib
Efficacia e sicurezza

Baricitinib



Baricitinib

- **Inibitore altamente selettivo di JAK1/JAK2**
  - Potenza e selettività molto elevate per JAK2 e JAK1
  - Minor potenza per JAK3 o TYK2
- **Rapidamente assorbito**
  - Picchi di concentrazione plasmatica raggiunti entro 1.5h post-dose (C_{max} = ~ 94-112 nM; 4-mg QD)
- **Breve emivita rispetto ai biologici**
  - ~12.5 h nei pazienti con AR
- **Clearence renale**
  - 69% eliminato attraverso le urine

Grazie alla sua PK (costante di dissociazione) e al legame transitorio, ci si aspetta che baricitinib inibisca il signaling citochinico solo per qualche ora al giorno.

Shi JG et al. *J Clin Pharm*acol. 2014;54(12):1354-61
O'Shea JJ et al. *Annu Rev Med* 2015;66:311-28
Zhang X et al. *Arthritis Rheumatol* 2015;67(Suppl. 10). Abstract 485

Norman P. *Expert Opin Investig Drugs* 2014;23(8):1067-77
Data on file, Eli Lilly and Company
Olumiant SmPC. Utrecht, The Netherlands: Eli Lilly Nederland B.V., 2017

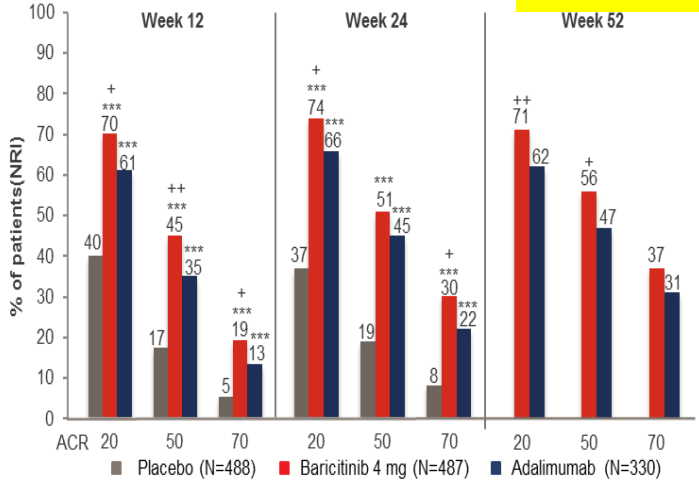
Efficacia di bariticitinib consistente in diverse popolazioni

Risposta ACR20/ACR50/ACR70

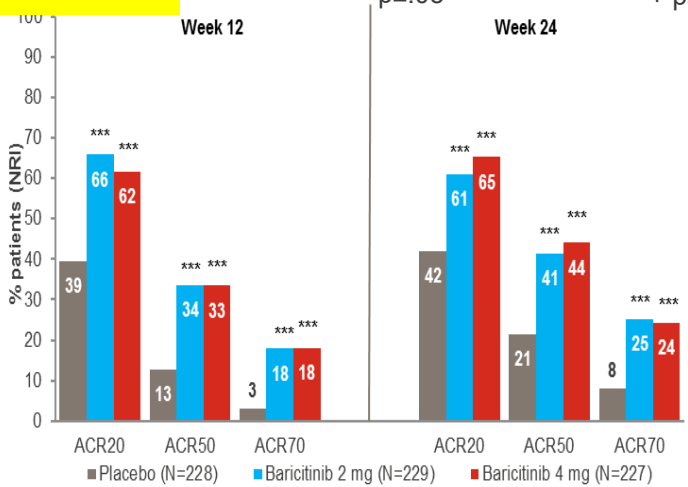
P-value vs. Placebo
** p≤.001
** p≤.01
* p≤.05

P-value vs. Adalimumab
+++ p≤.001
++ p≤.01
+ p≤.05

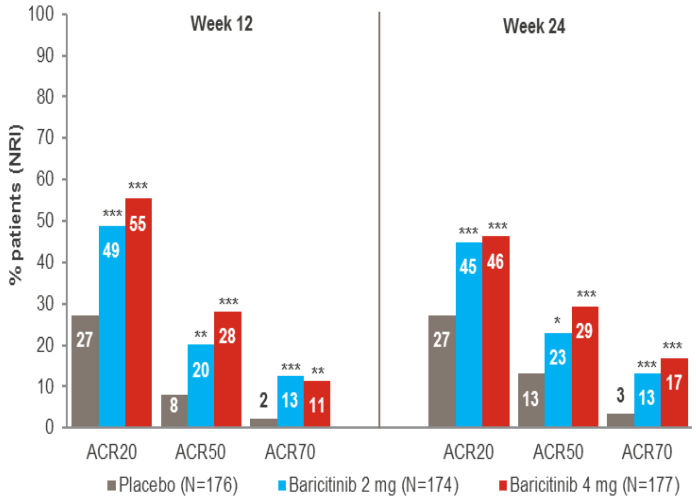
RA BEAM
MTX IR
Baricitinib vs Adalimumab



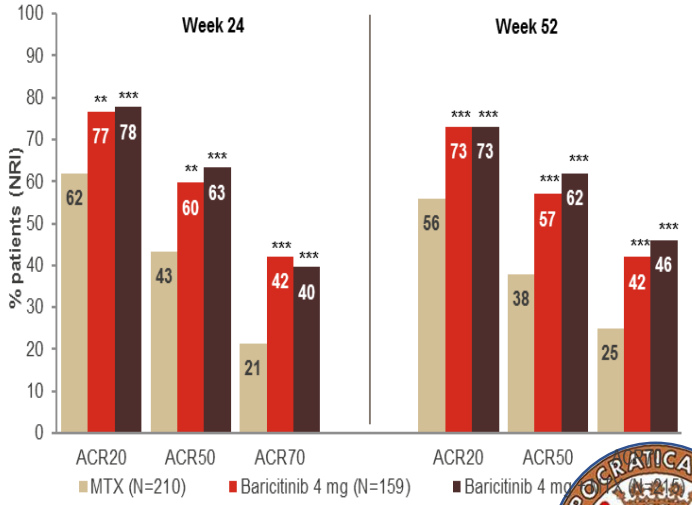
RA BUILD
csDMARD IR



RA BEACON
TNFi IR



RA BEGIN
DMARD NAIVE



1. Taylor PC, et al. N Engl J Med 2017;376:652-62
2. Dougados M. et al. Ann Rheum Dis 2017;76:88-95
3. Genovese MC, et al. *N Engl J Med* 2016;374:1243-52
4. Fleischmann R et al. *Arthritis Rheumatol* 2017;69:506-17

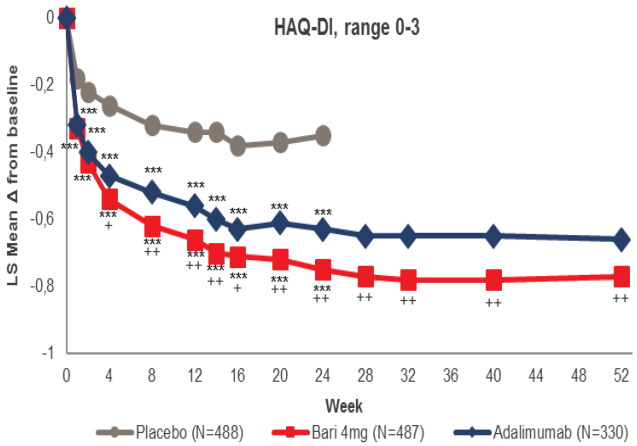
Efficacia di bariticitinib consistente in diverse popolazioni

HAQ-DI

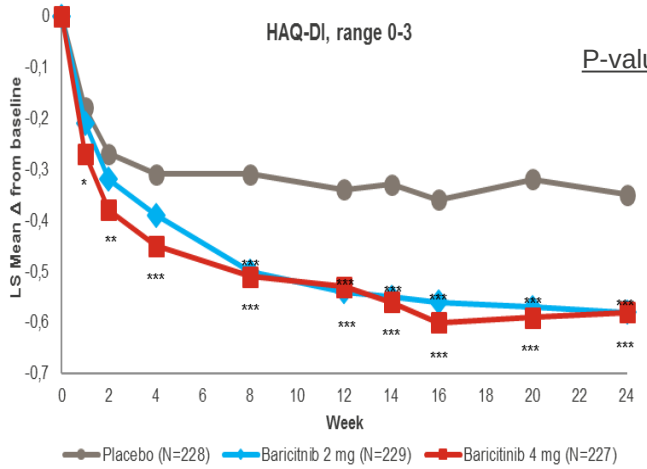
P-value vs. Adalimumab
+++ p≤.001
++ p≤.01
+ p≤.05

P-value vs. Placebo
*** p≤.001
** p≤.01
* p≤.05

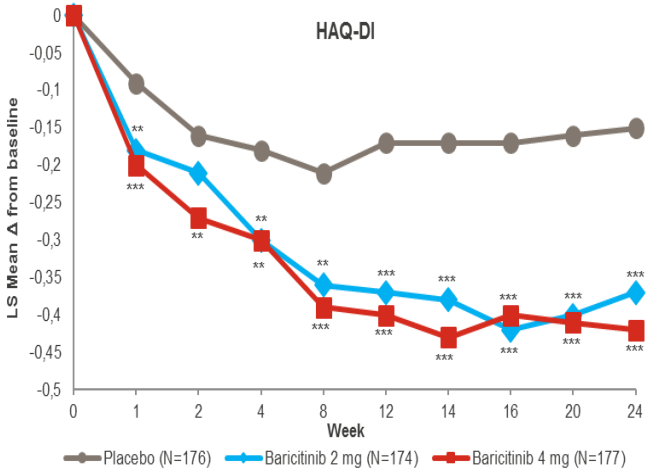
RA BEAM
MTX IR
Baricitinib vs Adalimumab



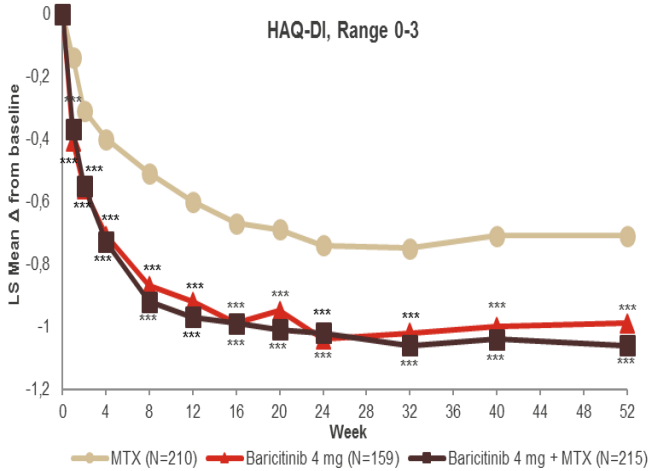
RA BUILD
csDMARD IR



RA BEACON
TNFi IR



RA BEGIN
DMARD NAIVE



1. Taylor PC, et al. N Engl J Med 2017;376:652-62
2. Dougados M. et al. Ann Rheum Dis 2017;76:88-95
3. Genovese MC, et al. *N Engl J Med* 2016;374:1243-52
4. Behrens F, Kruschmann R et al. *Arthritis Rheumatol* 2017;69:506-17

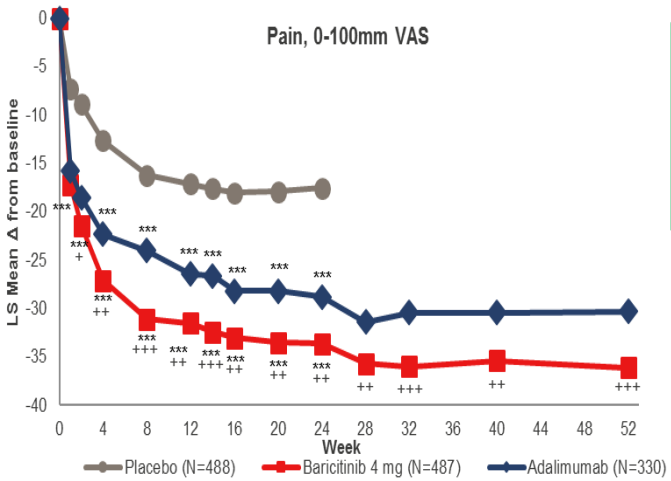
Efficacia di bariticitinib consistente in diverse popolazioni

PAIN

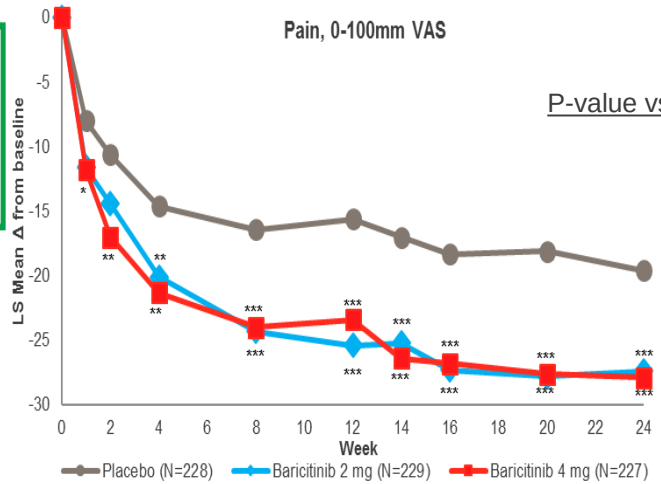
P-value vs. Adalimumab
+++ p≤.001
++ p≤.01
+ p≤.05

P-value vs. Placebo
*** p≤.001
** p≤.01
* p≤.05

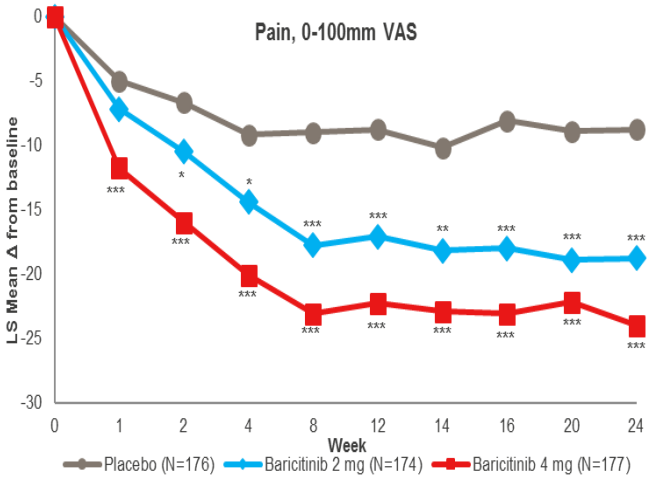
RA BEAM
MTX IR
Baricitinib vs Adalimumab



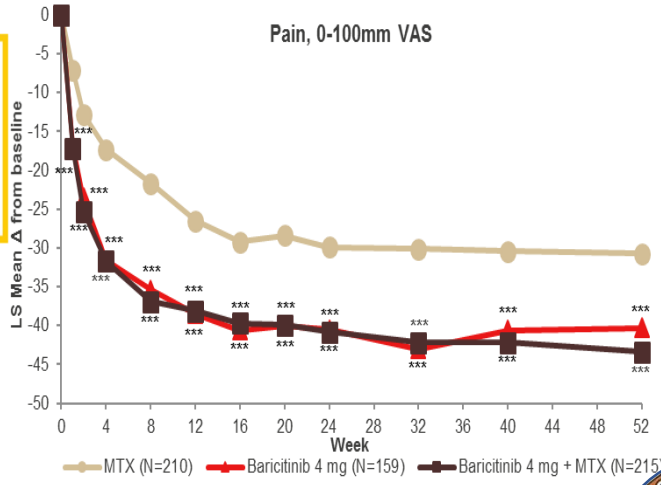
RA BUILD
csDMARD IR



RA BEACON
TNFi IR



RA BEGIN
DMARD NAIVE



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2. Dougados M. et al. Ann Rheum Dis 2017;76:88-95
3. Genovese MC, et al. *N Engl J Med* 2016;374:1243-52
4. Fleischmann R et al. *Arthritis Rheumatol* 2017;69:506-17

Punti chiave di baricitinib

Efficacia
- Outcomes clinicamente rilevanti:
  - Risposta ACR
  - LDA/remissione
  - Inibizione del danno strutturale

Superiorità
- Standard of Care
  - MTX e Adalimumab nei pazienti MTX IR

Miglioramento QoL
- Funzionalità fisiche e PROs, in particolare:
  - Pain
  - HAQ-DI

Safety
- Tra tutte le popolazioni di pazienti con AR e con trattamenti differenti precedenti per AR
- ~3500 pazienti esposti fino a 7 anni
- Profilo di sicurezza di Baricitinib accettabile in quei pazienti con AR, fino a 7 anni di esposizione.

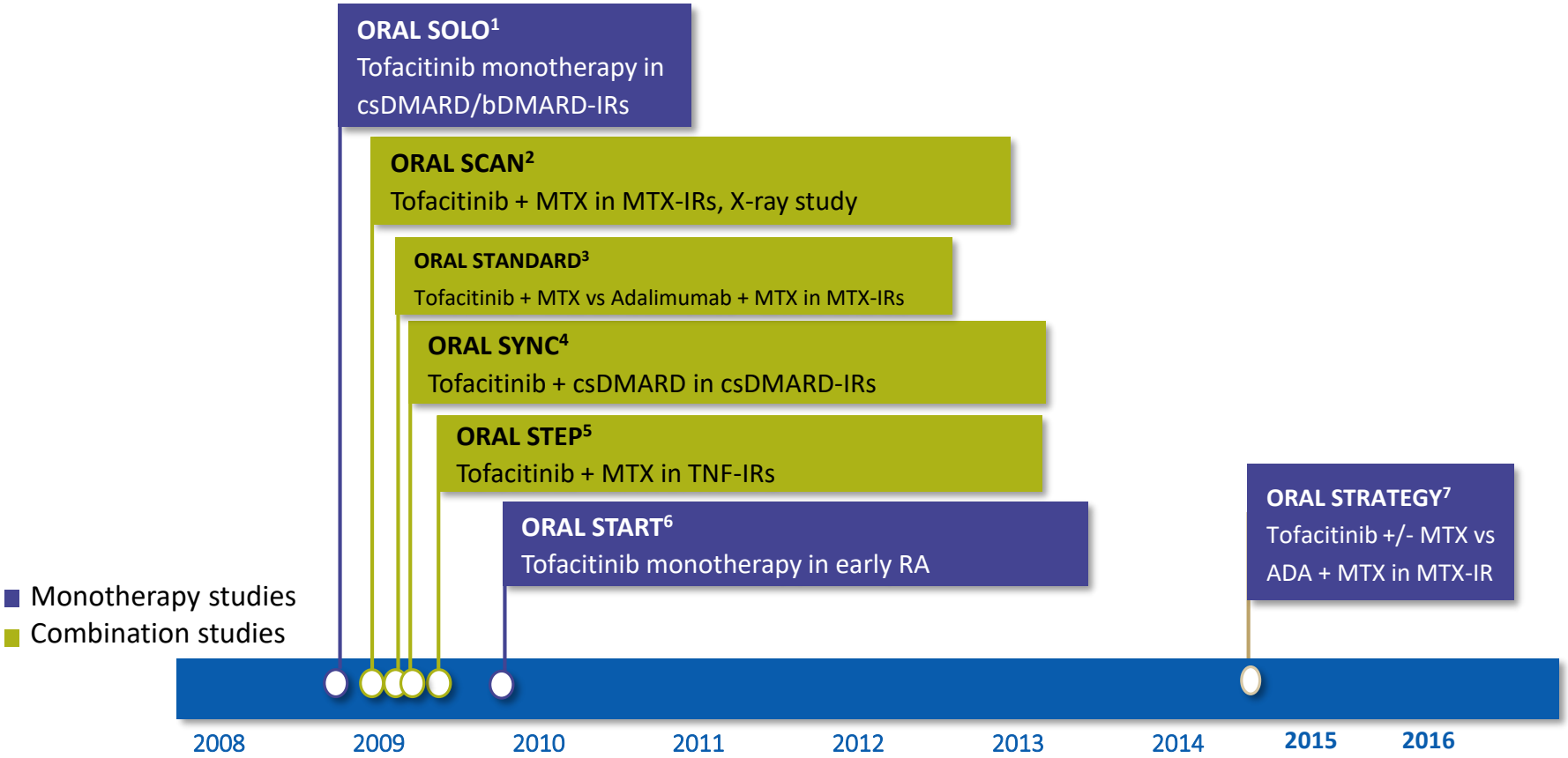
Real life
- Mancanza di dati real life
- Dati preliminary promettenti di real life relativamente all'esperienza di baricitinib (VAS pain)

Non c'è un aumentato rischio di:
- Infezioni serie
- Eventi tromboembolici
- MACE (major adverse cardiovascular events)
- Neoplasie

1. **Taylor PC, et al. *N Engl J Med* 2017;376:652-62**
2. **Dougados M. et al. *Ann Rheum Dis* 2016;(Ahead of print). doi:10.1136/annrheumdis-2016-210094**
3. **Genovese MC, et al. *N Engl J Med* 2016;374:1243-52**
4. **Fleischmann R et al. *Arthritis Rheumatol* 2016;(Ahead of print). doi: 10.1002/art.39953**

Tofacitinib
Efficacia e sicurezza

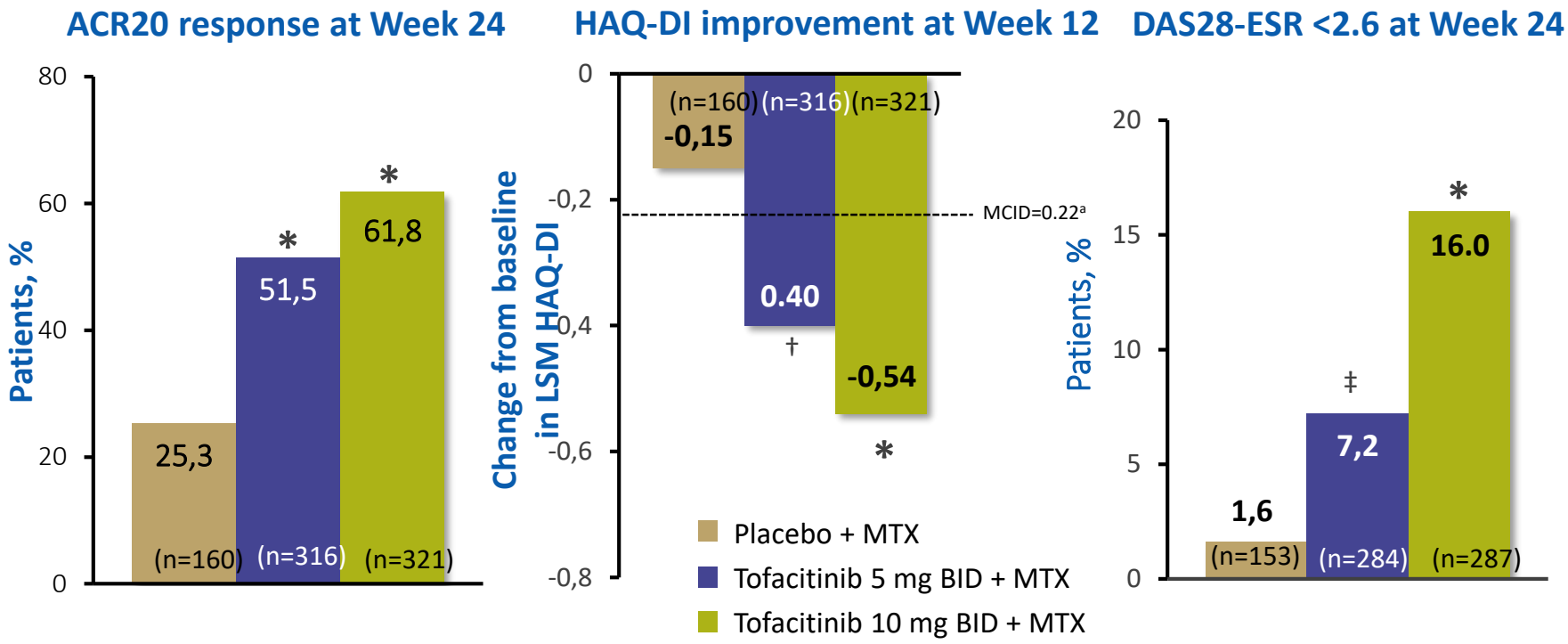
Tofacitinib: programma di studio clinico negli adulti affetti da AR



1. Fleischmann R, et al. N Engl J Med 2012;367(6):495–507; **2.** van der Heijde D, et al. Arthritis Rheum 2013:65:559–70;
3. van Vollenhoven RF, et al. N Engl J Med 2012:367(6):508–19; **4.** Kremer J, et al. Ann Intern Med 2013:159(4):253–61; **5.** Burmester GR, et al. Lancet 2013;381(9865):451–60;
6. Lee EG, et al. N Engl J Med 2014;370(25):2377–86; **7.** Fleischmann R, et al. Lancet 2017;390:457–69

ORAL Scan: obiettivi primari – ACR20, HAQ-DI, and DAS28-ESR

MTX-IR



Nei pazienti con MTX-IR, tofacitinib più MTX ha portato a miglioramenti significativamente maggiori nei segni e sintomi della RA (remissione ACR20 e DAS28-ESR) e nella funzione fisica (HAQ-DI) rispetto al solo MTX

*P<0.0001 vs placebo for analyses up to and including 6 months (the time at which all patients in the placebo group were switched to tofacitinib). †Nominal P<0.0001. ‡Significance not declared due to break in statistical hierarchy

ªA decrease of 0.22 in the HAQ-DI is considered the minimal clinically important difference

LSM, least squares mean

van der Heijde D, et al. Arthritis Rheum 2013:65:559–70

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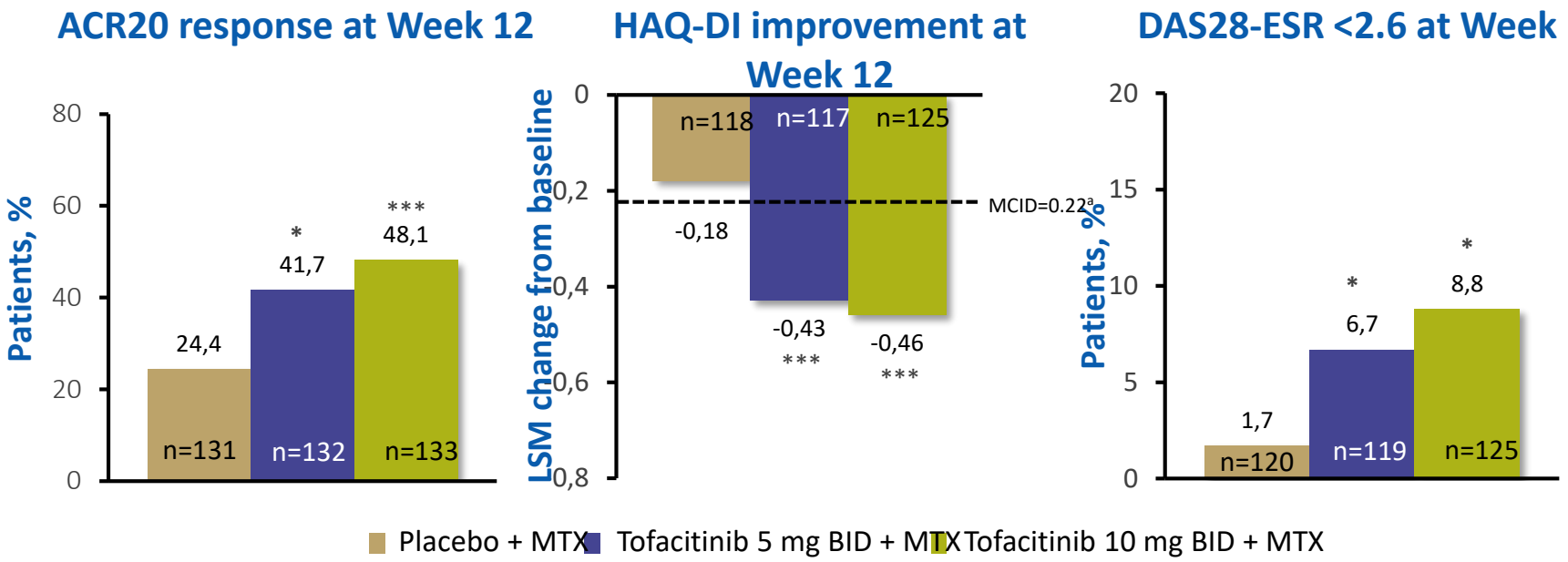
ORAL Step: obiettivi primari di efficacia

TNF-IR



In pazienti con una risposta inadeguata agli inibitori del TNF, tofacitinib più MTX ha portato a miglioramenti significativamente maggiori nei segni e sintomi della RA (remissione ACR20 e DAS28-ESR) e nella funzione fisica (HAQ-DI) rispetto al solo MTX

****P*≤0.05 vs placebo; ****P*<0.0001 vs placebo**

[a]A decrease of 0.22 in the HAQ-DI is considered the MCID

Burmester GR, et al. Lancet 2013;381:451–60

ORAL Strategy: Studio di fase 3b/4 di non-inferiorità per valutare la sicurezza e l'efficacia di tofacitinib +/- MTX vs adalimumab + MTX in pazienti MTX-IR

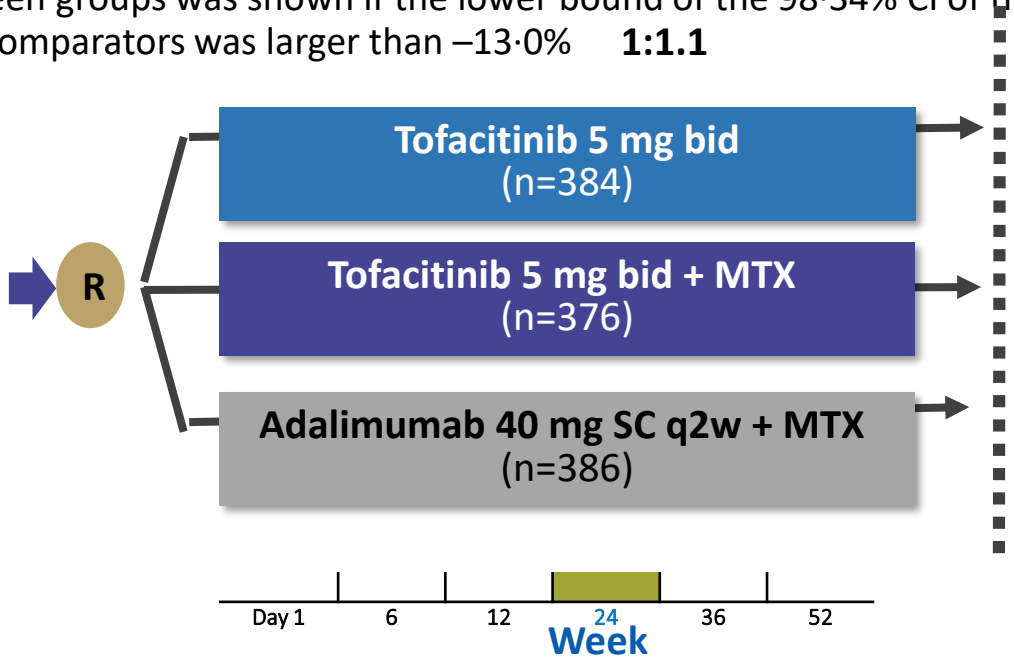
H2H monotherapy

Primary endpoint

- ACR50 at Month 6
- Non-inferiority between groups was shown if the lower bound of the 98·34% CI of the difference between comparators was larger than –13·0% **1:1.1**

Key inclusion criteria

- Active RA
- MTX-IR
- Prior bDMARD permitted



Fleischmann R, et al. Lancet 2017;390:457–69

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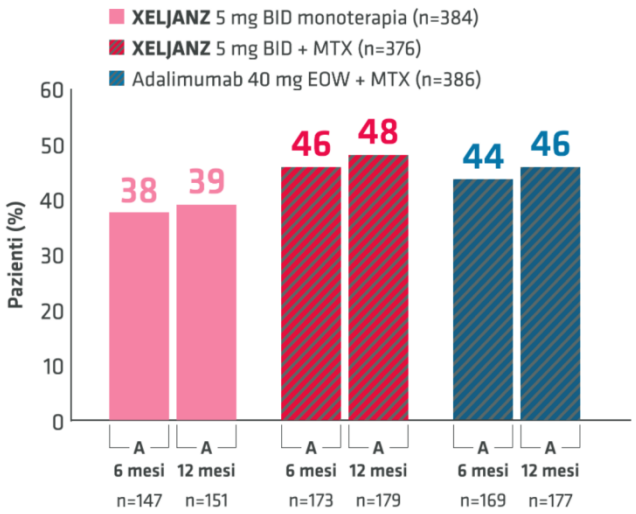
XELJANZ: EFFICACIA VS ADALIMUMAB – STUDIO ORAL STRATEGY[2]

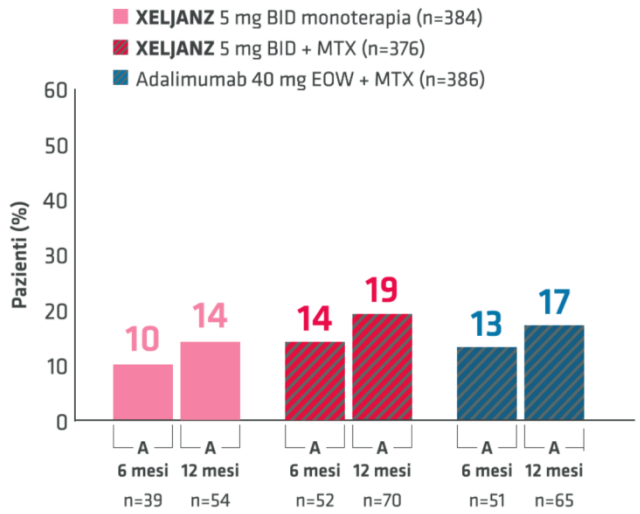
RCT

RISPOSTA CLINICA - ACR50



Elaborato da Tab. 2, Rif. 2

TASSO DI REMISSIONE - CDAI ≤2,8



Elaborato da Tab. 2, Rif. 2

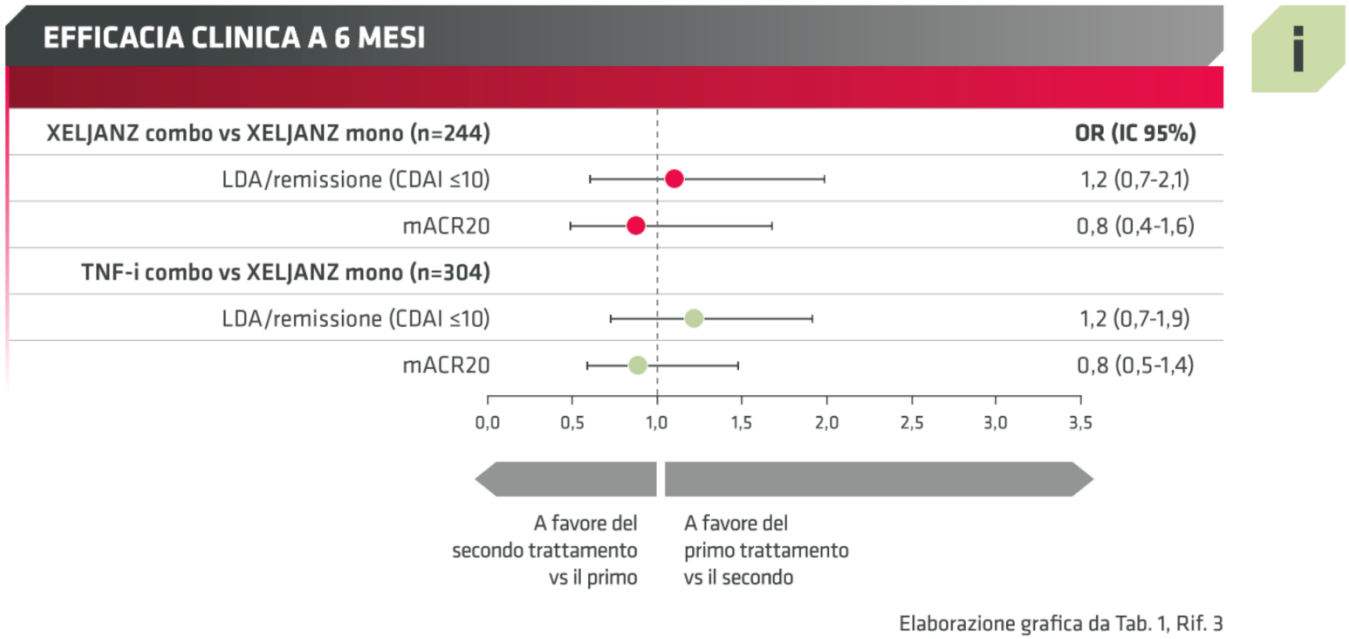
Pazienti con AR e risposta inadeguata a MTX:

- **XELJANZ** + MTX › non inferiore ad adalimumab + MTX[2]
- l'aggiunta di **XELJANZ** o di adalimumab a MTX **è ugualmente efficace** ed è più efficace rispetto allo *switch* a **XELJANZ** in monoterapia[2]

XELJANZ: EFFICACIA CLINICA – REGISTRO CORRONA[3]

In riferimento alle misurazioni degli *outcome* riportate non vi sono evidenze che **XELJANZ in monoterapia** sia meno efficace di **XELJANZ in combinazione** o dei TNF-i in combinazione[3]

RWD



Elaborazione grafica da Tab. 1, Rif. 3

Baricitinib e tofacitinib safety

TABLE 1 Incidence rates of adverse events of special interest in patients treated with tofacitinib or baricitinib in clinical development programmes for RA

Adverse events	Tofacitinib	Baricitinib
Serious infection	2.7 (2.5, 3.0)[a]	2.9 (2.5, 3.4)
Herpes zoster	3.9 (3.6, 4.2)[a]	3.2 (2.8, 3.7)
Tuberculosis	0.2 (0.1, 0.3)[a]	0.15 (0.07, 0.27)
Malignancy excluding NMSC	0.9 (0.8, 1.0)[a]	0.8 (0.6, 1.0)
NMSC	0.6 (0.5, 0.7)[a]	0.4 (0.2, 0.5)
Lymphoma	0.1 (0.1, 0.2)[a]	0.09 (0.03, 0.19)
MACE	0.58 (0.39, 0.88)[b]	0.5 (0.4, 0.7)
DVT/PE	DVT: 0 in PBO-controlled cohort and 0.1 (0, 0.3) in dose-comparison cohort[c] PE: 0 in PBO-controlled cohort and 0.1 (0, 0.4) for 5 mg bid and 0.2 (0, 0.4) for 10 mg bid in dose-comparison cohort[c]	DVT/PE: 0.5 (0.3, 0.7)
GI perforation	0.11 (0.07, 0.17)[a]	0.05 (0.01, 0.13)

Incidence rates (95% CIs) in RA patients treated with each JAK inhibitor were shown. Data for baricitinib were from reference [15] ($n = 3492$). [a]Data were from reference [12] ($n = 6194$). [b]Data were from reference [62] ($n = 3800$). [c]Data were from reference [47] ($n = 5368$). NMSC: non-melanoma skin cancer; MACE: major adverse cardiovascular event; DVT: deep vein thrombosis; PE: pulmonary embolism; PBO: placebo; GI: gastrointestinal; JAK: Janus kinase.

P. Moscato 11/10/2019

Rheumatology 2019;58:i34i42

Inibitori di JAK: **effetti sui parametri di laboratorio**

	Tofacitinib	Peficitinib	Baricitinib	Decernotinib	Filgotinib	ABT-494
Selectivity	JAK1, JAK3	JAK1, JAK3	JAK1, JAK2	JAK3	JAK1	JAK1
Lymphocyte Number	↓	No change	No change	↓	No change	↓
NK Cell Number	↓	N/A	↓*	N/A	No change	↓
Neutrophil Number	↓	↓	↓	↓	↓	↓
Haemoglobin Level	↑	↑	↓	No change	↑	↓
Platelet Count	↓	↓	No change	N/A	↓	N/A
Liver Transaminase Level	↑	N/A	↑	↑	No change	↑
Create Phosphokinase Level	↑	↑	↑	N/A	N/A	↑
HDL Level	↑	↑	↑	No change	↑	↑
LDL Level	↑	↑	↑	↑	No change	↑
Creatinine Level	↑	↑	↑	↑	↑	↑

Shown are general trends reported in the development program of each compound. The magnitude of change varies by compound and within each compound by dose. In some cases changes were seen at only certain doses. Notably grade changes (for example grade 3) for laboratory parameters can occur in the opposite direction of mean trends for a given parameter. For some drugs (for example decernotinib and peficitinib) the number of patients receiving the drug is limited and the estimations of laboratory change are less robust.

* Initial rise followed by a decrease.

Winthrop KL. Nat Rev Rheumatol 2017;13:234–243.

P. Moscato 11/10/2019

Upadacitinib
Piano di sviluppo clinico

Studi in corso su altri JAK inhibitors

RECENTE APPROVAZIONE FDA

TABLE 1 Overview of efficacy in phase II and III RA studies (full papers)

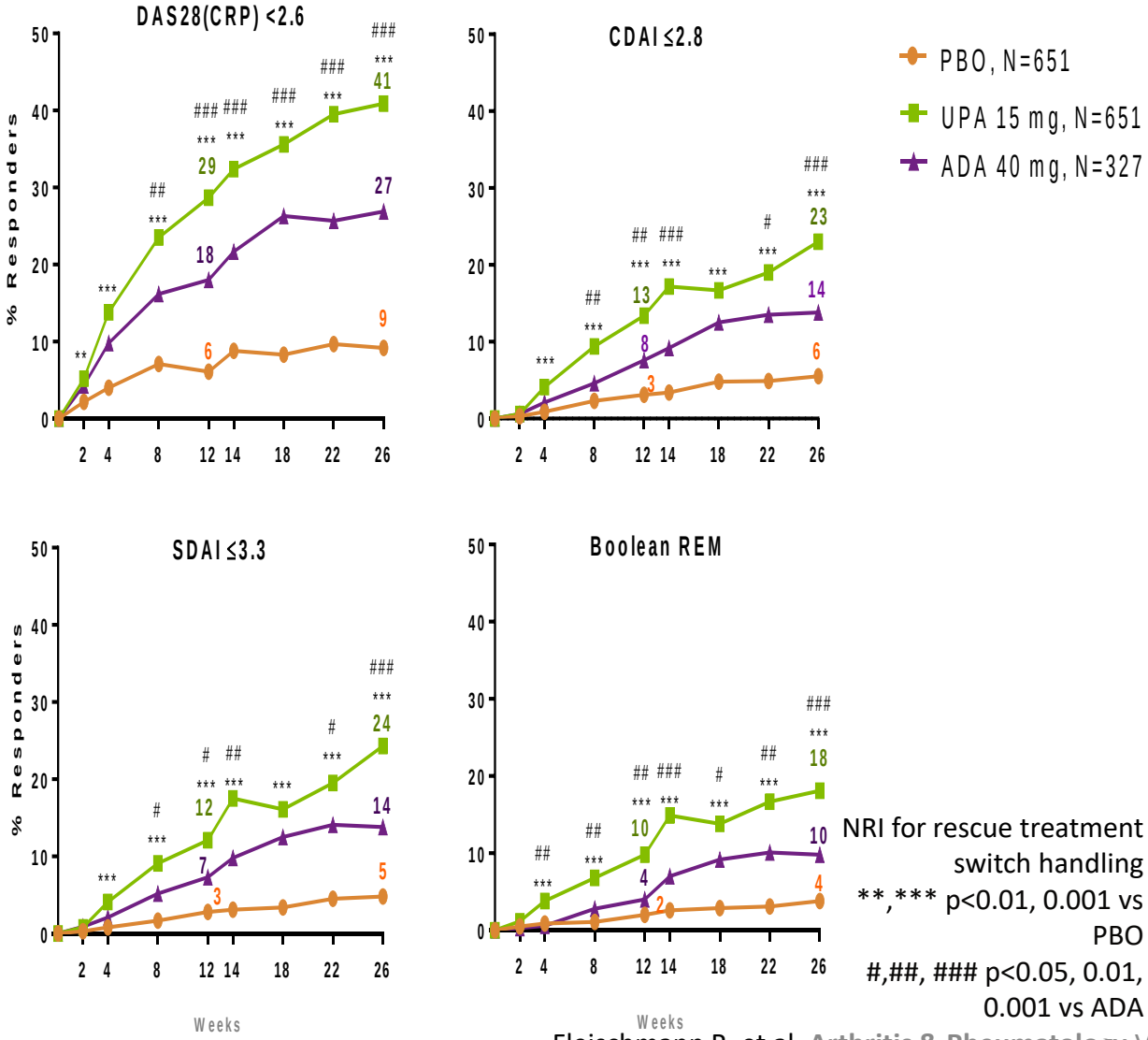
	Phase and reference	Type of patients	*n*	Combi or mono R/	ACR20 response[a]	
Filgotinib	Phase IIa [8]	MTX refr.	36+91	+MTX		
	Phase IIb [10]	MTX refr.	594	+MTX		
					100 mg/d[b]	200 mg/d[b]
	Phase IIb [11]	MTX refr.	283	Mono R/	+37% at 3 m 100 mg QD	+44% at 3 m 200 mg QD
Upadacitinib	Phase IIb [15]	MTX refr.	300	+MTX	+18% at 3 m 18 mg BID (NS)	+30% at 3 m 24 mg QD
	Phase IIb [16]	TNF refr.	276	+MTX	+38% at 3 m 12 mg BID	+36% at 3 m 18 mg BID
	Phase III [18]	DMARD refr.	661	+StablecsDMARD	+28% at 3 m 15 mg QD	+30% at 3 m 30 mg QD
	Phase III [19]	Biologic refr.	499	+Stable csDMARD	+37% at 3 m 15 mg QD	+28% at 3 m 30 mg QD
Peficitinib	Phase IIb [23]	Prior MTX or anti-TNF	281	Mono R/	+43.8% at 3 m 100 mg QD	+54.8% at 3 m 150 mg QD
	Phase IIb [24]	MTX refr.	378	+MTX	+2% at 3 m 100 mg QD (NS)	+13.3% at 3 m 150 mg QD (NS)
	Phase IIb [25]	Prior DMARD or biologic	289	+LimitedDMARD	+18.9% at 3 m 100 mg QD	+26.9% at 3 m 150 mg QD
Decernotinib	Phase IIb [27]	Prior DMARD or biologic	204	Mono R/	+35.7% at 3 m 100 mg BID	+36.6% at 3 m 150 mg BID
	Phase IIb [28]	MTX refr.	358	+MTX	+48.4% at 3 m 150 mg QD	+38.6/+49.8%at 3 m 200 mg/d[c]
	Phase IIb [29]	DMARD refr.	43	+DMARD		

BREVACTA/SUMMACTA

[a]ACR20 response = ACR20 response on top of placebo response. [b]In the study with Ref. [10] all doses were tested in one and two gifts [c]In the study with Ref. [28] the 200 mg dose was tested in one and two gifts. PubMed accessed 1 July 2018. BID: twice daily; d: day; DQ: once daily; m: month; *n*: number of patients in study; NS: non-significant; refr.: refractory.

Westhovens, Rheumatology 2019;58:i27i33

SELECT-COMPARE: DAS28(CRP) <2.6 and Clinical Remission Over 26 Weeks (NRI)

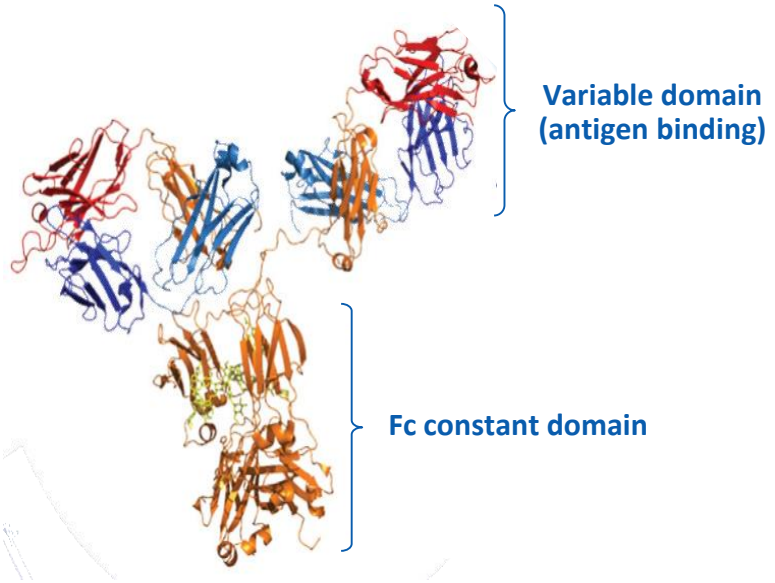


NRI for rescue treatment switch handling
,* p<0.01, 0.001 vs PBO
#,##, ### p<0.05, 0.01, 0.001 vs ADA

Fleischmann R, et al. **Arthritis & Rheumatology** Vol. 0, No. 0, Month 2019, pp 1–13

Sarilumab e il suo obiettivo

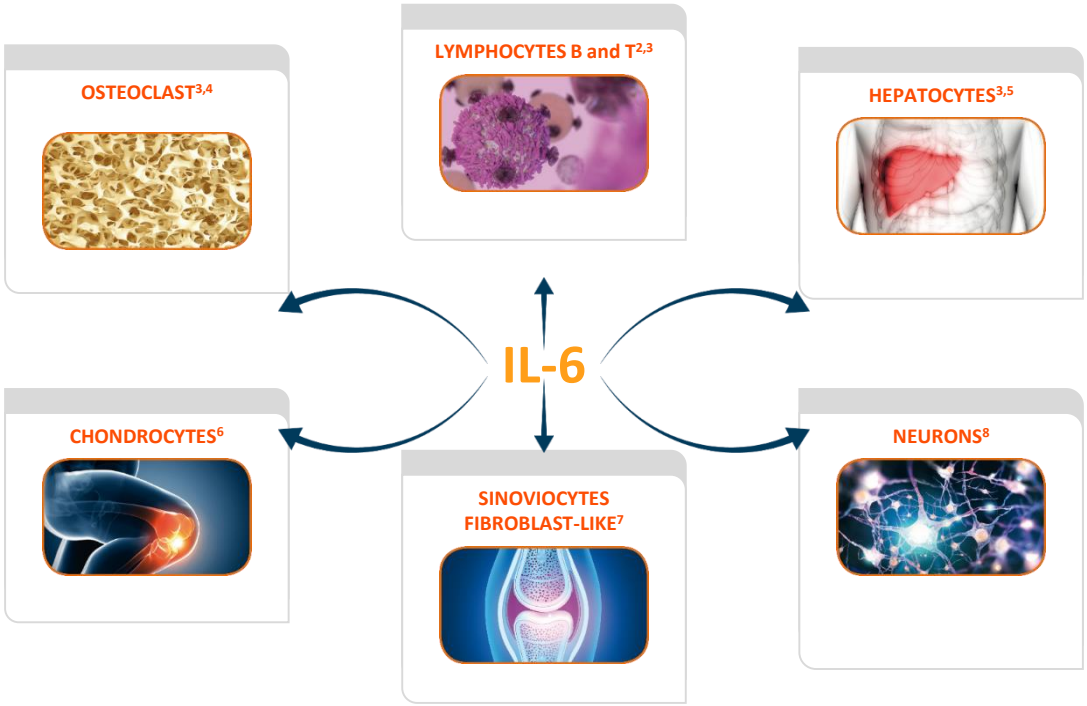
- Sarilumab è un anticorpo monoclonale anti-IL-6 del recettore IgG1 anti-IL-6 umano (anti-IL-6Rα) che si lega selettivamente all'IL-6R legato alla membrana ed a quello solubile
- Legandosi a IL-6Rα con alta affinità1, sarilumab blocca il legame di IL-6 e interrompe la cascata di segnalazione mediata da citochine



1. Rafique A, Martin J, Blome M, et al. Evaluation of the binding kinetics and functional bioassay activity of sarilumab and tocilizumab to the human IL-6 receptor alpha. Ann Rheum Dis. 2013;72 (Suppl 3):A797.

THE IMPORTANCE OF TARGETING IL6 IN RA

IL-6 is a pleiotropic cytokine,
which mediates numerous local and systemic manifestations in the patient with AR[2]



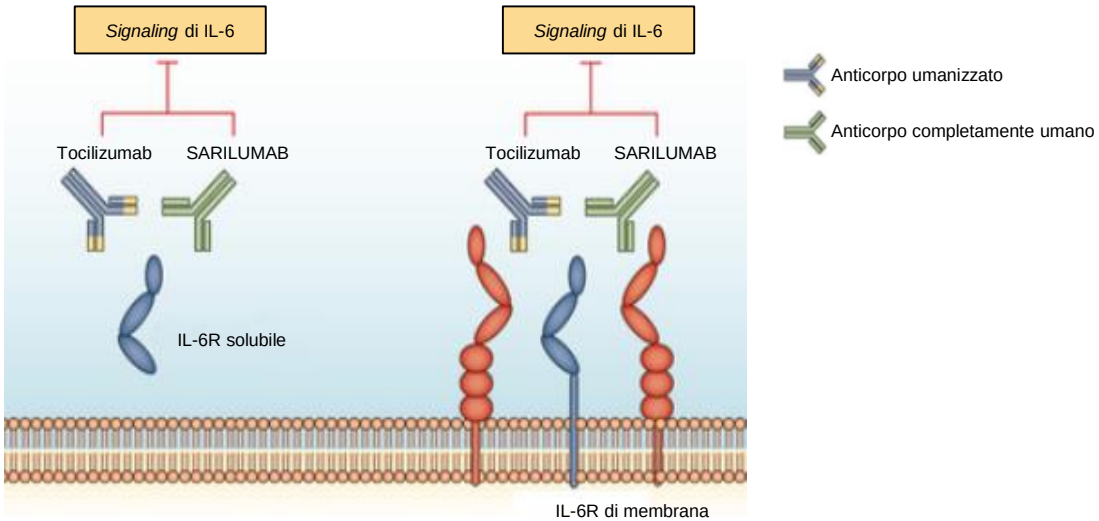
1. Boyapati A. et al.; Arthritis Res Ther 2016;18 (1): 225.
2. Dayer J.M., Choy E.; Rheumatology 2010; 49: 15-24.
3. Naka T. et al.; Arthritis Res 2002; 4 (Suppl.3): S233-42.
4. Axmann R. et al.; Arthritis Rheumatol 2009; 60 (9): 2747-56.
5. Andrews N.C.; J Clin Invest 2004; 113 (9): 1251–1253.
6. Hashizume M., Mihara M.; Arthritis 2011; 2011: 765624.
7. Yang X. et al.; Mediators Inflamm 2016; 2016: 6813016.
8. Choy E.H.S.; Calabrese L.H. et al.; Rheumatology (Oxford) 2018; 57 (11): 1885-1895.

SARILUMAB : ANTICORPO MONOCLONALE UMANO CON ALTA AFFINITA’

Affinità di legame al recettore IL-6R

~ 20 volte superiore

a quella di tocilizumab[1]

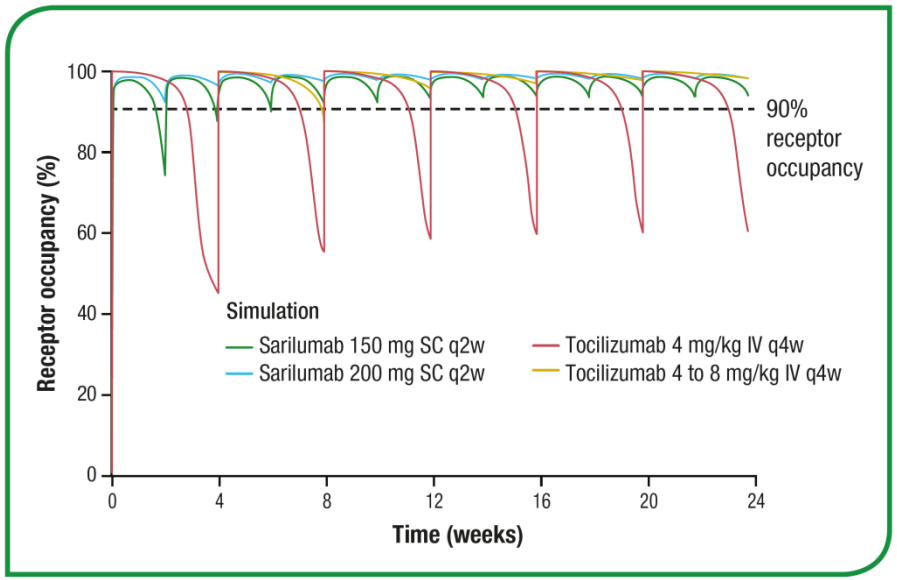


1. Raimondo M.G. et al.; Drug Des Devel Ther 2017; 11: 1593-1603.
2. Ruderman E.R.; Nat Rev Rheumatol 2015; 11 (6): 321-322.

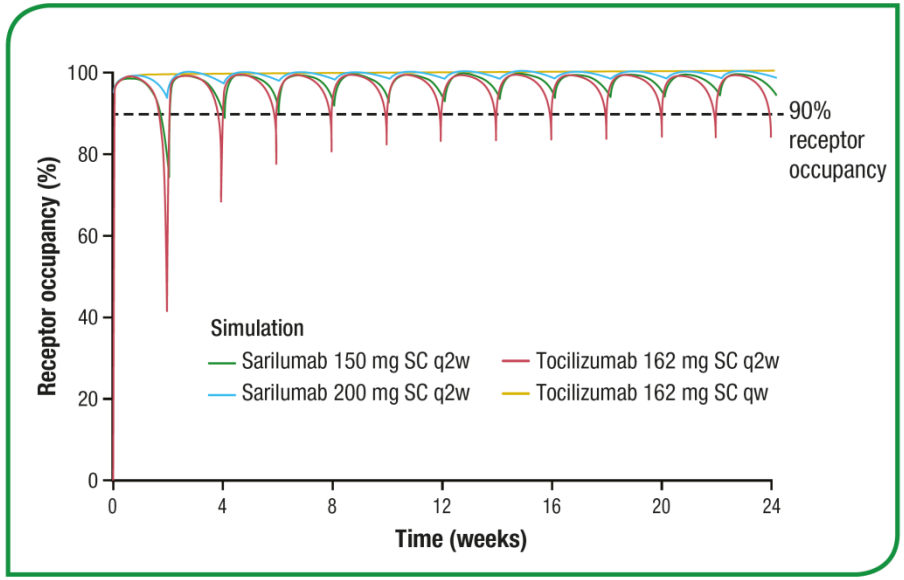
IL-6R receptor occupancy over 24 weeks: Comparison of sarilumab SC with tocilizumab IV or SC

Key results

ASCERTAIN



MOBILITY-A and BREVACTA/SUMMACTA

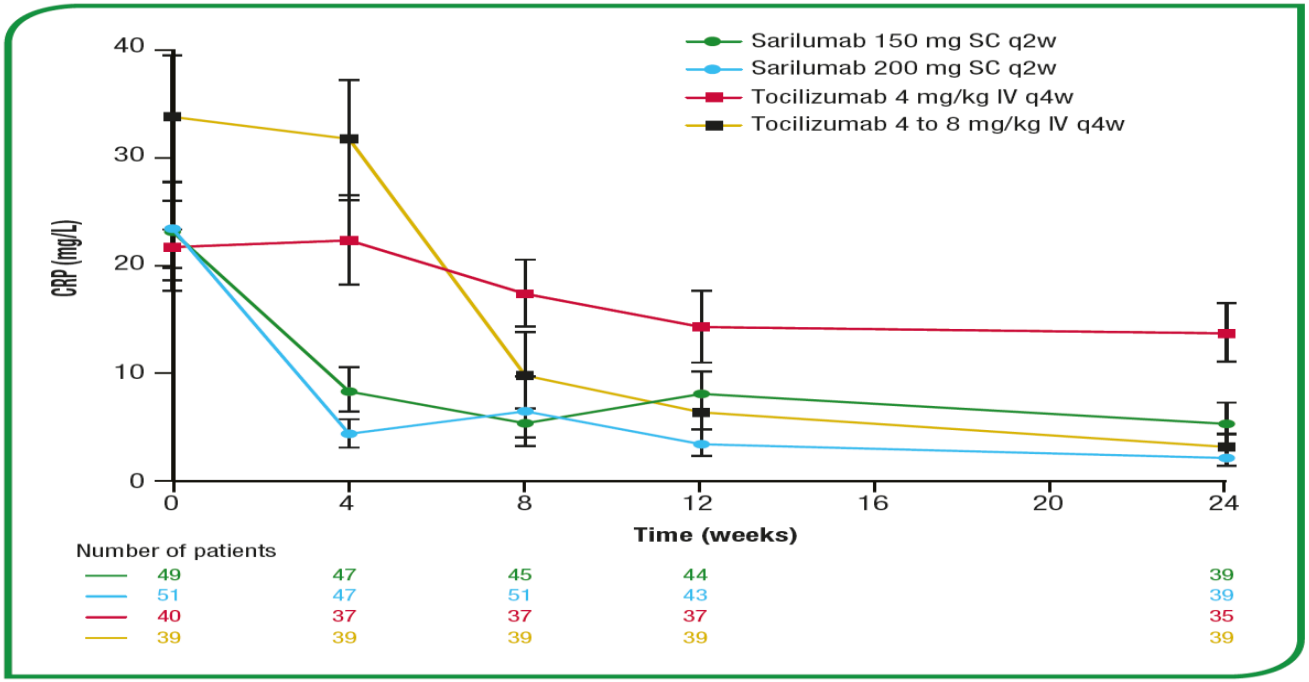


FRI0106 Xu C, et al. EULAR 2019. Friday, June 14, 11:15-11:30

Observed CRP levels over 24 weeks: Comparison of sarilumab SC and tocilizumab IV or SC

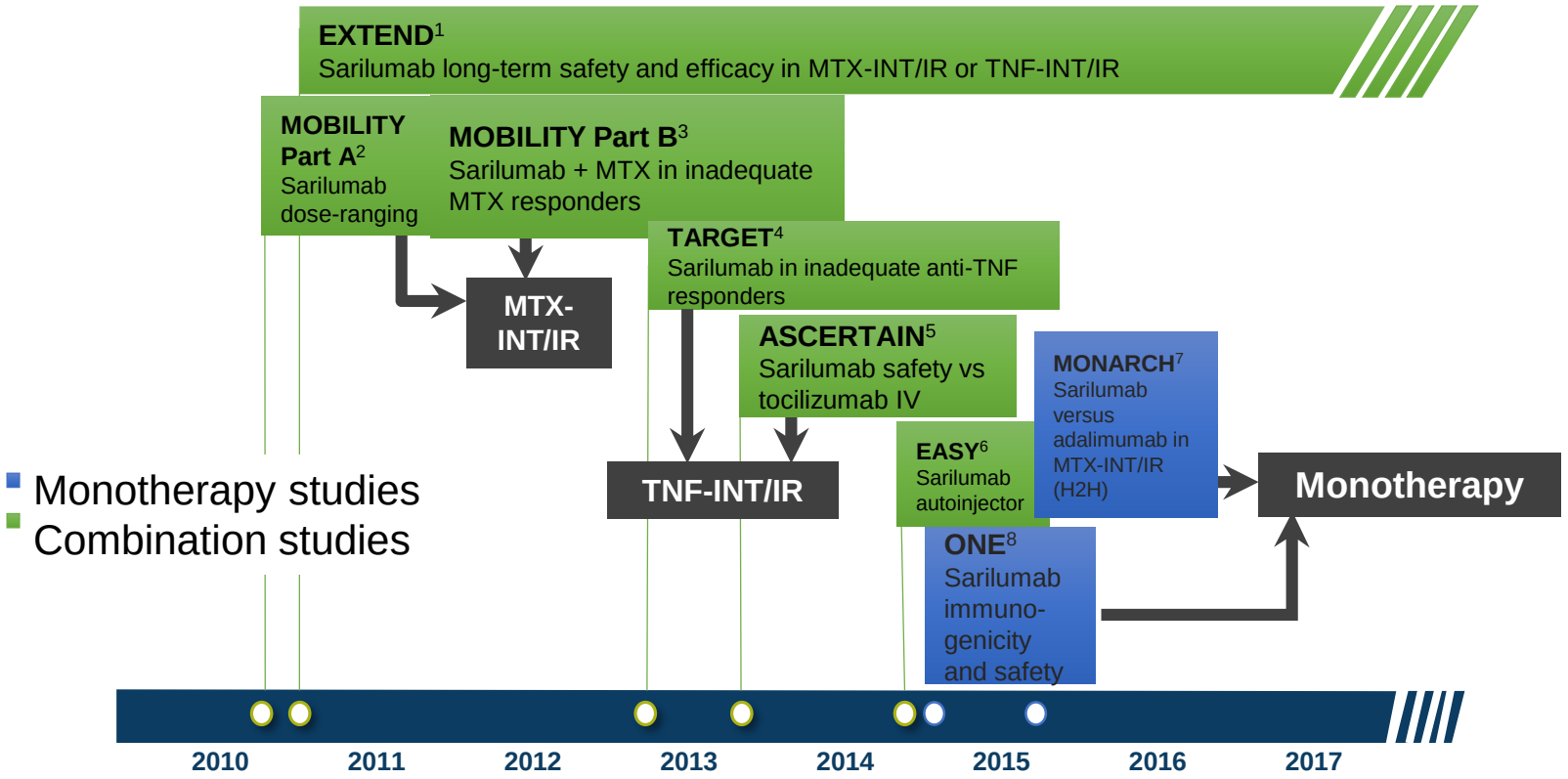
Key results

ASCERTAIN



FRI0106 Xu C, et al. EULAR 2019. Friday, June 14, 11:45–13:30.

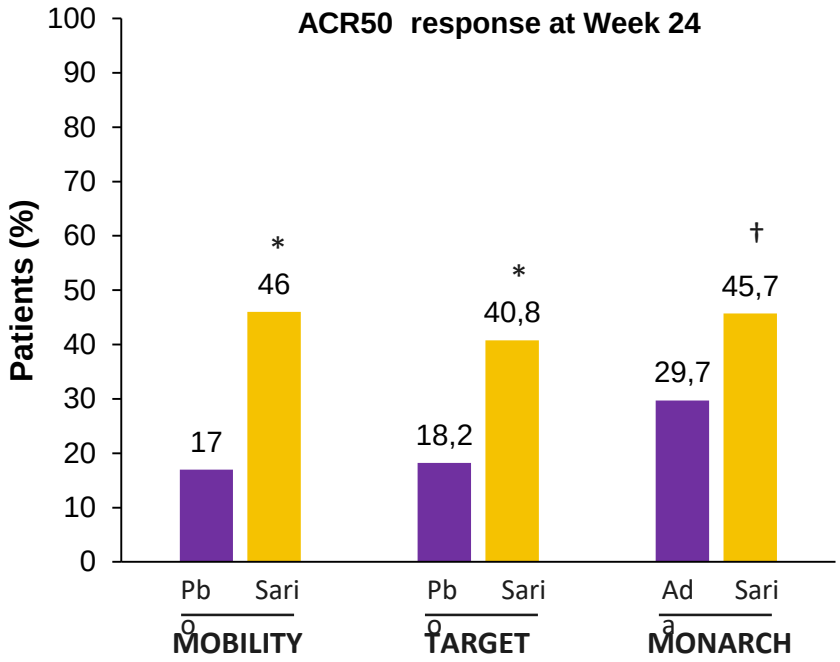
COMPLETE SUBCUTANEOUS DEVELOPMENT PROGRAM



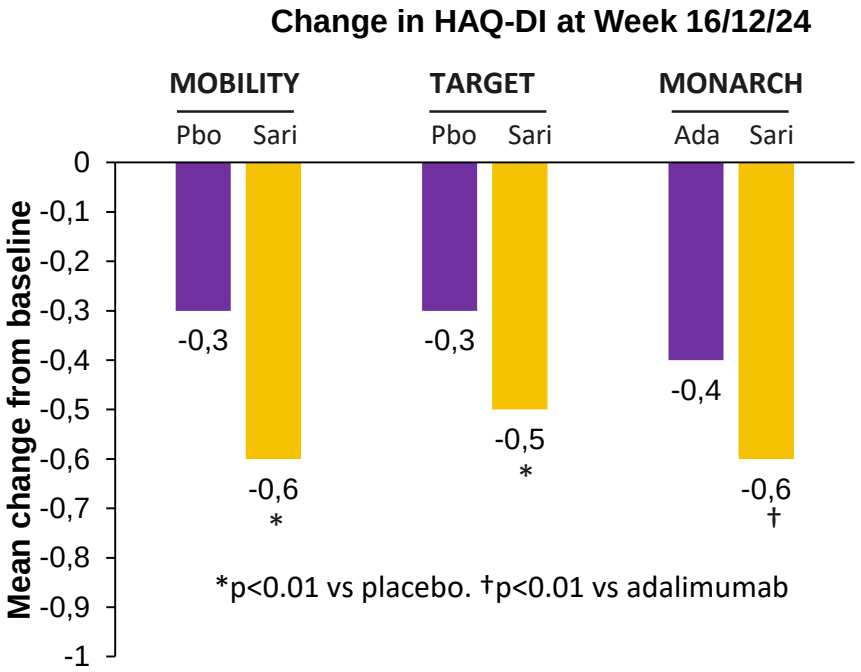
H2H, head-to-head;
INT, intolerant;
IR, inadequate responder

1. Clinical trials.gov NCT01146652. Accessed January 25, 2017; 2. Huizinga TWJ, et al. Ann Rheum Dis 2014;73:1626–34; 3. Genovese MC, et al. Arthritis Rheumatol 2015;67(6):1424–37; 4. Fleischmann R, et al. Arthritis Rheumatol 2017;69(2):277–90; 5. Clinical trials.gov NCT01768572. Accessed January 25, 2017; 6. Kivitz A., et al Rheumatol Ther. https://doi.org/10.1007/s40744-017-0090-2 7. Burmester GR, et al. Ann Rheum Dis 2016 Nov 17 [Epub ahead of print]; 8. Clinical trials.gov NCT02121210. Accessed January 25, 2017.

SARILUMAB 200 MG Q2W: CONSISTENCY OF EFFICACY IN RA PATIENT WITH UNMET MEDICAL NEED



*p<0.01 vs placebo. †p<0.01 vs adalimumab



*p<0.01 vs placebo. †p<0.01 vs adalimumab

Genovese MC, et al. EULAR 2017.

MONOTERAPIA

Maggior numero di pazienti in remissione clinica con SARILUMAB *vs*. adalimumab[1]

5X

La **probabilità di raggiungere la remissione** secondo il parametro DAS28-VES **con SARILUMAB in monoterapia** è risultata

circa 5 volte superiore

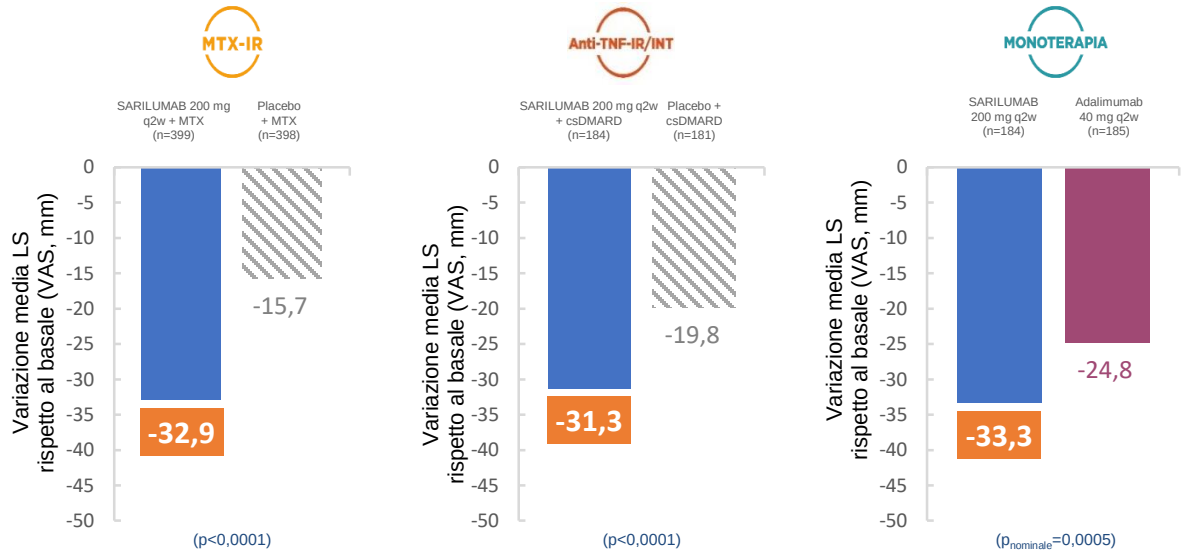
a quella di adalimumab alla settimana 24 (OR=4,88; p<0,0001)[2]

EFFICACIA SUL DOLORE

MTX-IR | Anti-TNF-IR/INT | MONOTERAPIA

SARILUMAB ha migliorato in modo significativo il punteggio di valutazione globale del paziente[1-3]

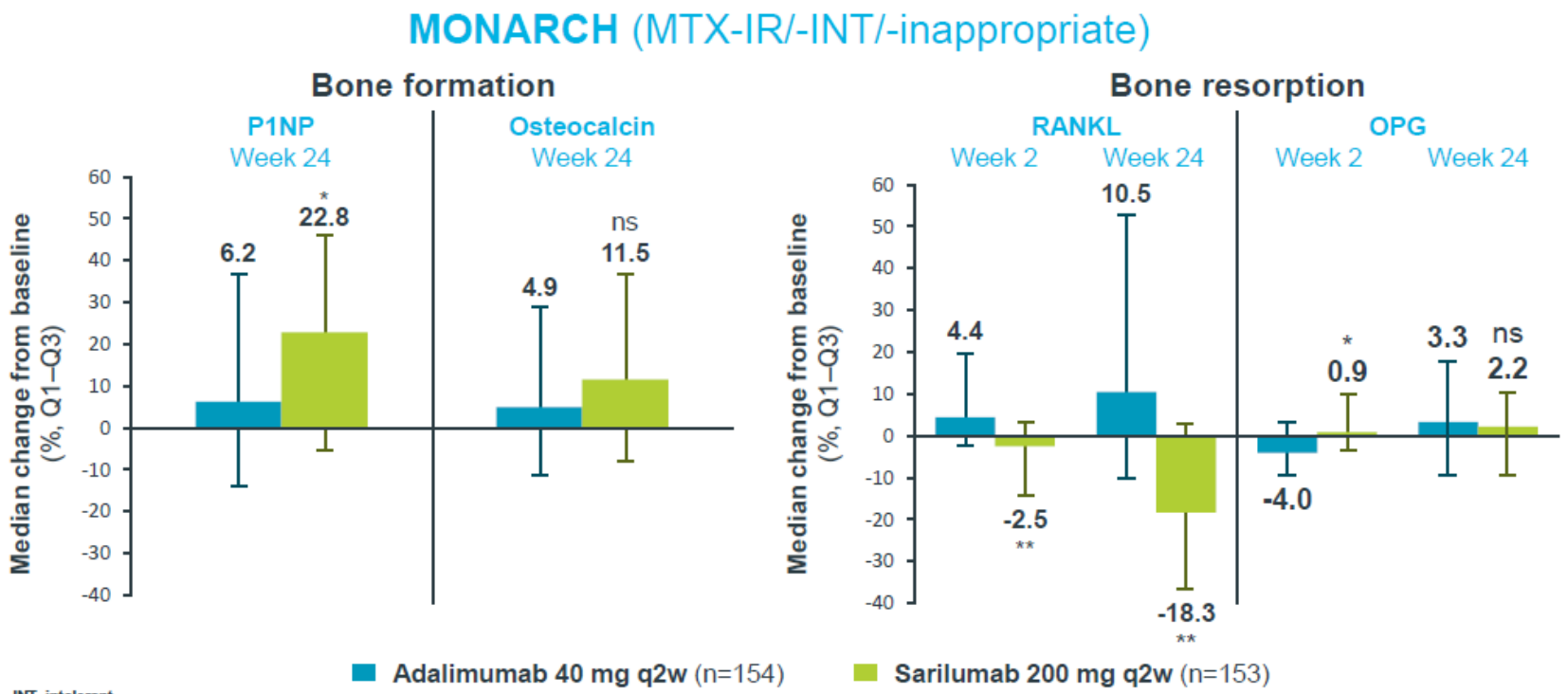
VARIAZIONE DELLA PtGA DAL BASALE ALLA SETTIMANA 24[1-3]



Variazione media dal basale alla settimana 24 della PtGA (VAS) nel gruppo SARILUMAB 200 mg q2w e nei gruppi di confronto degli studi MOBILITY, TARGET e MONARCH.
I dati sono espressi come medie dei minimi quadrati (LS, *least squares*).
Rappresentazione grafica di dati da Tabella 2 di 1, Tabella 2 di 2 e Tabella supplementare 4 di 3. Originali in appendice.

EFFICACIA SUI BIOMARCATORI DI RIMODELLAMENTO OSSEO

Sarilumab monotherapy increased P1NP and osteocalcin, and decreased RANKL relative to adalimumab monotherapy



INT, intolerant

*Adjusted p<0.05 versus adalimumab; **Adjusted p<0.01 versus adalimumab (Benjamini–Hochberg procedure)

a. Numeric differences only for osteocalcin.

Gabay C, et al. *Ann Rheum Dis* 2017;76(Suppl. 2):570

SARILUMAB E EMOGLOBINA GLICATA

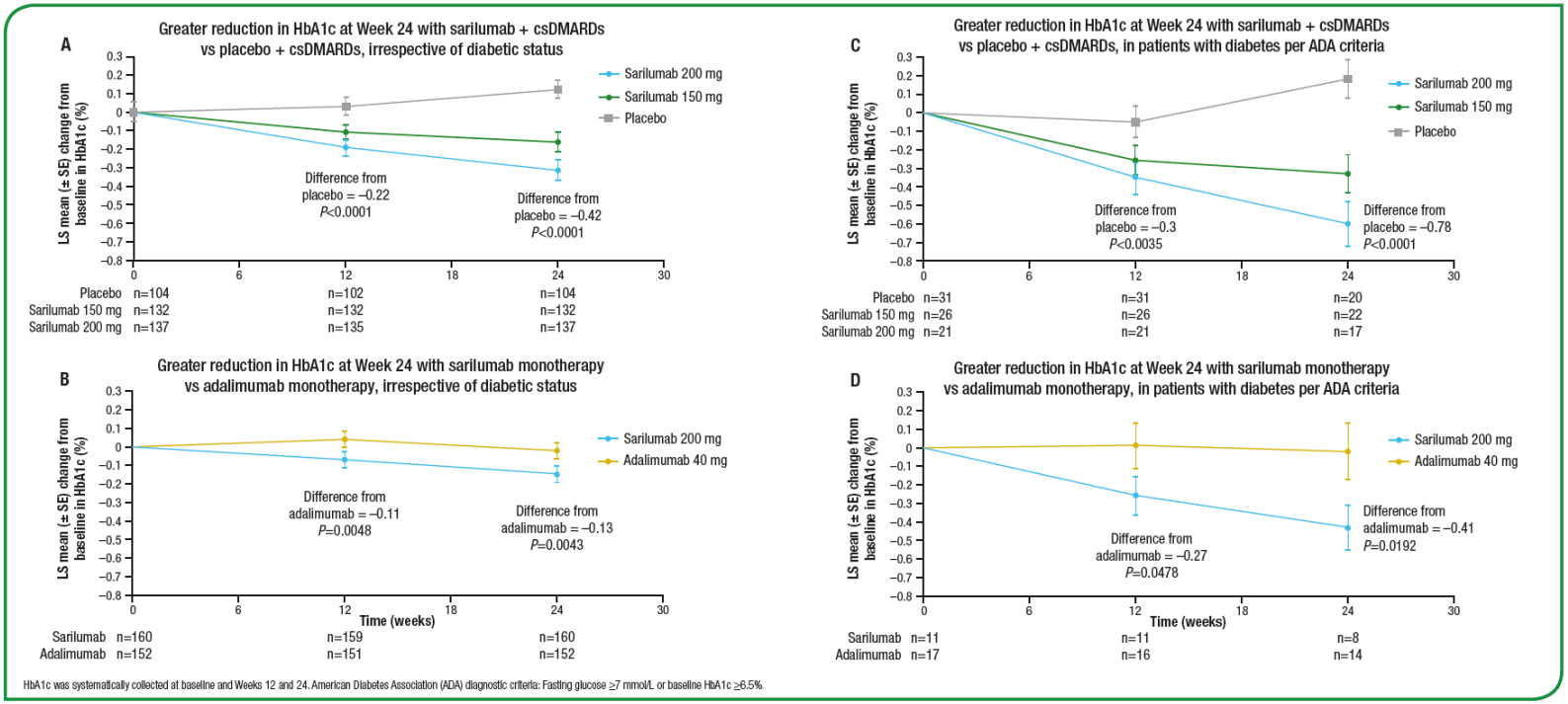
Key results

Patients with RA and Type 2 diabetes treated with sarilumab had greater improvements in HbA1c than those treated with adalimumab or placebo

TARGET

MONARCH

All patients | **Patients with diabetes**



HbA1c was systematically collected at baseline and Weeks 12 and 24. American Diabetes Association (ADA) diagnostic criteria: Fasting glucose ≥7 mmol/L or baseline HbA1c ≥6.5%

ADA, American Diabetes Association

SAT0121 Genovese M, et al. EULAR 2019. Saturday, June 15, 10:30-12:00

Il profilo di sicurezza di Sarilumab è coerente con gli effetti di classe previsti

- The safety of KEVZARA® was evaluated in 2887 patients
- The most common adverse drug reactions: neutropenia, increased ALT, injection site erythema, upper respiratory infections and urinary tract infections
- The most common serious adverse drug reactions: infections

BREVACTA/SUMMACTA

Adverse drug reactions in clinical studies

System organ class	Frequency[a]	Adverse reaction
Infections and infestations	Common	Upper respiratory tract infection
		Urinary tract infection
		Nasopharyngitis
		Oral herpes
Blood and lymphatic disorders	Very common	Neutropenia
	Common	Thrombocytopenia
Metabolism and nutrition disorders	Common	Hypercholesterolaemia
		Hypertriglyceridaemia
Hepatobiliary disorders	Common	Transaminases increased
General disorders and administration site conditions	Common	Injection site erythema
		Injection site pruritus

[a]The frequency of adverse reactions listed above is defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness

SARILUMAB

NUOVA OPZIONE PER IL TRATTAMENTO DELL'ARTRITE REUMATOIDE[1]

Completamente umano

Elevata affinità recettoriale

Programma di sviluppo per via sottocutanea

Efficacia dimostrata sui PROs e manifestazioni extraarticolari

*Una volta tolto dal frigorifero, KEVZARA® deve essere somministrato entro 14 giorni e non deve essere conservato al di sopra di 25 °C.[3]

RCP Sarilumab

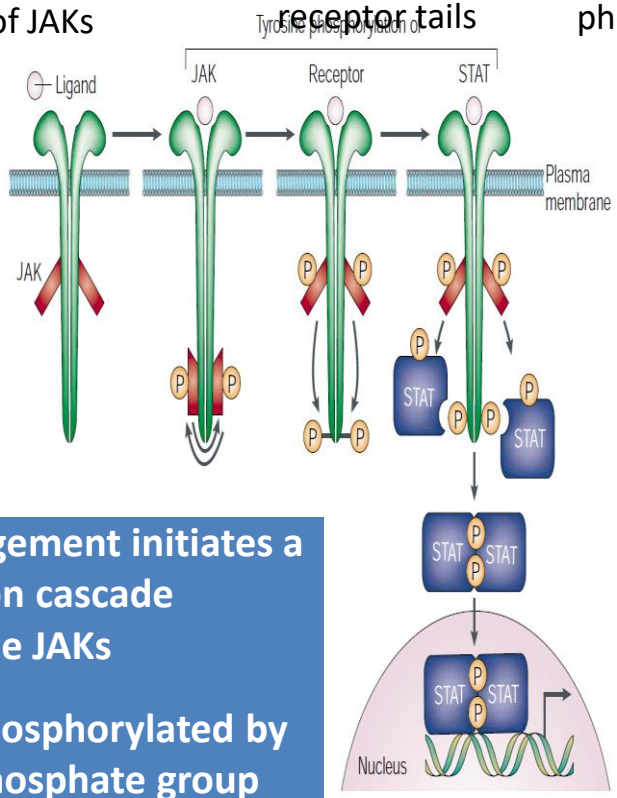
GRAZIE PER L'ATTENZIONE

The JAK–STAT pathway

1. Ligand (cytokine) binding cross-links receptors and allows transphosphorylation and activation of JAKs

2. Activated JAKs phosphorylate receptor tails

3. STAT proteins dock on the phosphorylated receptor tails, and are phosphorylated by the activated JAKs



4. Phosphorylated STATs dissociate from the receptor and dimerize

5. STAT dimer enters the nucleus and activates gene transcription

Receptor engagement initiates a phosphorylation cascade mediated by the JAKs

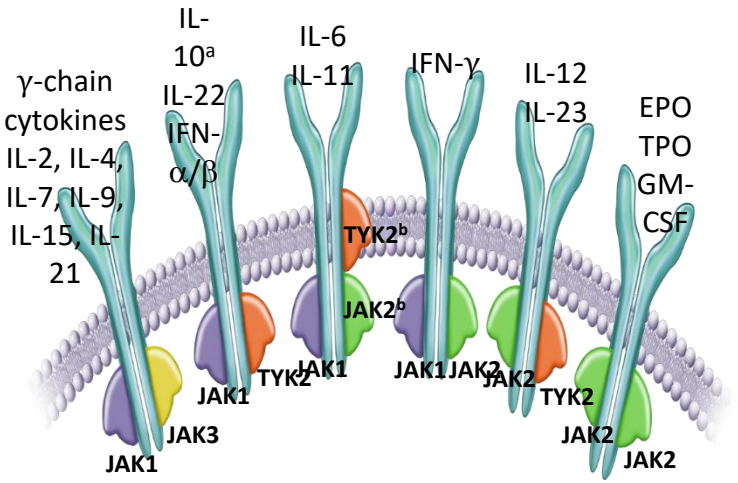
Proteins are phosphorylated by transfer of a phosphate group from ATP to a tyrosine residue

- ATP, adenosine triphosphate

- Levy D, Darnell Jr JE. Nat Rev Mol Cell Biol 2002;3:651–62

The JAK–STAT pathway

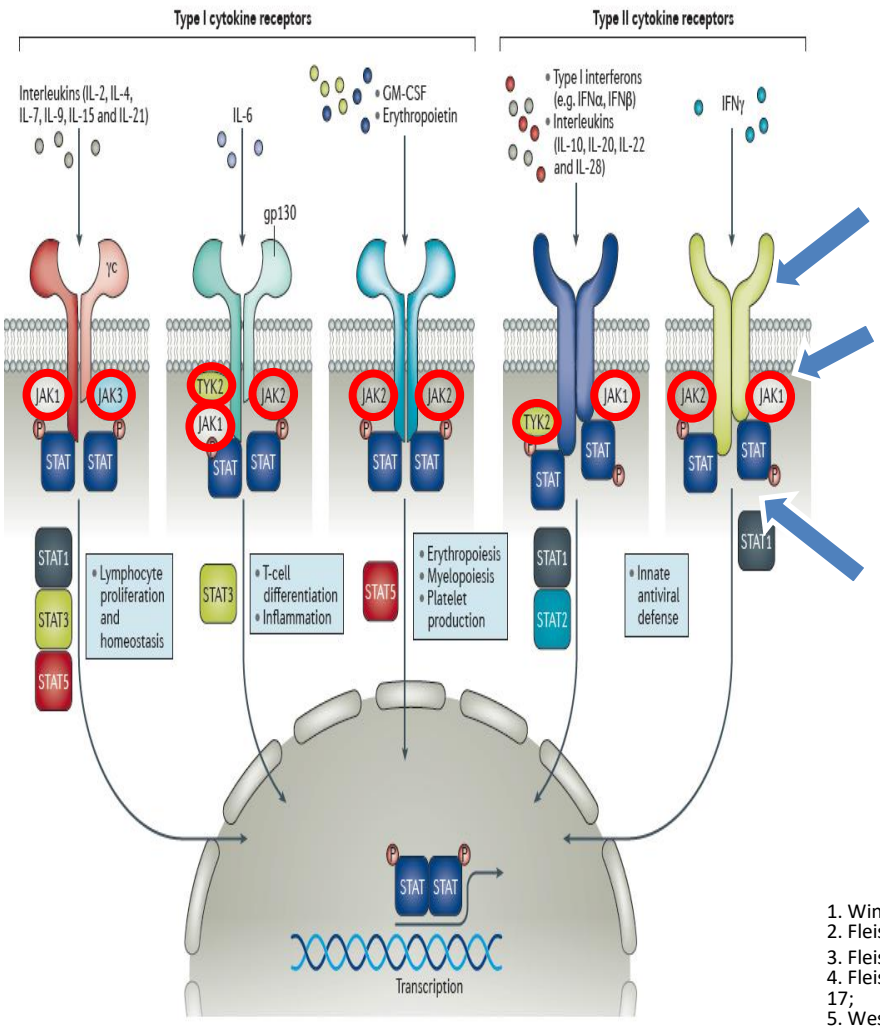
- There are four members of the JAK/TYK family
  - JAK1, JAK2, JAK3, and TYK2
- These are required for signaling downstream of cytokines and growth factors
- Each cytokine/growth factor receptor is associated with a pair of JAK family members
- Certain cytokines/growth factors are implicated in RA pathogenesis (eg IL-6, GM-CSF, IFN, [TNF])



- [a]IL-10/IL-22 may have pro- or anti-inflammatory activities depending on the cellular environment and/or disease state
[b]Type II cytokine receptors such as those for gp130 subunit sharing receptors for IL-6 and IL-11 as well as IL-10, IL-19, IL-20, and IL-22, mainly signal through JAK1, but also associate with JAK2 and TYK2
EPO, erythropoietin; GM-CSF, granuloctye

- Cohen S. Int J Clin Rheumatol 2012;7:413–23; O'Shea JJ, et al. Annu Rev Med 2015;66:311–28;
- Levy D, Darnell Jr JE. Nat Rev Mol Cell Biol 2002;3:651–62; Schwartz DM, et al. Nat Rev Rheumatol 2016;12:25–36;
Ghoreschi K, et al. Immunol Rev 2009;228:273–87; Sanjabi S, et al. Curr Opin Pharmacol 2009;9:447–53;
Winthrop KL. Nat Rev Rheumatol 2017;13:234–43; Firestein GS, McInnes IB. Immunity 2017;46:183–96

The JAK–STAT pathway in cytokine signaling[1]



Tofacitinib[2,3]

- Small-molecule pan-JAK inhibitor
- Oral dosing with/without MTX

Baricitinib[4]

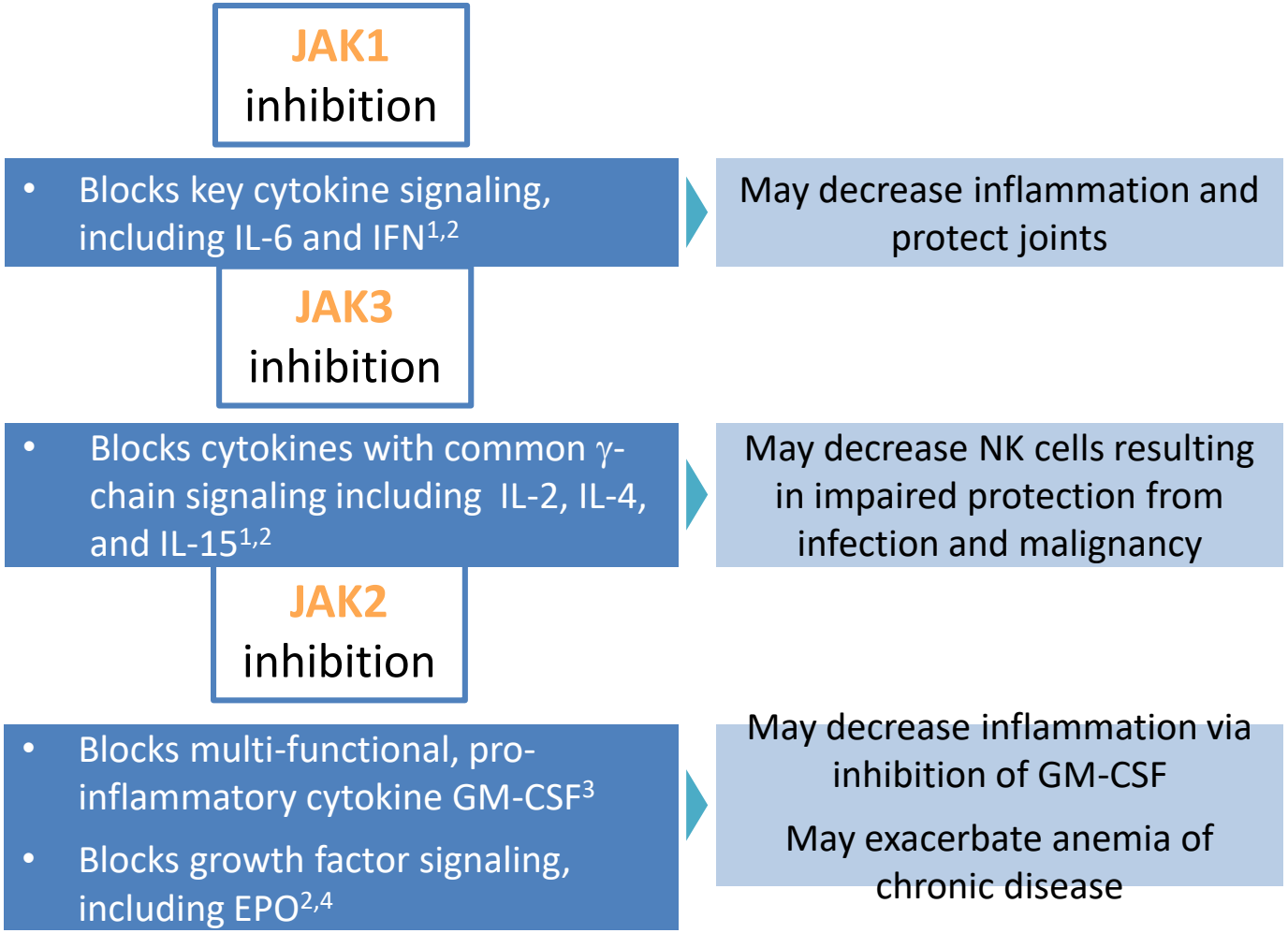
- Small-molecule JAK1/2 inhibitor
- Oral dosing with/without MTX

Upadacitinib[7]

- Small-molecule selective JAK1 inhibitors
- Oral dosing being assessed with/without MTX

1. Winthrop KL, et al. Nat Rev Rheumatol 2017;13:234–43;
2. Fleischmann R, et al. Lancet 2017;390:457–66;
3. Fleischmann R, et al. N Engl J Med 2012;367:495–507;
4. Fleischmann R, et al. Arthritis Rheumatol 2017;69:506–17;
5. Westhovens R, et al. Ann Rheum Dis 2017;76:998–1008;
6. Kavanaugh A, et al. Ann Rheum Dis 2017;76:1009–19;
7. Parmentier JM, et al. BMC Rheum [In press]

JAK signaling: Key cytokines and potential clinical impact

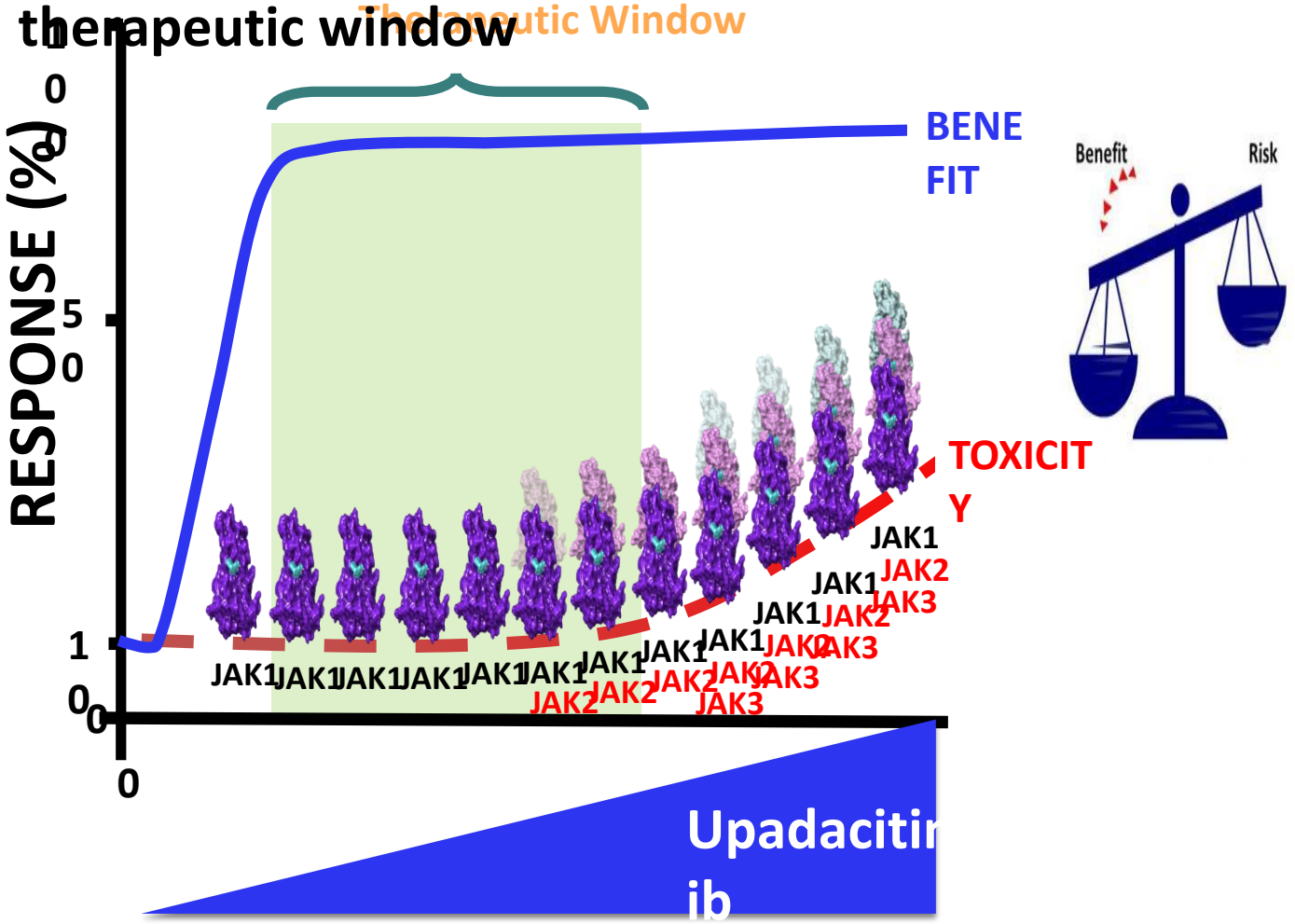


- NK, natural killer

1. O'Shea JJ, et al. Ann Rheum Dis 2013;72:ii111–5; 2. Kiu H, Nicholson SE. Growth Factors 2012;30:88–106;
3. Brizzi MF, et al. J Biol Chem 1996;271:3562–7; 4. Kremer JM, et al. Arthritis Rheumatol 2009;60:1895–905

Upadacitinib: Rationale behind engineering JAK1 selectivity

JAK1 selectivity potentially achieves a broader therapeutic window



Tofa and Bari Phase III Trials

	Tofacitinib	Baricitinib
TNF-IR	**ORAL-STEP** Tofa 5 + MTX; Tofa 10 + MTX; PBO + MTX	**RA-BEACON** Bari 2 + csDMARD; Bari 4 + csDMARD; PBO + csDMARD
MTX-IR	**ORAL SCAN** Tofa 5 + MTX; Tofa 10 + MTX; PBO + MTX **ORAL STRATEGY** (MTX-IR) Tofa 5 + MTX; Tofa 5; ADA + MTX;	**RA-BEAM** (MTX-IR) Bari 4 + MTX; ADA 4 + MTX; PBO + MTX
csDMARDs-IR	**ORAL SYNC** Tofa 5 + csDMARD; Tofa 10 + csDMARD; PBO + csDMARD	**RA-BUILD** Bari 2 + MTX; Bari 4 + MTX; PBO + MTX
MTX-naive	**ORAL START** Tofa 5; Tofa 10; MTX	**RA-BEGIN** Bari 4; Bari 4 + MTX; MTX
Mono	**ORAL SOLO** (csDMARDs or bDMARDs-IR) Tofa 5; Tofa 10; PBO **ORAL STRATEGY** (MTX-IR) Tofa 5 + MTX; Tofa 5; ADA + MTX **ORAL START** (MTX-naive) Tofa 5; Tofa 10; MTX	------- ------- **RA-BEGIN** (MTX-naive) Bari 4; Bari 4 + MTX; MTX
H2H	**ORAL STANDARD** (MTX-IR) Tofa 5 + MTX; Tofa 10 + MTX; ADA + MTX; PBO + MTX	**RA-BEAM** (MTX-IR) Bari 4 + MTX; ADA 4 + MTX; PBO + MTX
Step-down	-----	**RA-BEYOND**

Pharmacokinetics Data: Tofa vs Bari

		TOFACITINIB	BARICITINIB
ABSORPTION			
	Oral Bioavailability	74%	79%
	T1/2	~ 3 h	9.5-12.5 h
	Tmax	1.1 h	1.0 h
	Cmax	Whitin 0.5-1 h	1.08
	Steady state concentrations	24-48 h	48 h
DISTRIBUTION			
	Volume of Distribution	87 L	76 L
	Protein Binding	~ 40%	~ 50%
METABOLISM			
	Hepatic Metabolism	70%	5%
	CYP3A4	Primarily	~10%
	CYP2C19	Minor	0
	Metabolites	8	4
ELIMINATION			
	Renal Excretion	30%	69%
	Fecal Excretion	0	~20%

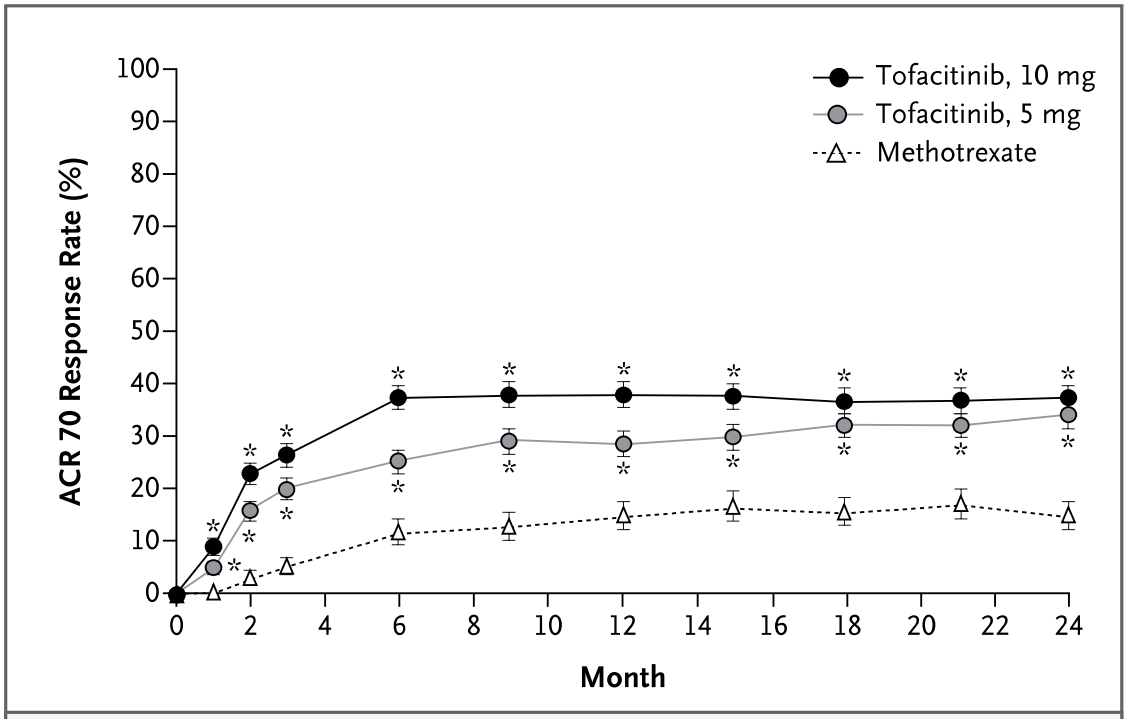
The NEW ENGLAND JOURNAL of MEDICINE

DMARD-naive

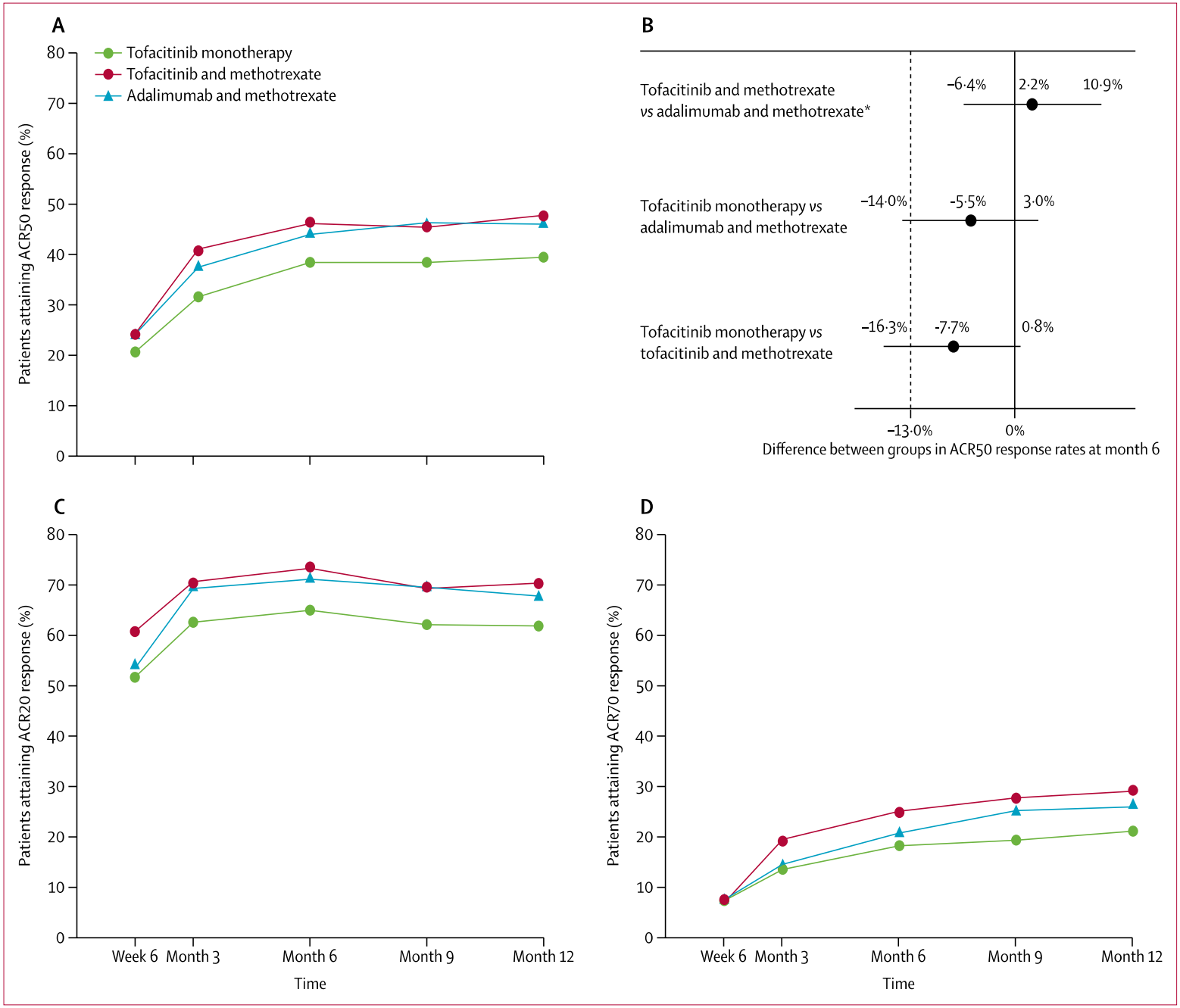
ORIGINAL ARTICLE

Tofacitinib versus Methotrexate in Rheumatoid Arthritis

Eun Bong Lee, M.D., Roy Fleischmann, M.D., Stephen Hall, M.D., Bethanie Wilkinson, Ph.D., John D. Bradley, M.D., David Gruben, Ph.D., Tamas Koncz, M.D., Sriram Krishnaswami, Ph.D., Gene V. Wallenstein, Ph.D., Chuanbo Zang, Ph.D., Samuel H. Zwillich, M.D., and Ronald F. van Vollenhoven, M.D., for the ORAL Start Investigators*



TOFA vs ADA
&
Mono vs combo



Fleischmann R et al. *Lancet* 2017; S0140-6736(17)31618-5.

RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL ARTICLE

Safety and maintenance of response for tofacitinib monotherapy and combination therapy in rheumatoid arthritis: an analysis of pooled data from open-label long-term extension studies

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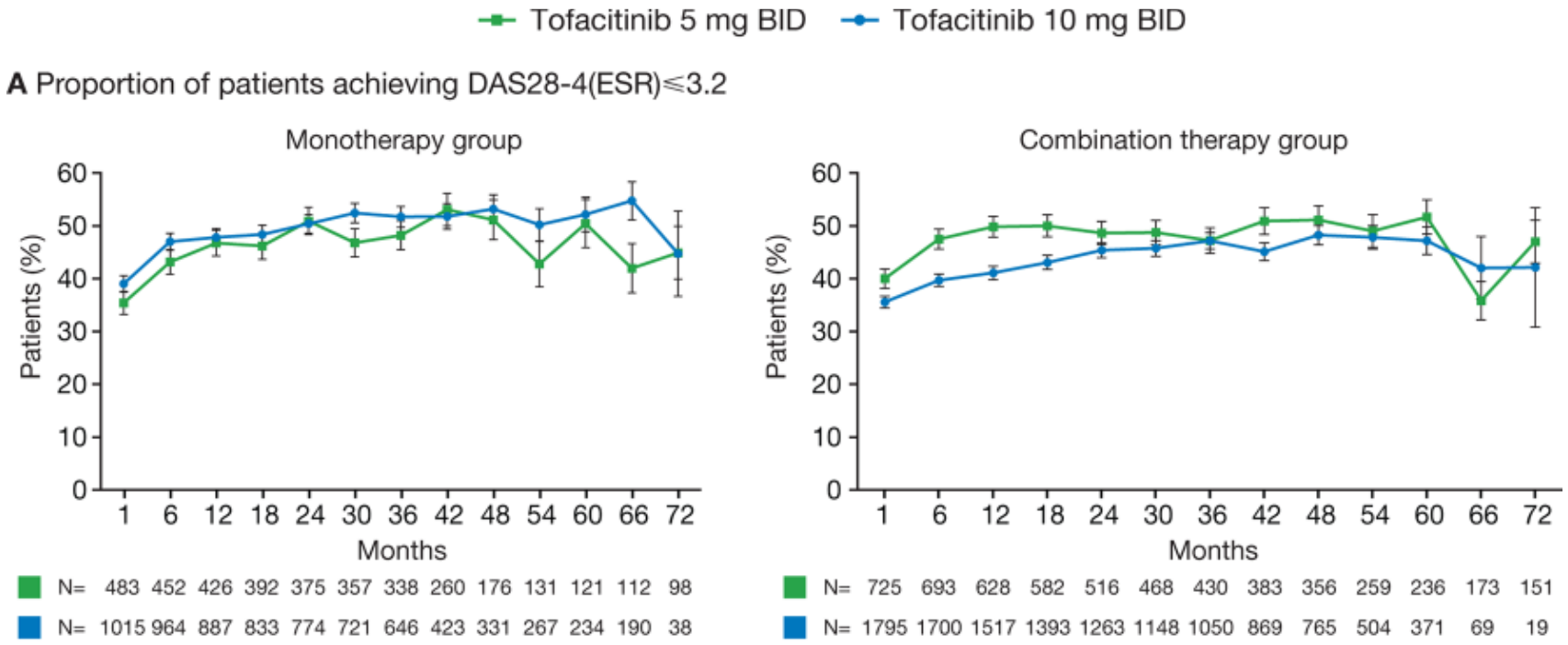
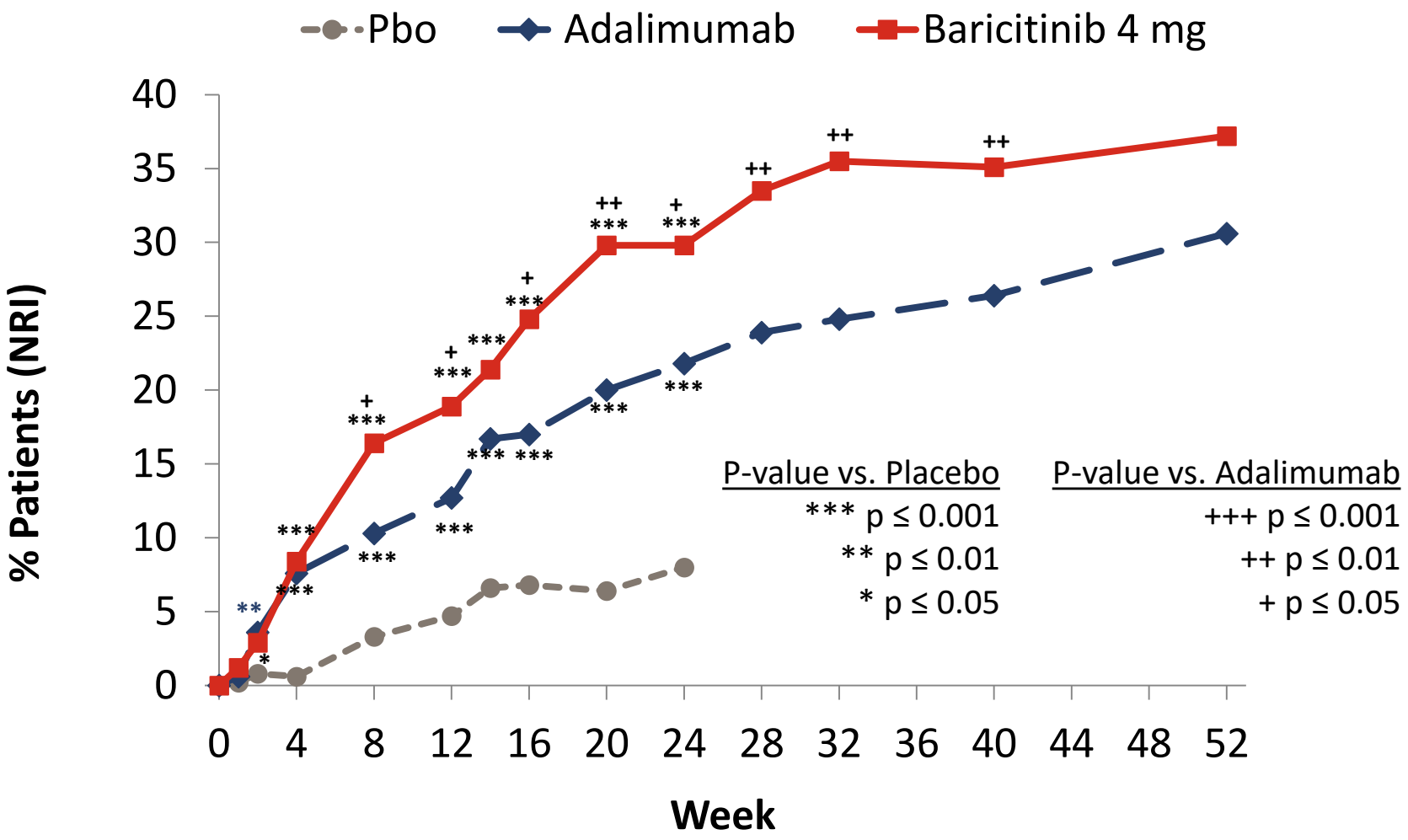


ACR70 Over Time



Unless already rescued patients in placebo group switched to baricitinib at Week 24. Data shown for baricitinib group as randomized.

Taylor PC. NEJM 2017

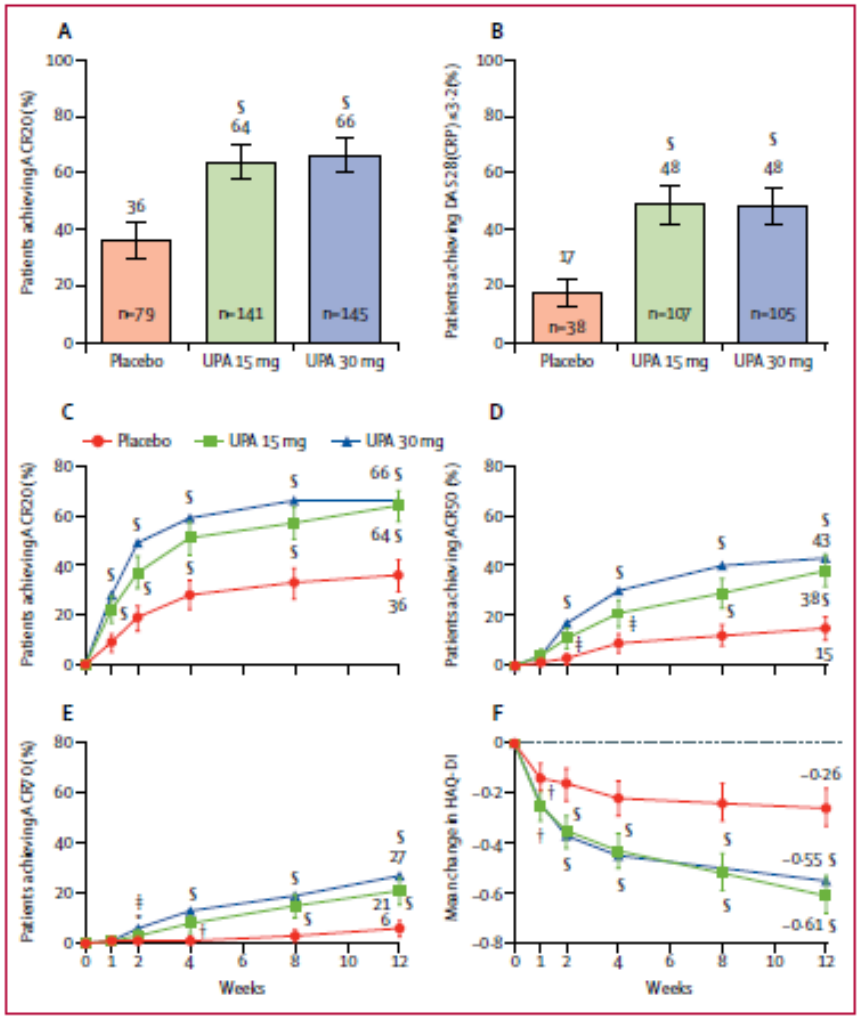
New targets: tomorrow

Overview of ABT-494 RA Phase III program (upadacitinib, JAK-1 selective)

	MTX-IR Signs & symptoms Structure	csDMARD-IR Signs & symptoms	MTX-IR Signs & symptoms	Biologic-IR Signs & symptoms	MTX-naïve Signs & symptoms Structure
	SELECT COMPARE STUDY	SELECT NEXT STUDY	SELECT MONOTHERAPY STUDY	SELECT BEYOND STUDY	SELECT EARLY STUDY
Type of therapy	Combo	Combo	Mono	Combo	Mono
Background	MTX	csDMARDs	–	csDMARDs	–
Active comparator	ADA	–	MTX	–	MTX
Arms	1. 15 QD 2. Placebo 3. ADA	1. 15 QD 2. 30 QD 3. PBO	1. 15 QD 2. 30 QD 3. MTX	1. 15 QD 2. 30 QD 3. PBO	1. 7.5 QD 2. 15 QD 3. 30 QD 4. MTX
Duration of Period 1	48 weeks	12 weeks	14 weeks	24 weeks	48 weeks
Sample size	1500	600	600	450	975

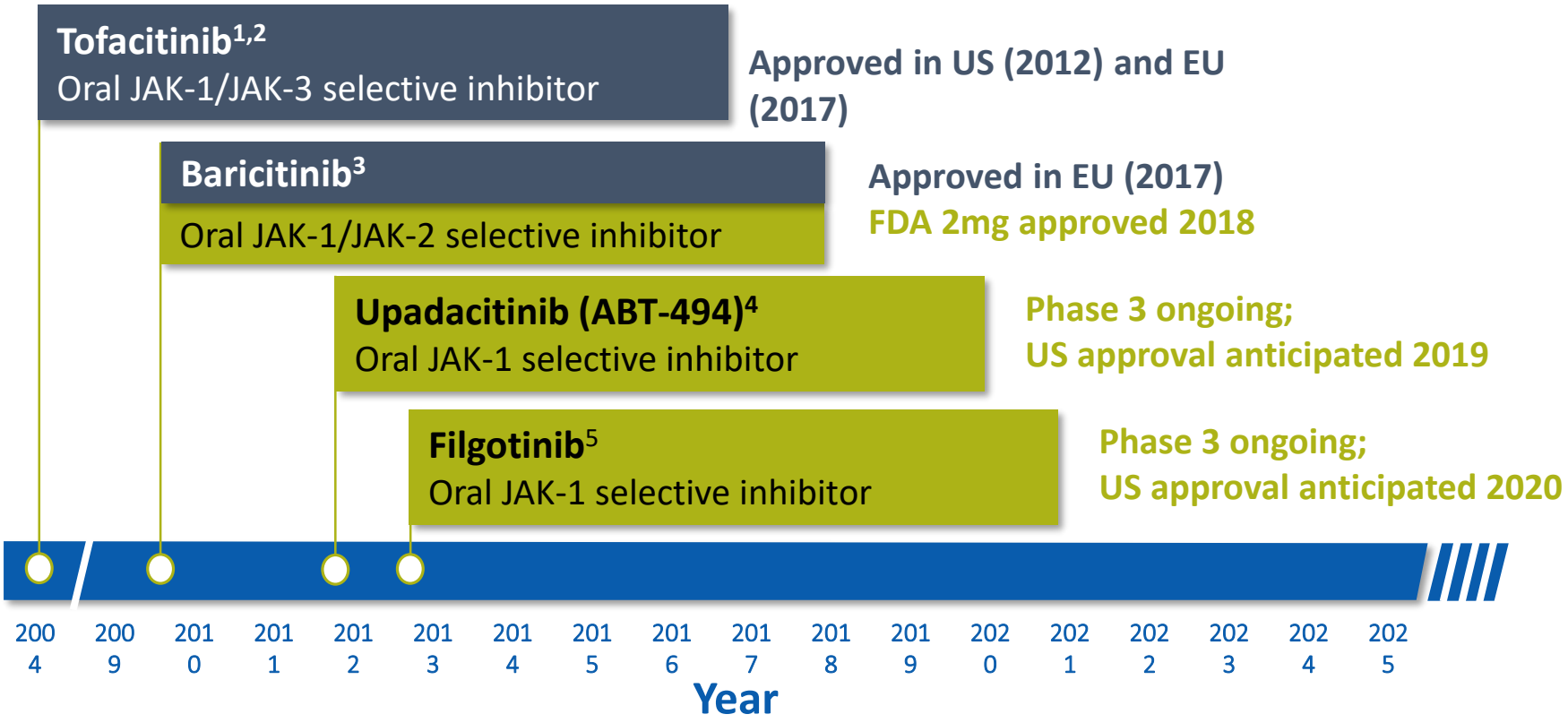
Total size of Phase III program: N=~4,125 RA patients

Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial



Burmester GR, et al. Lancet 2018

JAK inhibitors approvati o in sviluppo per l'AR



1. Xeljanz US product information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203214s000lbl.pdf. Accessed December 8, 2017
2. Xeljanz summary of product characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004214/WC500224911.pdf. Accessed December 8, 2017
3. Olumiant summary of product characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004085/WC500223723.pdf. Accessed December 8, 2017
4. Burmester G, et al. Arthritis Rheum 2017; 69(Suppl. 10):1904; 5.