Ρευματοειδής αρθρίτιδα και σπονδυλοαρθροπάθειες
Κλινική έρευνα

Εαρινές Ημέρες Ρευματολογίας
Καλαμάτα, Ιούνιος 2019

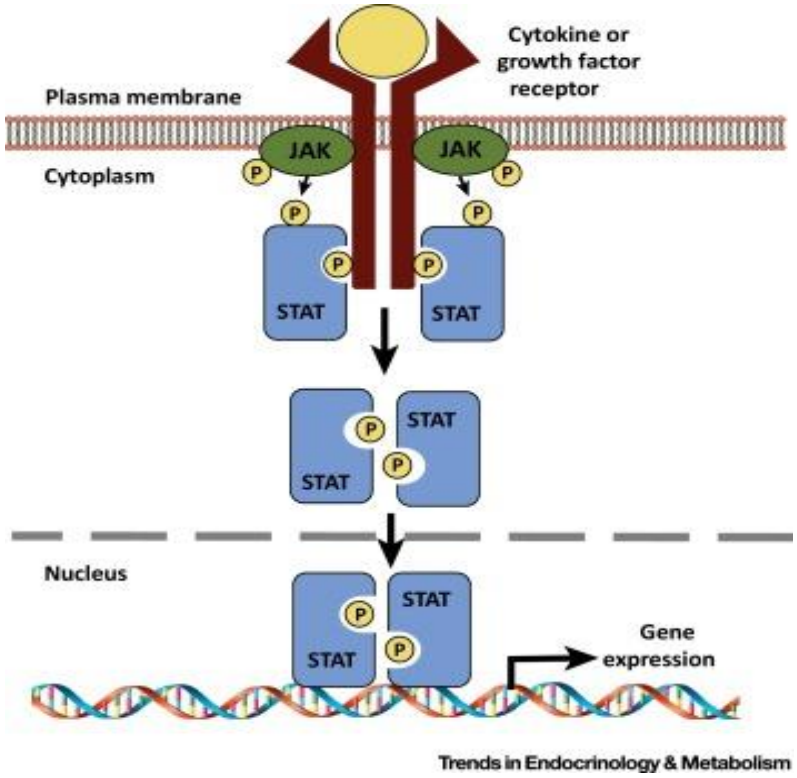
Δαούσης Δημήτρης
Αναπλ. καθηγητής Παθολογίας/Ρευματολογίας
Ιατρική Σχολή Πανεπιστημίου Πατρών

Μεθοδολογία

- PubMed
  - Rheumatoid arthritis
  - Clinical trials
  - 3/2018-2019
  - 108 results

  - Spondyloarthritis
  - 30 results

Jakinibs-Μια καινούργια θεραπευτική κατηγορία με ταχεία εξέλιξη



- **Υπάρχουν τέσσερα μέλη της οικογένειας JAK: JAK1, JAK2, JAK3, και TYK2**

Παράδειγμα κυτταροκινών που σηματοδοτούν μέσω συνδυασμών JAK/STAT[1–3]

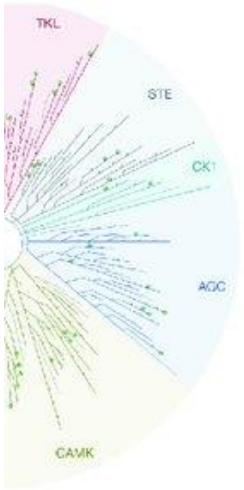
Κυτταροκίνες γ-αλυσίδας[2]	IFN-γ	IL-10 IL-22	IL-12 IL-23	IL-6 IL-11	EPO TPO GM-CSF
JAK1 JAK3	JAK1 JAK2	JAK1 TYK2	JAK2 TYK2	JAK1 JAK2 TYK2	JAK2 JAK2
STAT 1, 3, 5, 6	STAT 1, 3, 5	STAT 1, 3, 5	STAT 3, 4	STAT 1, 3, 5	STAT 5

Κόκκινο = επικρατέστερες STAT

Η μελλοντική έρευνα μπορεί να βοηθήσει στην πρόβλεψη επιδράσεων της αναστολής JAK σε διαφορετικούς ασθενείς και να επιτρέψει στους γιατρούς να λαμβάνουν τεκμηριωμένες αποφάσεις σχετικά με το ποιο ζεύγος JAK πρέπει να στοχεύουν σε κάθε ασθενή[4]

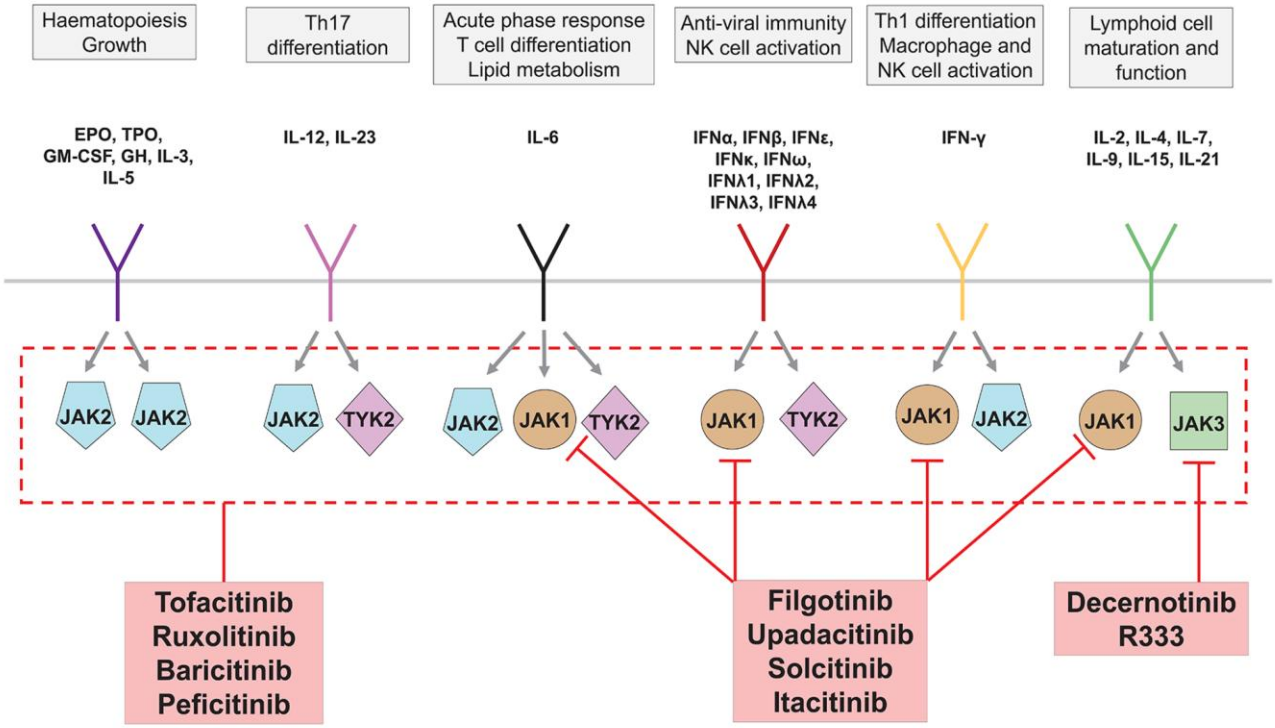
Next generation jakinibs

- Εκλεκτική στόχευση
  Jak1 ή Jak3

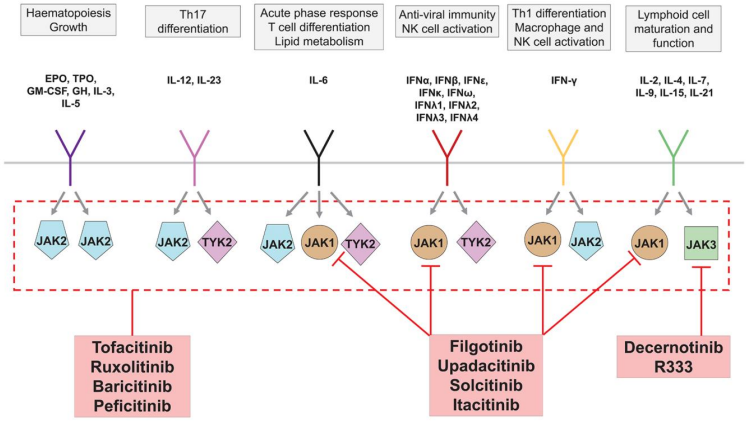


B

Target
JAK1
JAK2
JAK3
TYK2



Selective vs non-selective jakinibs



- Θεωρητικά η εκλεκτική στόχευση θα βελτίωνε την ασφάλεια και θα περιόριζε το εύρος ενδείξεων
- Στην πράξη όμως δεν φάνηκε σαφές όφελος όσον αφορά την ασφάλεια
- Μάλλον δεν περιορίζεται ιδιαίτερα το φάσμα ενδείξεων
- Όλα δοκιμάζονται σε όλα!!!

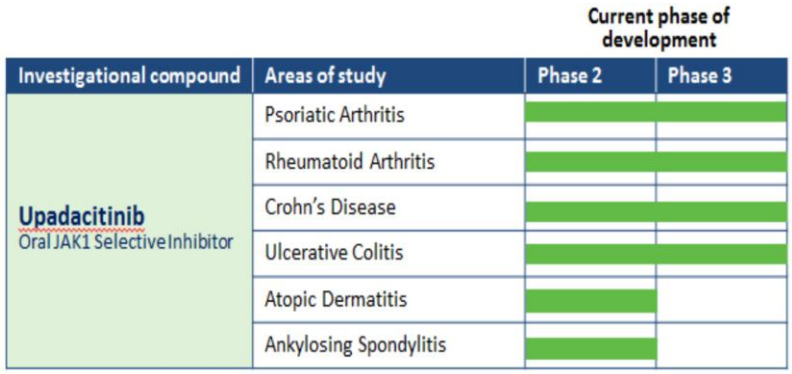
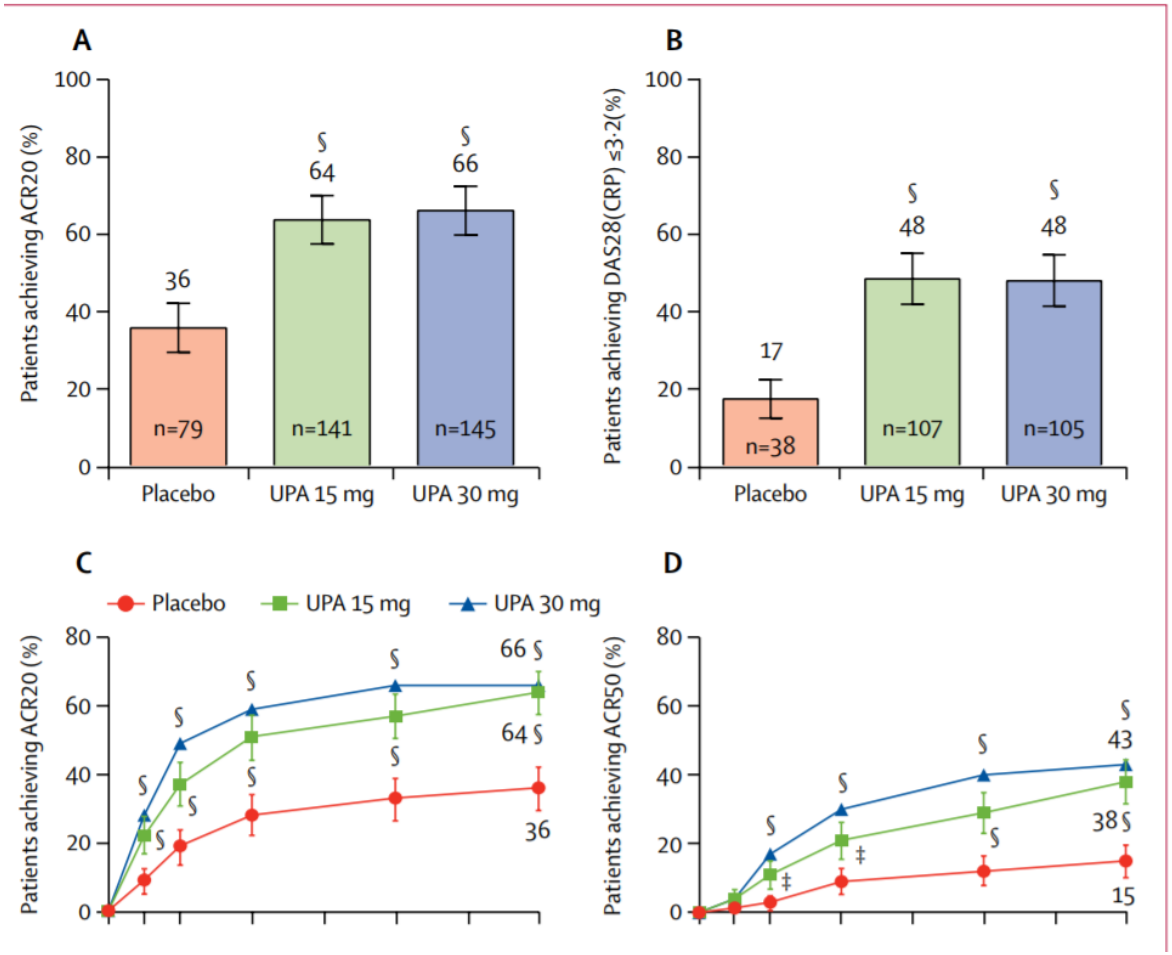


Figure. Upadacitinib Clinical Trials
Source: ClinicalTrials.gov.

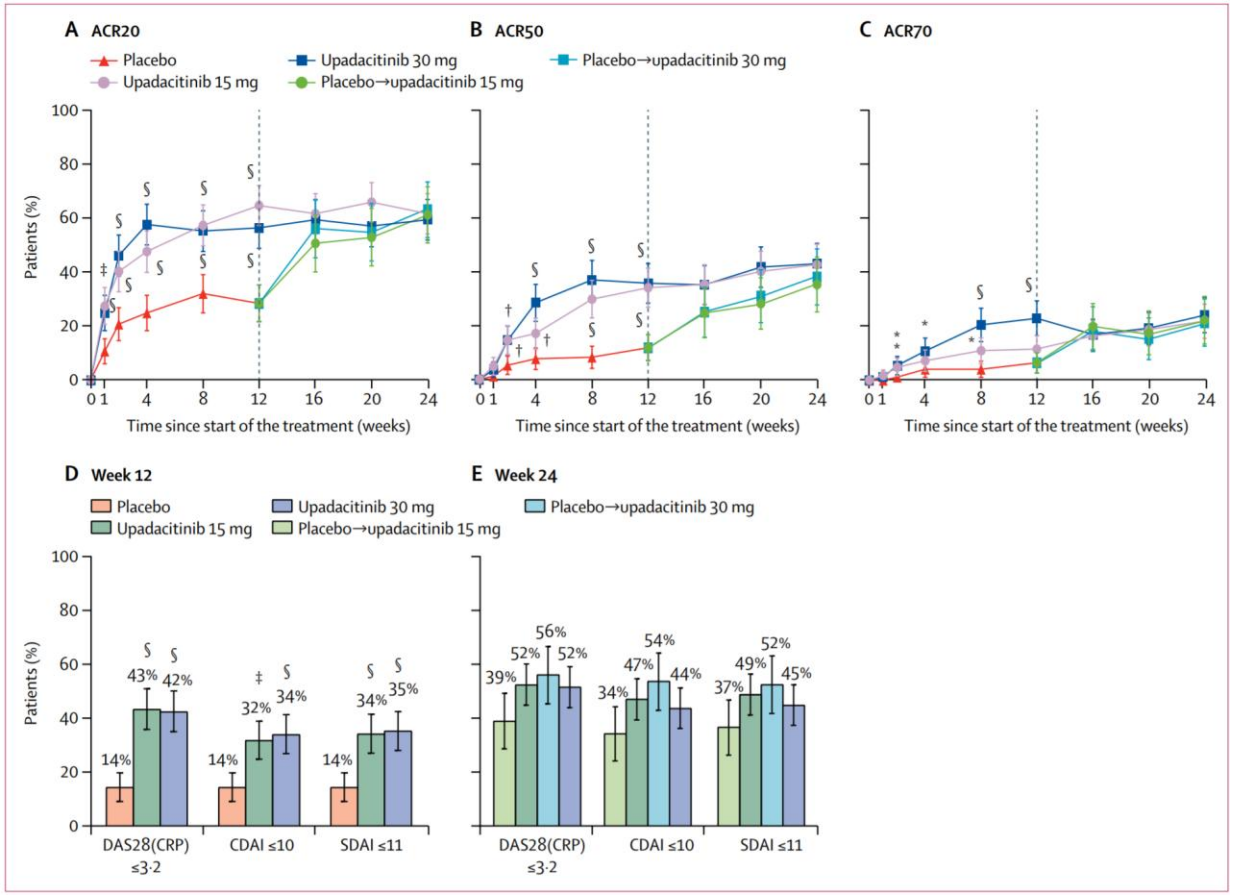
Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial

Gerd R Burmester, Joel M Kremer, Filip Van den Bosch, Alan Kivitz, Louis Bessette, Yihan Li, Yijie Zhou, Ahmed A Othman, Aileen L Pangan, Heidi S Camp



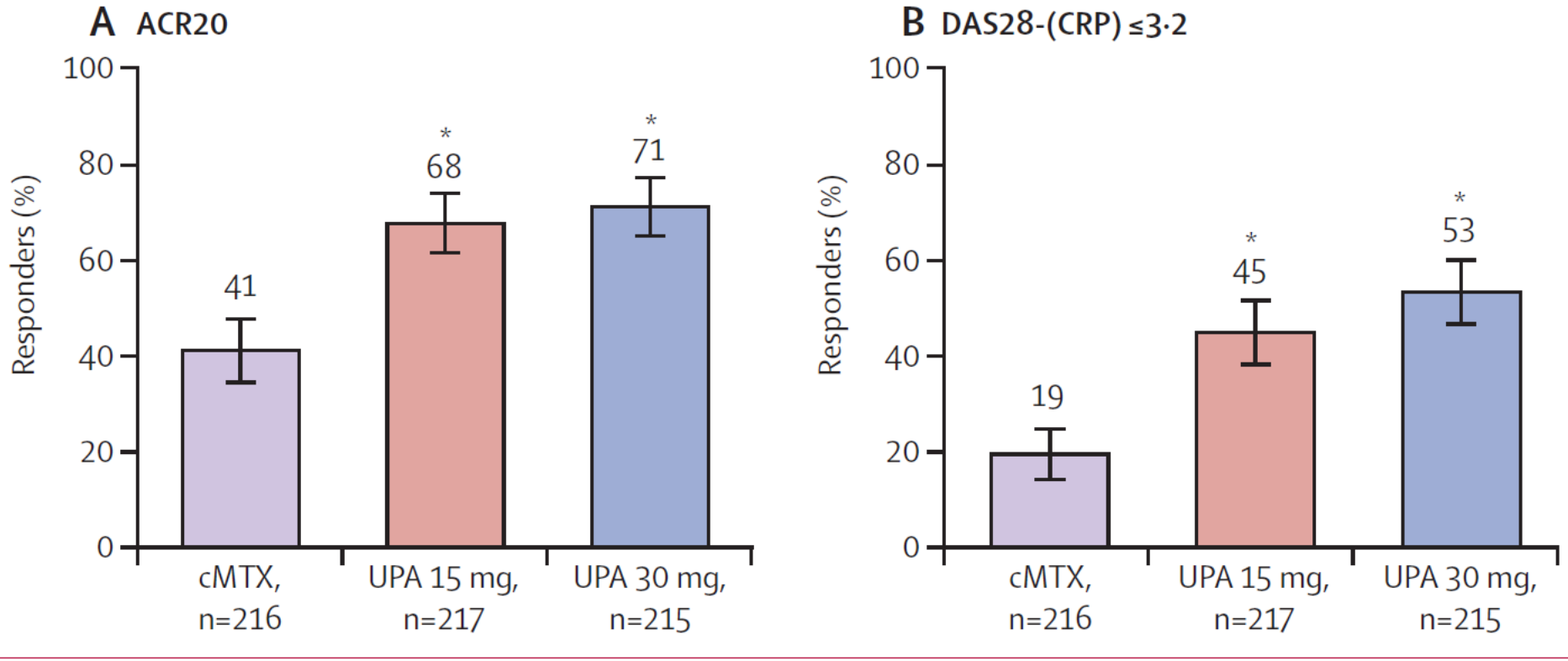
Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial

Mark C Genovese, Roy Fleischmann, Bernard Combe, Stephen Hall, Andrea Rubbert-Roth, Ying Zhang, Yijie Zhou, Mohamed-Eslam F Mohamed, Sebastian Meerwein, Aileen L Pangan



Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inadequate response to methotrexate (SELECT-MONOTHERAPY): a randomised, placebo-controlled, double-blind phase 3 study

Josef S Smolen, Aileen L Pangan, Paul Emery, William Rigby, Yoshiya Tanaka, Juan Ignacio Vargas, Ying Zhang, Nemanja Damjanov, Alan Friedman, Ahmed A Othman, Heidi S Camp, Stanley Cohen



Scandinavian Journal of Rheumatology

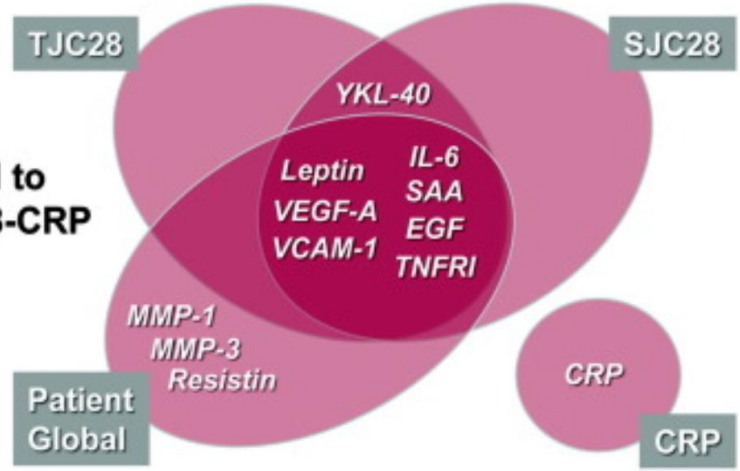
ISSN: 0300-9742 (Print) 1502-7732 (Online) Journal homepage: https://www.tandfonline.com/loi/irhe20

Predictive value of a multi-biomarker disease activity score for clinical remission and radiographic progression in patients with early rheumatoid arthritis: a post-hoc study of the OPERA trial

$$\text{DAS28-CRP} = 0.56\sqrt{\text{TJC}} + 0.28\sqrt{\text{SJC}} + 0.14\text{PG} + 0.36\log(\text{CRP} + 1) + 0.96$$

$$\text{MBDA Score} = (0.56\sqrt{\text{PTJC}} + 0.28\sqrt{\text{PSJC}} + 0.14\text{PPG} + 0.36\log[\text{CRP} + 1] + 0.96) \times 10.53 + 1$$

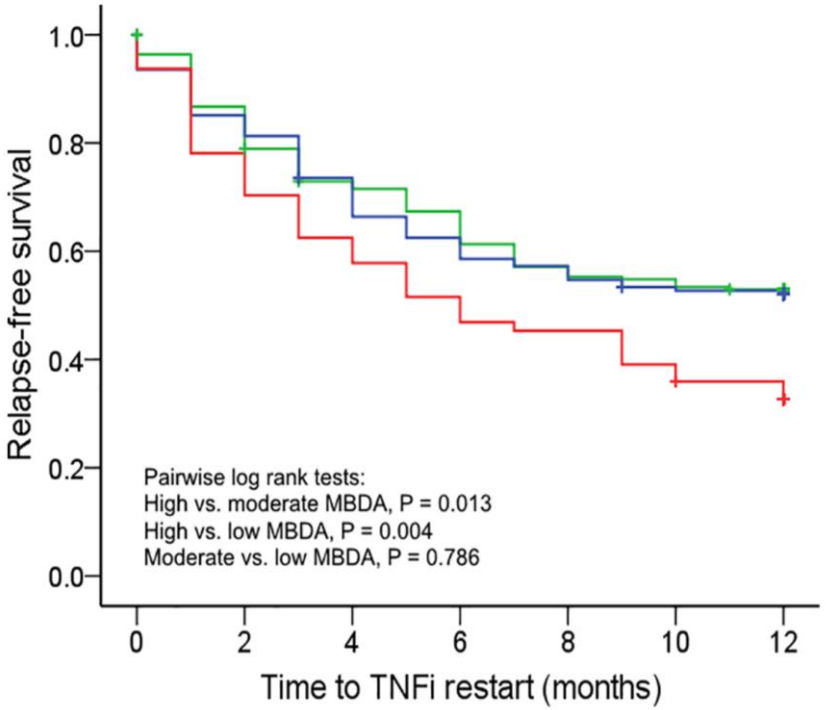
Biomarkers Used to Predict Each DAS28-CRP Component

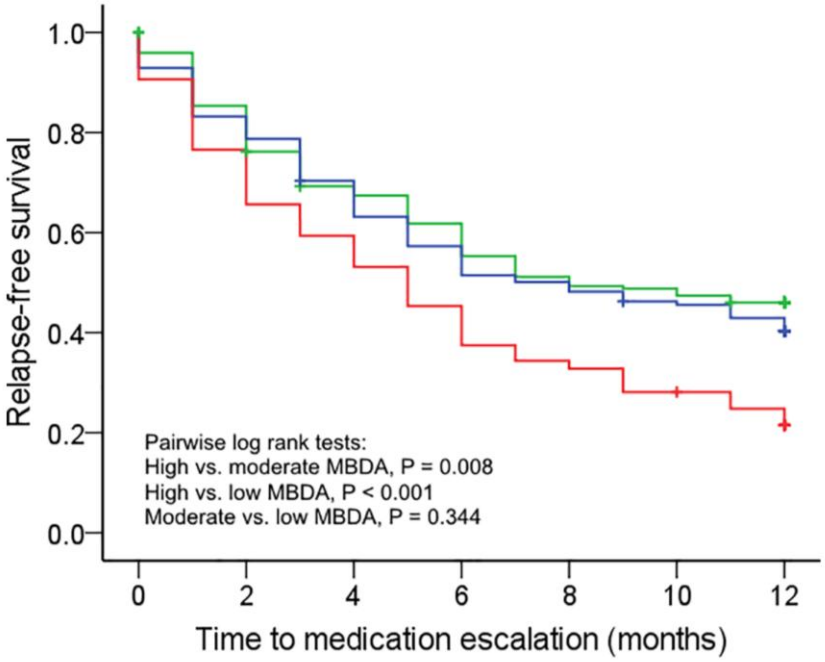


PLOS ONE

RESEARCH ARTICLE

Multi-biomarker disease activity score as a predictor of disease relapse in patients with rheumatoid arthritis stopping TNF inhibitor treatment





Original Investigation

February 5, 2019

More

Effect of Magnetic Resonance Imaging vs Conventional Treat-to-Target Strategies on Disease Activity Remission and Radiographic Progression in Rheumatoid Arthritis

The IMAGINE-RA Randomized Clinical Trial

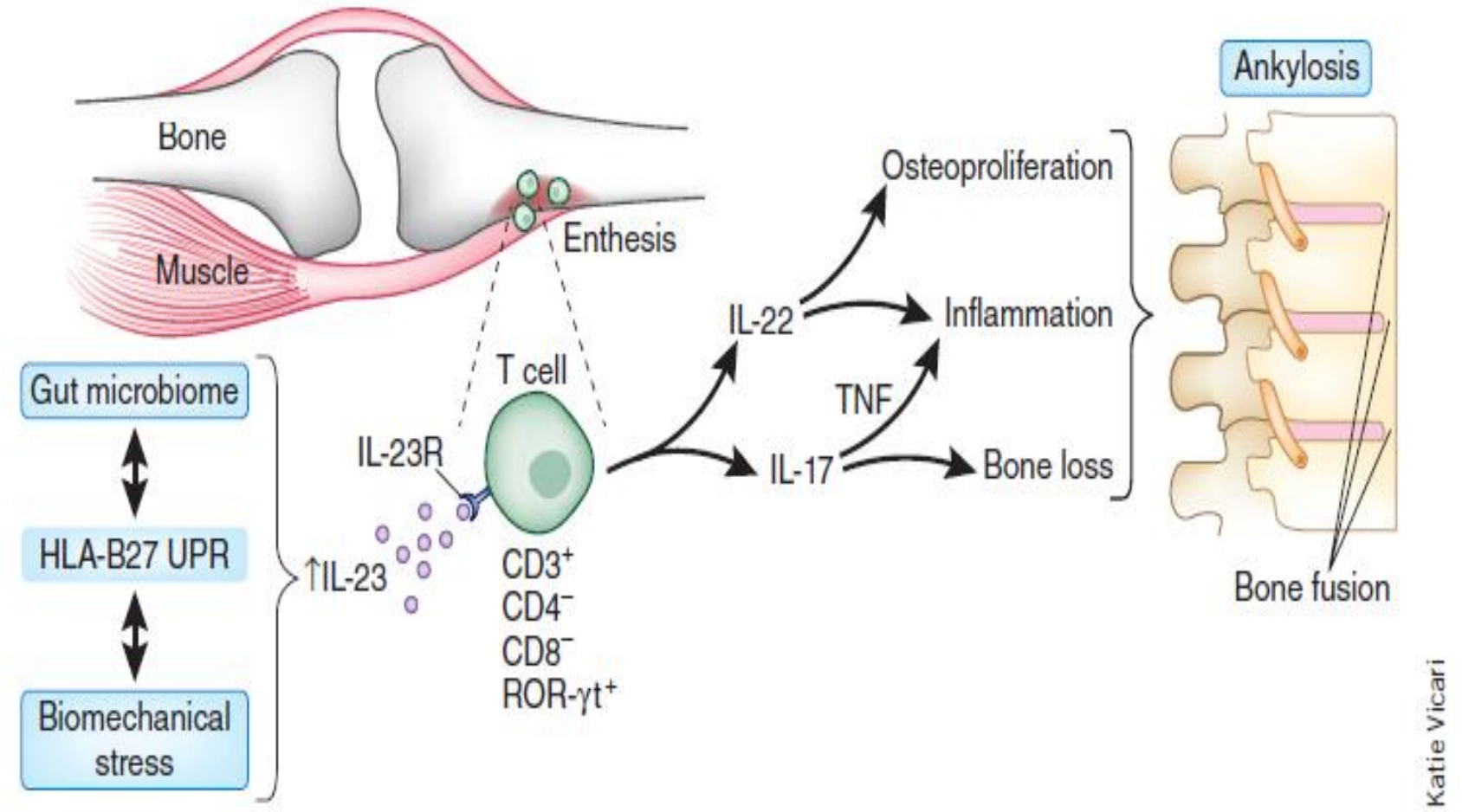
Signe Møller-Bisgaard, MD, PhD[1,2]; Kim Hørslev-Petersen, MD, DMSc[3]; Bo Ejbjerg, MD, PhD[1,4]; et al

Author Affiliations

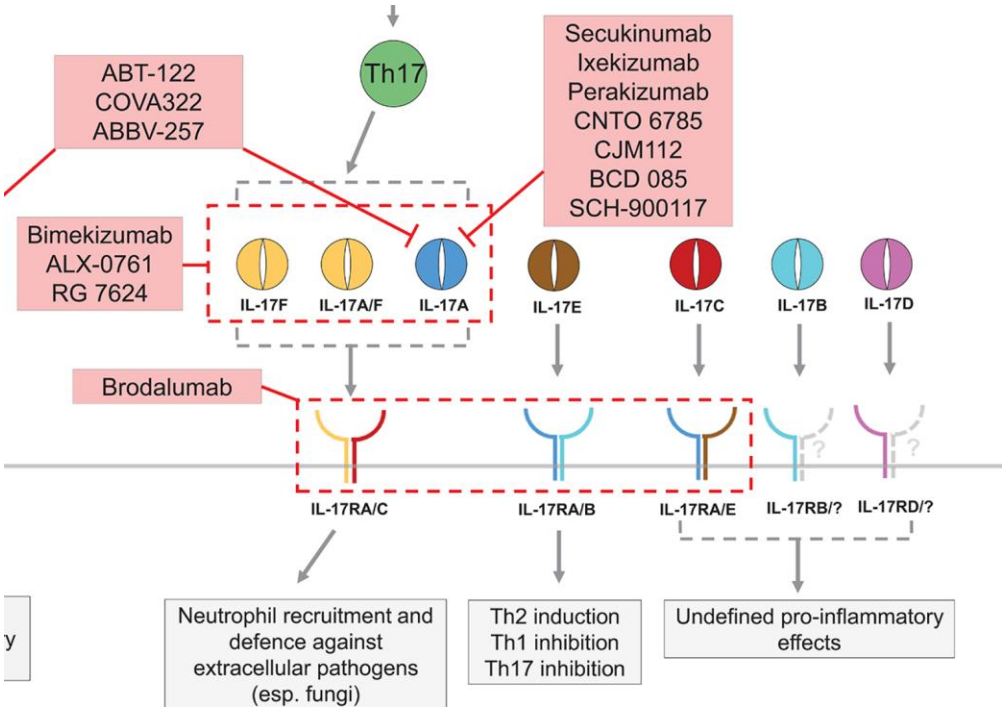
JAMA. 2019;321(5):461-472. doi:10.1001/jama.2018.21362

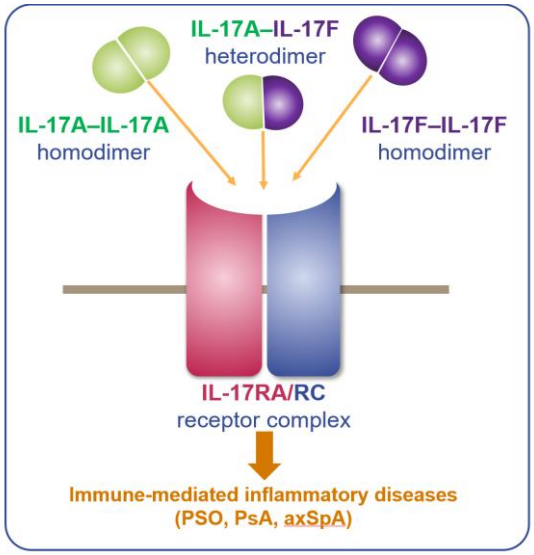
Conclusions and Relevance Among patients with RA in clinical remission, an MRI-guided treat-to-target strategy compared with a conventional treat-to-target strategy did not result in improved disease activity remission rates or reduce radiographic progression. These findings do not support the use of an MRI-guided strategy for treating patients with RA.

ΣΠΑ. Στοχεύοντας τον άξονα IL-23/IL-17



Νεότεροι αναστολείς IL-17
Η IL-17 δεν είναι ένα μόριο....





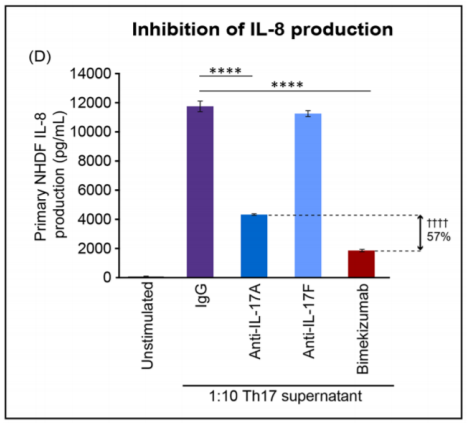
Bimekizumab

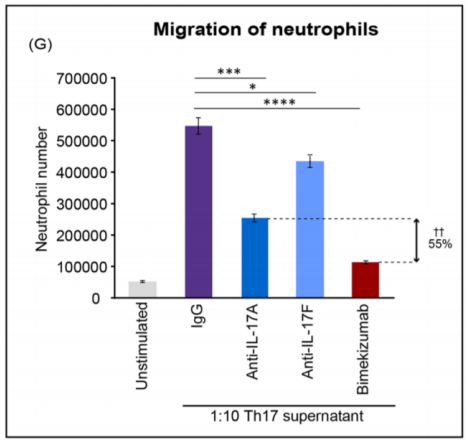
- Inhibitor of IL-17A/F
- Αποτελεσματικό σε όλο το φάσμα ΣΠΑ

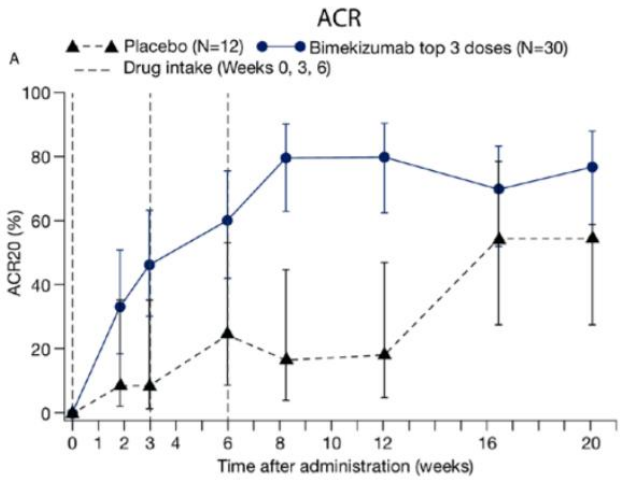
OPEN ACCESS

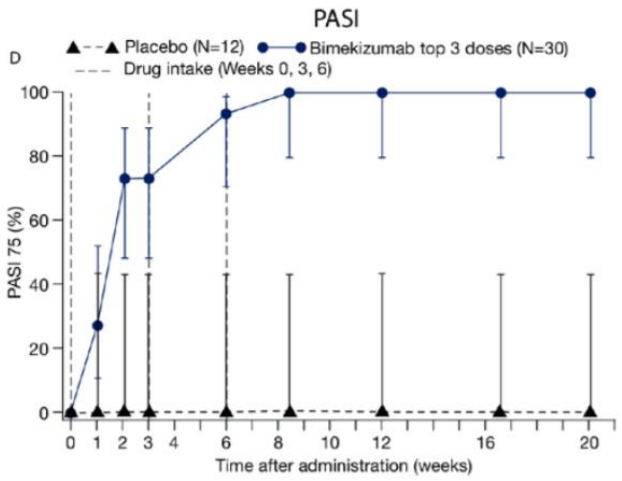
EXTENDED REPORT

Dual IL-17A and IL-17F neutralisation by bimekizumab in psoriatic arthritis: evidence from preclinical experiments and a randomised placebo-controlled clinical trial that IL-17F contributes to human chronic tissue inflammation

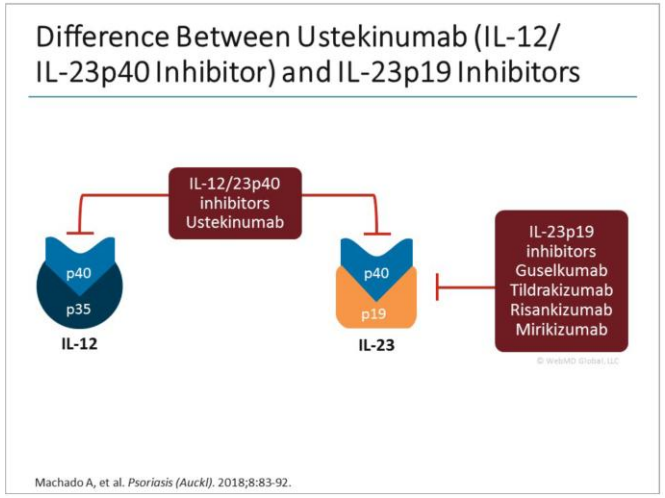








Επικεντρώνοντας στην IL-23….



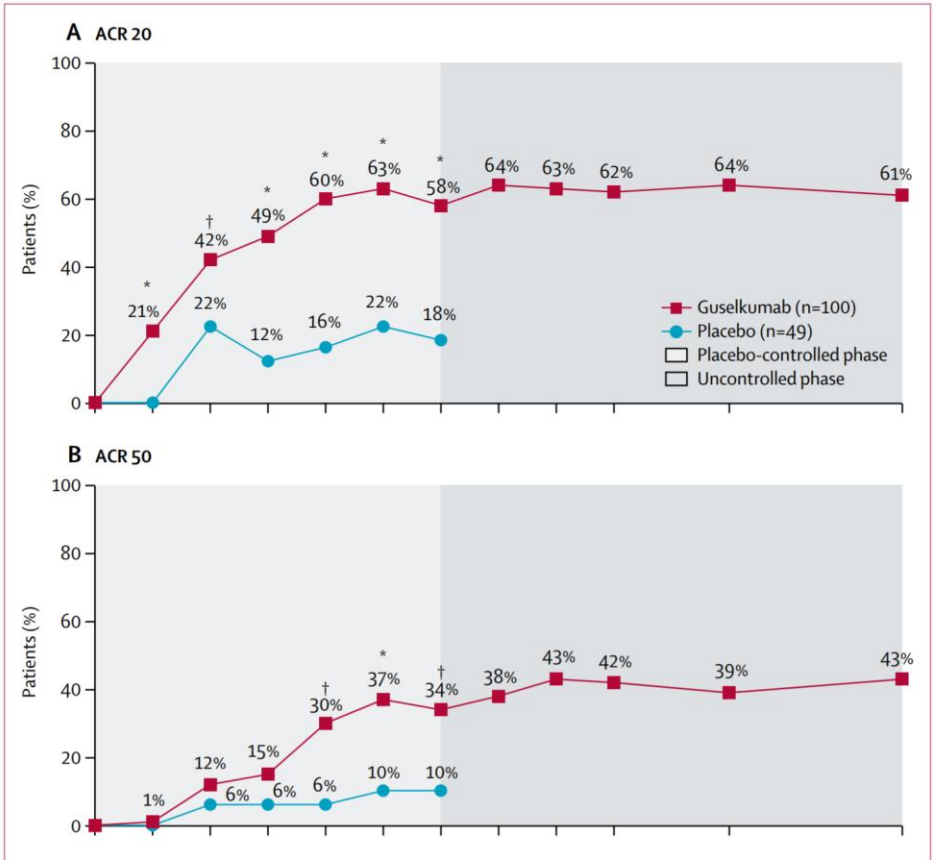
Η αναστολή της IL-12 δεν φαίνεται να προσφέρει κάτι

IL-23 Inhibitors in Moderate-to-Severe Psoriasis -- Approved and in Latest Development Stages

Agent[a]	Mode of action	Dosing[b]	EMA approval
Ustekinumab	IL-12/IL-23p40 inhibitor	45/90 mg (weight ≤ 100 kg/> 100 kg) at W0, W4, and then every 12 weeks	Yes
Guselkumab	IL-23p19 inhibitor	100 mg at W0, W4, and then every 8 weeks	Yes
Tildrakizumab	IL-23p19 inhibitor	100 and 200 mg (weight ≤ 90 kg and > 90 kg) at W0, W4, and then every 12 weeks	Yes
Risankizumab	IL-23p19 inhibitor	90/180 mg at W0, W4, and then every 12 weeks	Pre-approval
Mirikizumab[b]	IL-23p19 inhibitor	30/100/300 mg at W0 and W8[c]	Phase 3

Efficacy and safety of guselkumab in patients with active psoriatic arthritis: a randomised, double-blind, placebo-controlled, phase 2 study

Atul Deodhar, Alice B Gottlieb*, Wolf-Henning Boehncke, Bin Dong, Yuhua Wang, Yanli Zhuang, William Barchuk, Xie L Xu, Elizabeth C Hsia, on behalf of the CNTO1959PSA2001 Study Group*



PASI75	6/48 (13%)	77/98 (79%)
PASI50	14/48 (29%)	85/98 (87%)
PASI90	3/48 (6%)	65/98 (66%)
PASI100	3/48 (6%)	39/98 (40%)

Οι εκλεκτικοί αναστολείς της IL-23 δεν δουλεύουν στην αξονική ΣΠΑ

Article Text

Article info

Citation Tools

Clinical and epidemiological research

PDF

Risankizumab, an IL-23 inhibitor, for ankylosing spondylitis: results of a randomised, double-blind, placebo-controlled, proof-of-concept, dose-finding phase 2 study

Dominique Baeten[1], Mikkel Østergaard[2, 3], James Cheng-Chung Wei[4, 5], Joachim Sieper[6], Pentti Järvinen[7], Lai-Shan Tam[8], Carlo Salvarani[9, 10], Tae-Hwan Kim[11], Alan Solinger[12], Yakov Datsenko[13], Chandrasena Pamulapati[12], Sudha Visvanathan[12], David B Hall[12], Stella Aslanyan[12], Paul Scholl[12], Steven J Padula[14]

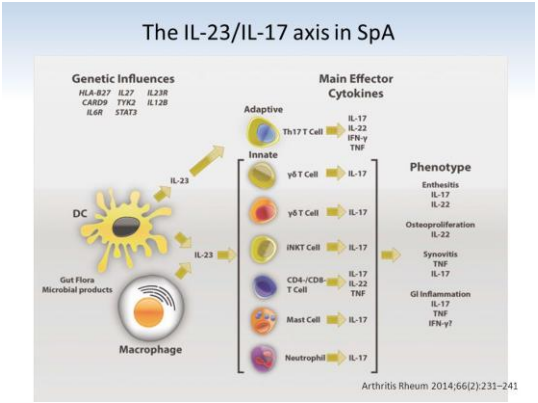
Διαφορές μεταξύ φαρμάκων που δρουν στον ίδιο άξονα

IL12/23 and Il-23 inhibitors

- Psoriasis ✓
- PsA-Peripheral SpA ✓
- AS, Axial SpA ✗
- IBD ✓
- uveitis ✗

Il-17 inhibitors

- Psoriasis ✓
- PsA-Peripheral SpA ✓
- AS, Axial SpA ✓
- IBD ✗
- uveitis ✗



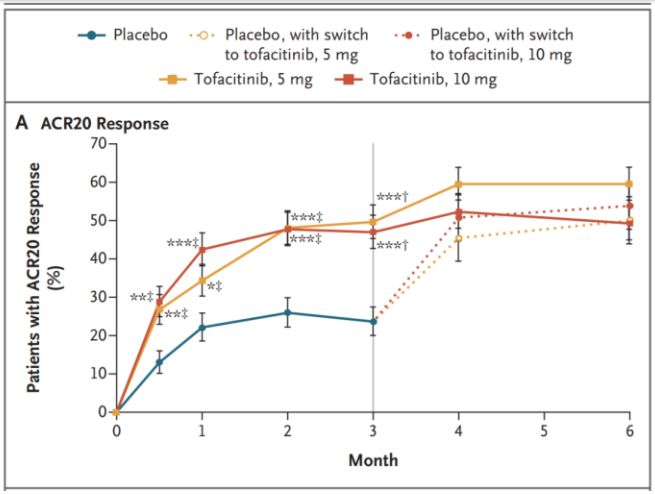
Jakinibs και στις ΣΠΑ

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tofacitinib for Psoriatic Arthritis in Patients with an Inadequate Response to TNF Inhibitors

Dafna Gladman, M.D., William Rigby, M.D., Valderilio F. Azevedo, M.D., Ph.D., Frank Behrens, M.D., Ricardo Blanco, M.D., Andrzej Kaszuba, M.D., Ph.D., Elizabeth Kudlacz, Ph.D., Cunshan Wang, Ph.D., Sujatha Menon, Ph.D., Thijs Hendrikx, Ph.D., and Keith S. Kanik, M.D.



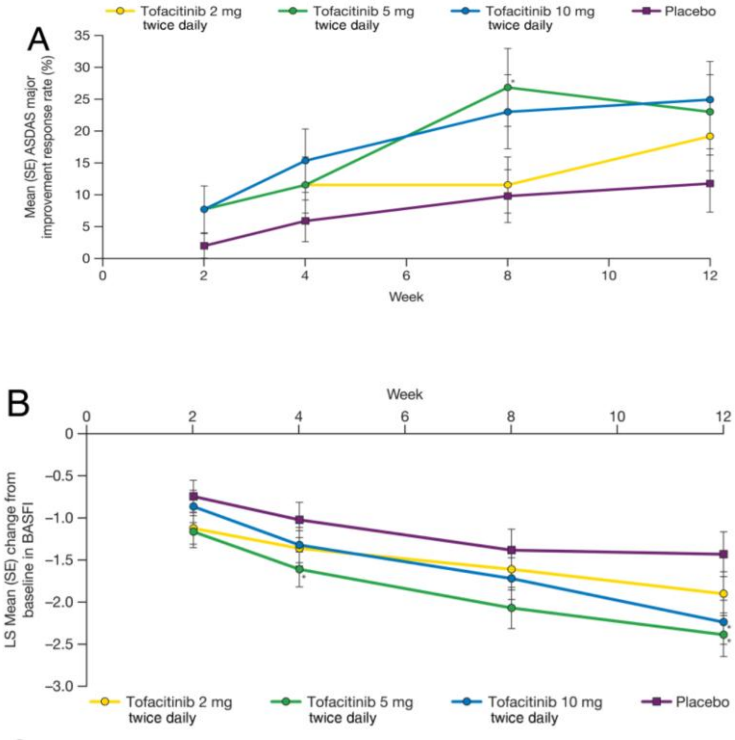
ARD Online First, published on January 27, 2017 as 10.1136/annrheumdis-2016-210322
Clinical and epidemiological research

OPEN ACCESS

EXTENDED REPORT

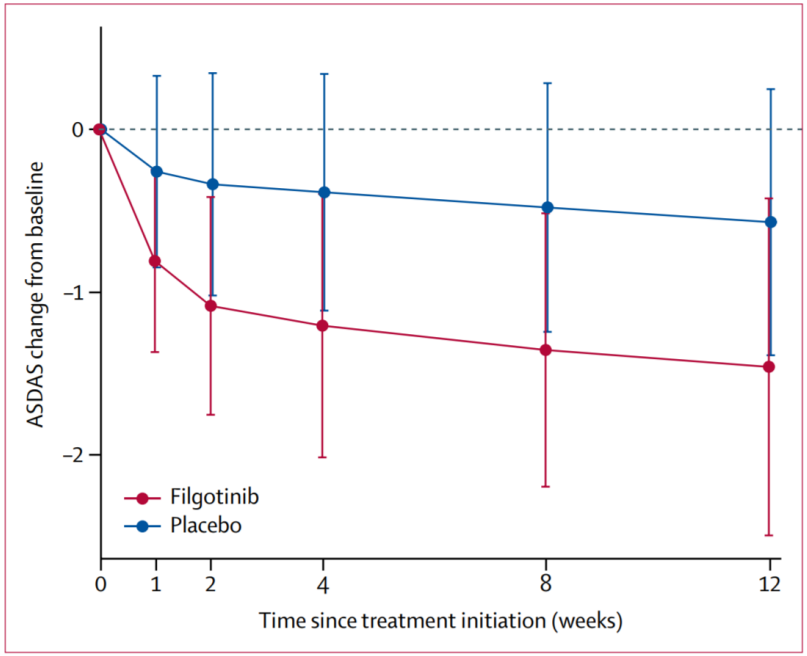
Tofacitinib in patients with ankylosing spondylitis: a phase II, 16-week, randomised, placebo-controlled, dose-ranging study

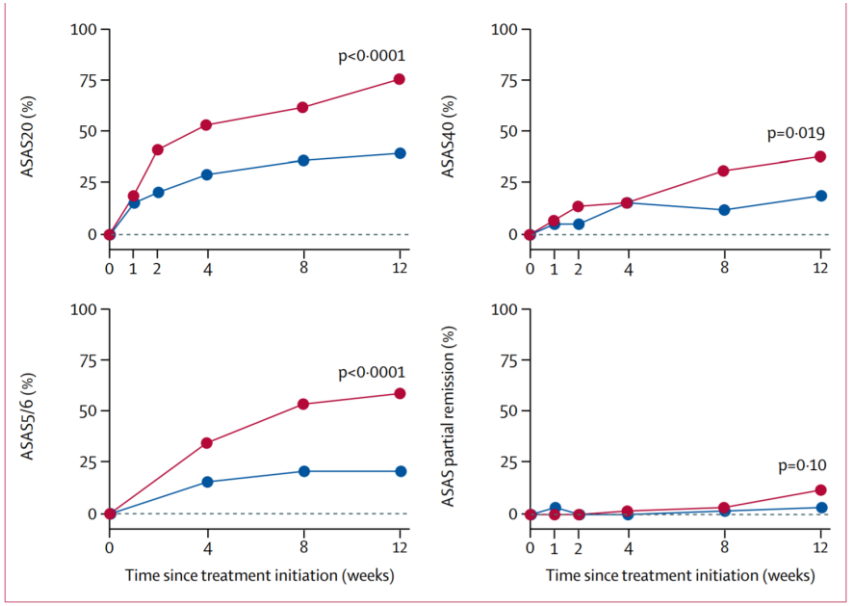
Désirée van der Heijde,[1] Atul Deodhar,[2] James C Wei,[3] Edit Drescher,[4] Dona Fleishaker,[5] Thijs Hendrikx,[6] David Li,[6] Sujatha Menon,[5] Keith S Kanik[5]



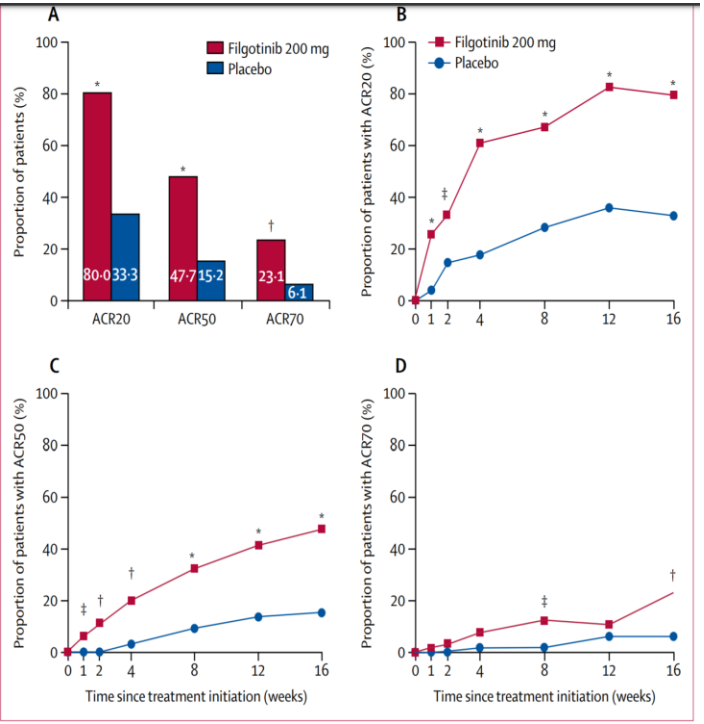
Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active ankylosing spondylitis (TORTUGA): results from a randomised, placebo-controlled, phase 2 trial

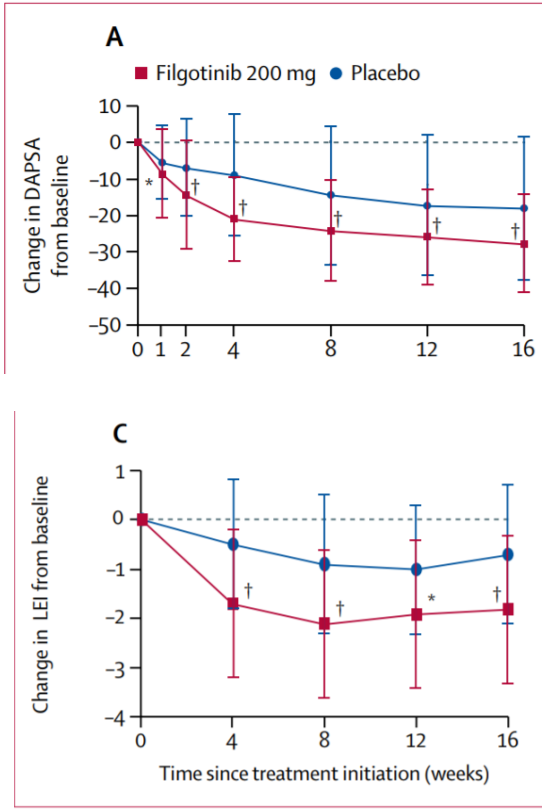
Désirée van der Heijde, Xenofon Baraliakos, Lianne S Gensler, Walter P Maksymowych, Vira Tseluyko, Oleg Nadashkevich, Walid Abi-Saab, Chantal Tasset, Luc Meuleners, Robin Besuyen, Thijs Hendrikx, Neelufar Mozaffarian, Ke Liu, Joy M Greer, Atul Deodhar, Robert Landewé

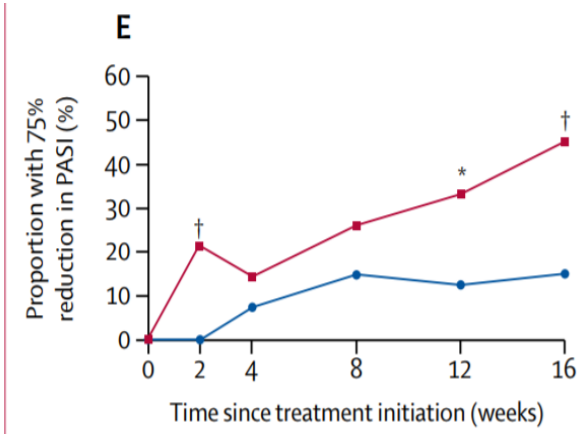




Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active psoriatic arthritis (EQUATOR): results from a randomised, placebo-controlled, phase 2 trial





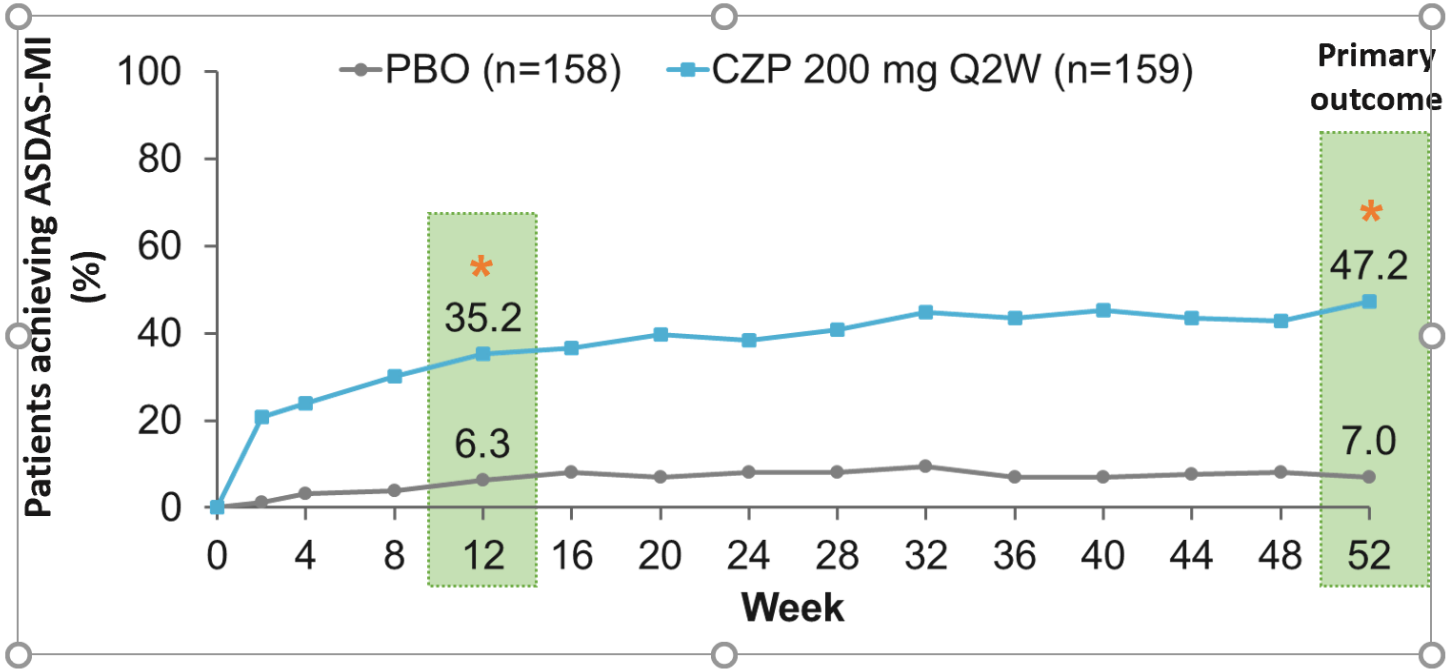


Article tpye: Full Length

Nr-AxSpA

A 52-Week Randomized Placebo-Controlled Trial of Certolizumab Pegol in Non-Radiographic Axial Spondyloarthritis

Primary Outcome: ASDAS-MI at Week 52



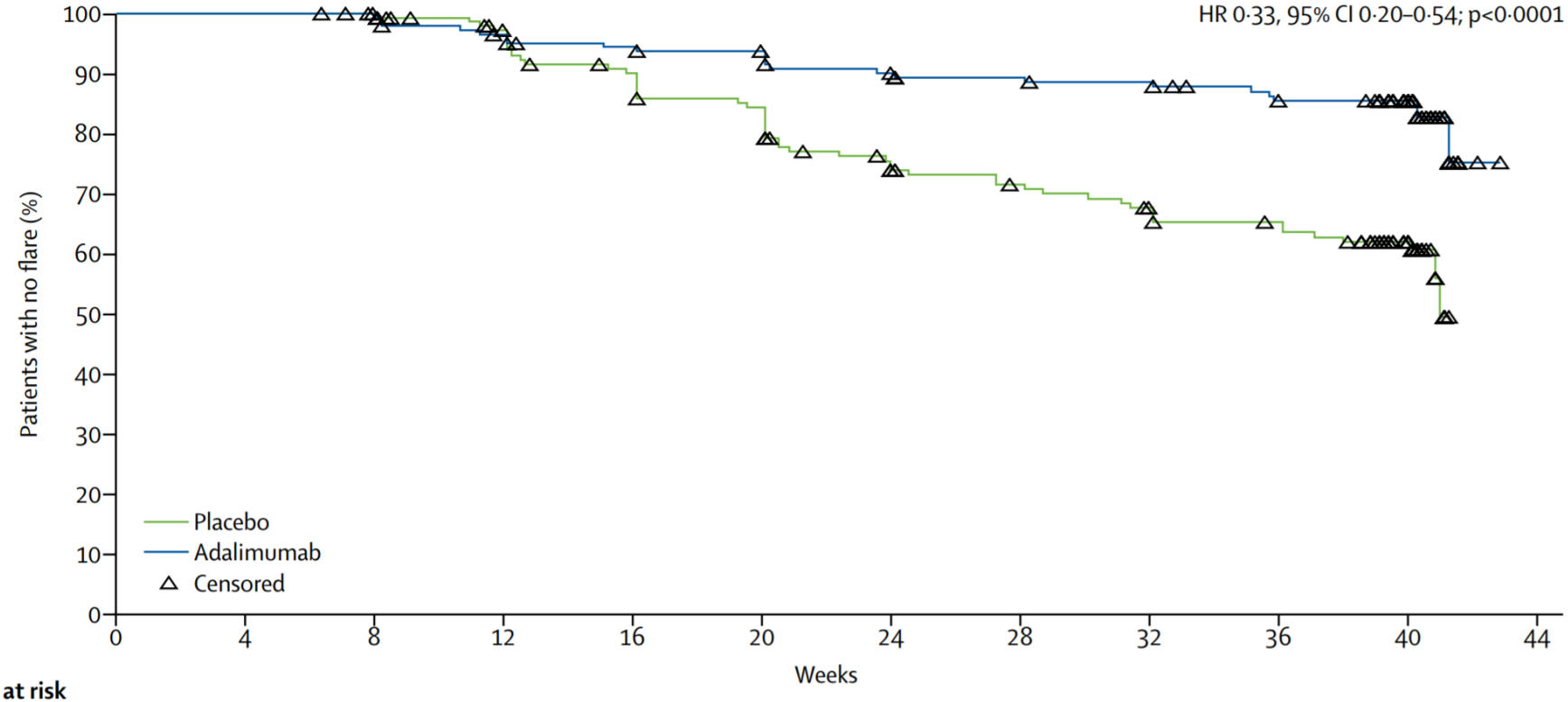
Deodhar A et al. ACR 2018. Oral Presentation 1868.

- *p<0.001 CZP vs PBO. Full Analysis Set. ASDAS-MI: Ankylosing Spondylitis Disease Activity Score – Major Improvement; FAS: full analysis set; NRI: non-responder imputation; PBO: placebo; CZP: certolizumab pegol; SC: standard care

Email: jimdaoussis@hotmail.com

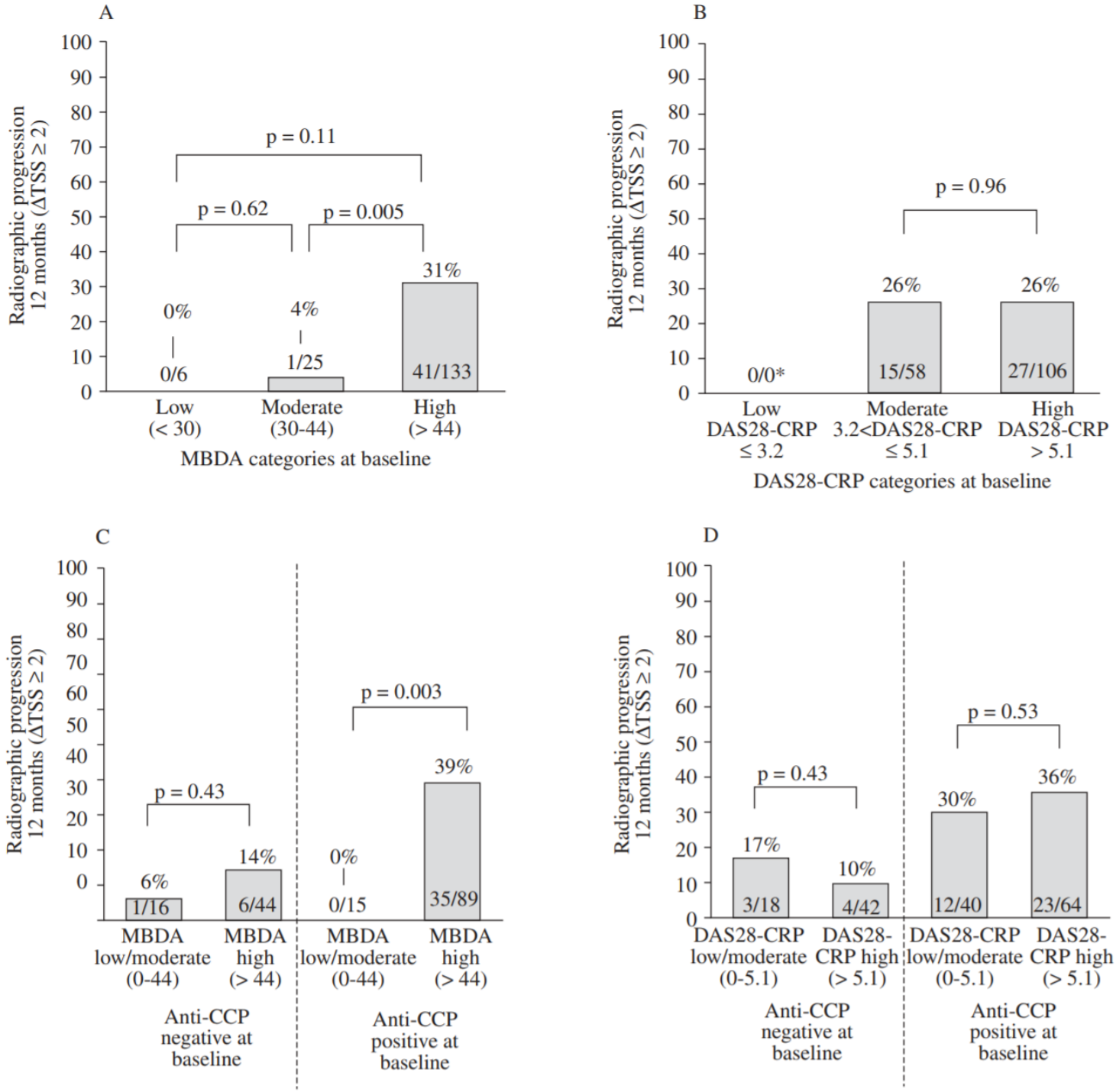
Efficacy and safety of continuing versus withdrawing adalimumab therapy in maintaining remission in patients with non-radiographic axial spondyloarthritis (ABILITY-3): a multicentre, randomised, double-blind study

Robert Landewé, Joachim Sieper, Philip Mease, Robert D Inman, Robert G Lambert, Atul Deodhar, Helena Marzo-Ortega, Marina Magrey, Uta Kiltz, Xin Wang, Mei Li, Sheng Zhong, Nael M Mostafa, Apinya Lertratanakul, Aileen L Pangan, Jaclyn K Anderson



Number at risk (number censored)

Placebo	153 (0)	153 (0)	152 (0)	140 (4)	127 (14)	118 (22)	101 (36)	93 (39)	87 (44)	81 (47)	60 (51)	0 (54)


A
Radiographic progression
12 months (ΔTSS ≥ 2)
p = 0.11
p = 0.62
p = 0.005
0%
0/6
4%
1/25
31%
41/133
Low
(< 30)
Moderate
(30-44)
High
(> 44)
MBDA categories at baseline
B
Radiographic progression
12 months (ΔTSS ≥ 2)
p = 0.96
0/0*
26%
15/58
26%
27/106
Low
DAS28-CRP
≤ 3.2
Moderate
3.2<DAS28-CRP
≤ 5.1
High
DAS28-CRP
> 5.1
DAS28-CRP categories at baseline
C
Radiographic progression
12 months (ΔTSS ≥ 2)
p = 0.43
p = 0.003
6%
1/16
14%
6/44
0%
0/15
39%
35/89
MBDA
low/moderate
(0-44)
MBDA
high
(> 44)
MBDA
low/moderate
(0-44)
MBDA
high
(> 44)
Anti-CCP
negative at
baseline
Anti-CCP
positive at
baseline
D
Radiographic progression
12 months (ΔTSS ≥ 2)
p = 0.43
p = 0.53
17%
3/18
10%
4/42
30%
12/40
36%
23/64
DAS28-CRP
low/moderate
(0-5.1)
DAS28-
CRP high
(> 5.1)
DAS28-CRP
low/moderate
(0-5.1)
DAS28-
CRP high
(> 5.1)
Anti-CCP
negative at
baseline
Anti-CCP
positive at
baseline

RHEUMATOLOGY

Rheumatology 2018;57:1364–1369
doi:10.1093/rheumatology/key105
Advance Access publication 20 April 2018

Concise report

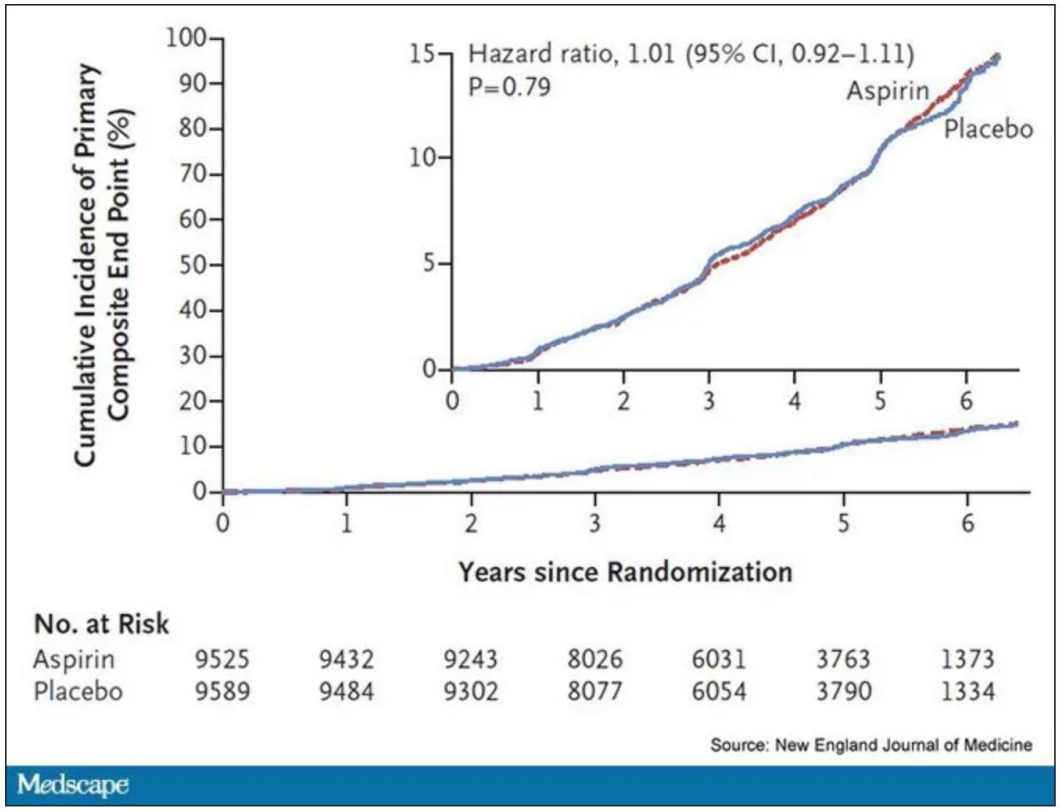
The potential benefits of aspirin for primary cardiovascular prevention in rheumatoid arthritis: a secondary analysis of the PRECISION Trial

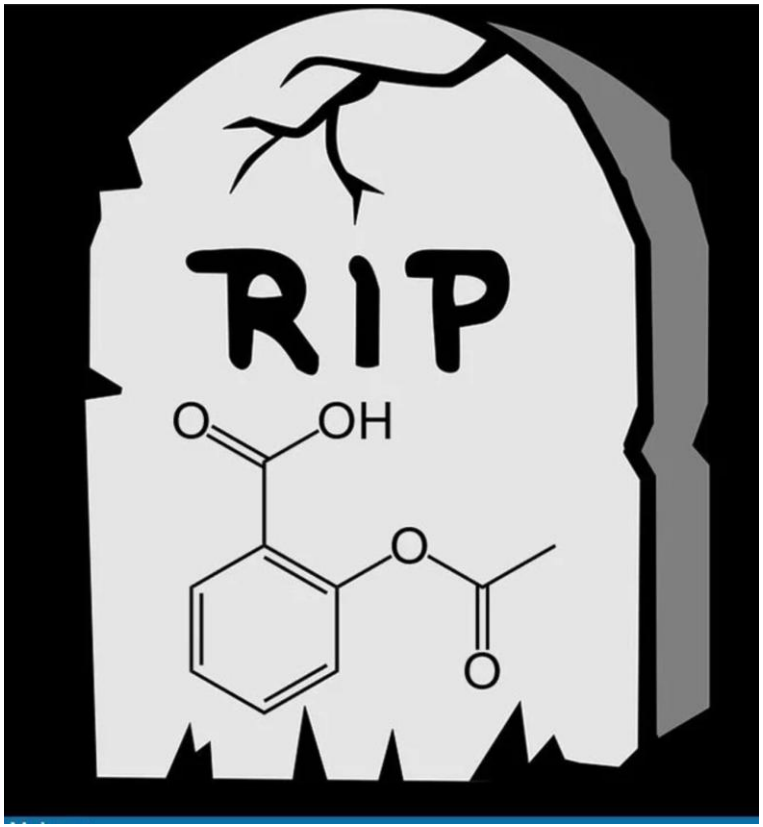
Daniel H. Solomon[1], Peter Libby[1], Neville D. Yeomans[2], Qiuqing Wang[3], Kathy E. Wolski[3], Steven E. Nissen[3] and M. Elaine Husni[3]

TABLE 2 Incidence rate and relative risks for major NSAID toxicity among RA subjects in PRECISION trial

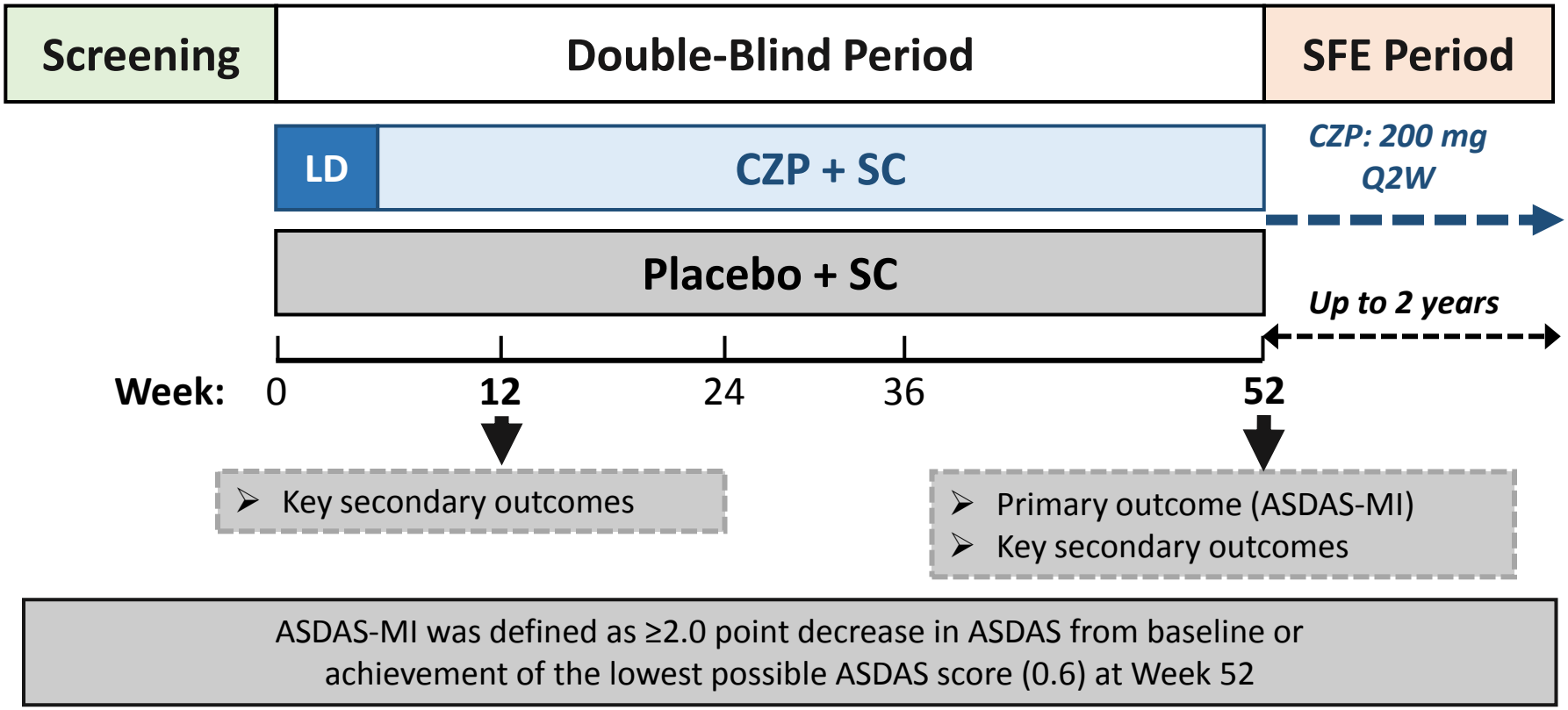
Outcomes	Aspirin use ($n = 540$)		Non-aspirin use ($n = 1312$)		P-value[a]	Hazard ratios (95% CI)	
	Events, n (%)	Incidence rate	Events, n (%)	Incidence rate		Age- and gender-adjusted	Fully adjusted[b]
Major NSAID toxicity	37 (6.9)	3.30	79 (6.0)	2.94	0.50	0.95 (0.64, 1.40)	1.08 (0.69, 1.69)
MACE[c]	22 (4.1)	1.93	37 (2.8)	1.36	0.16	1.23 (0.72, 2.10)	NA
Clinically significant GI events	8 (1.5)	0.70	10 (0.8)	0.37	0.15	1.72 (0.68, 4.40)	NA
Renal events	3 (0.6)	0.26	16 (1.2)	0.59	0.20	0.39 (0.11, 1.34)	NA
All-cause mortality	12 (2.2)	1.04	31 (2.4)	1.13	0.86	0.72 (0.37, 1.40)	NA

Το τέλος της ασπιρίνης στη πρωτογενή πρόληψη...





Study Design

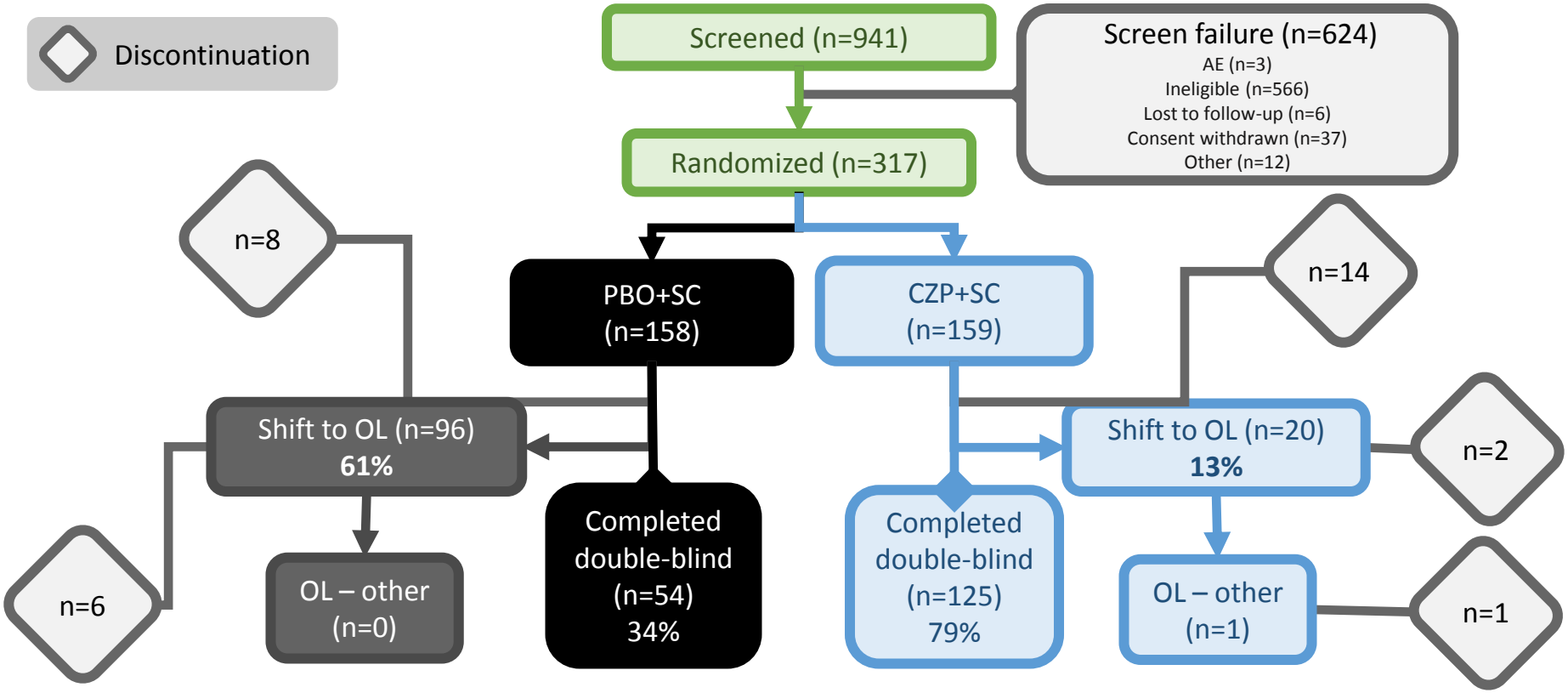


ASDAS-MI was defined as ≥2.0 point decrease in ASDAS from baseline or achievement of the lowest possible ASDAS score (0.6) at Week 52

Deodhar A et al. ACR 2018. Oral Presentation 1868.

- Patients were permitted to withdraw from the study drug at any timepoint. SFE: safety follow-up extension; CZP: certolizumab pegol; SC: standard care; LD: loading dose; OL: open-label; Q2W: every 2 weeks; ASDAS-MI: Ankylosing Spondylitis Disease Activity Score – Major Improvement

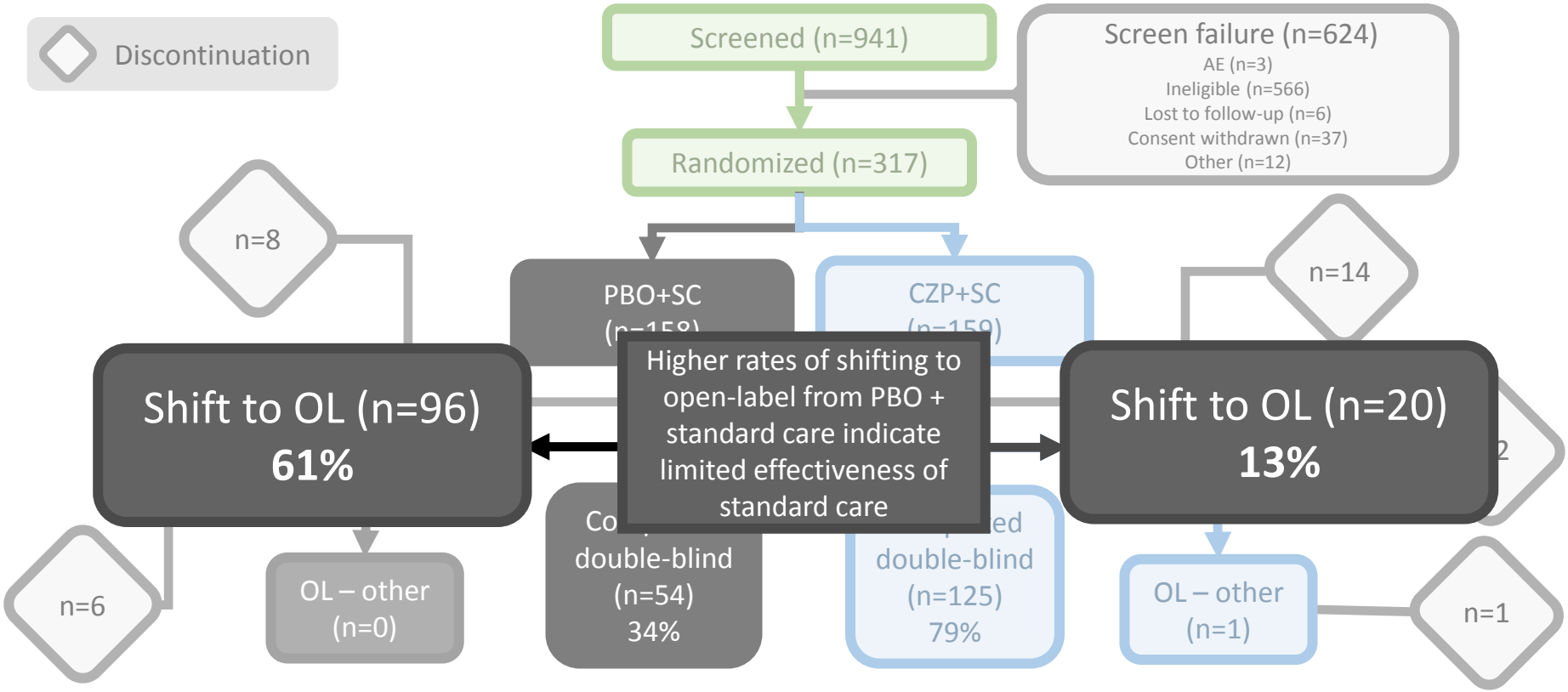
Patient Disposition at Week 52



Deodhar A et al. ACR 2018. Oral Presentation 1868.

- AE: adverse event; CZP+SC: certolizumab pegol + standard care; PBO+SC: placebo + standard care; OL: open-label

Patient Disposition at Week 52



Deodhar A et al. ACR 2018. Oral Presentation 1868.

- AE: adverse event; CZP+SC: certolizumab pegol + standard care; PBO+SC: placebo + standard care; OL: open-label