EULAR 2021-SpA

Δαούσης Δημήτρης
Αναπλ καθηγητής Παθολογίας/Ρευματολογίας
Ιατρική Σχολή Πανεπιστημίου Πατρών

Webinar ERE Jun 2021

Τι νεότερο στις ΣΠΑ από το EULAR 2021

- 12 συνεδρίες με θεμα ΑΣ, ΣΠΑ, ΨΑ (invited lectures, oral presentations)
- Έμφαση σε νέα φάρμακα και μηχανισμούς
- Υποκειμενική αξιολόγηση….

Κλινικά δεδομένα- AxSpA

OP014

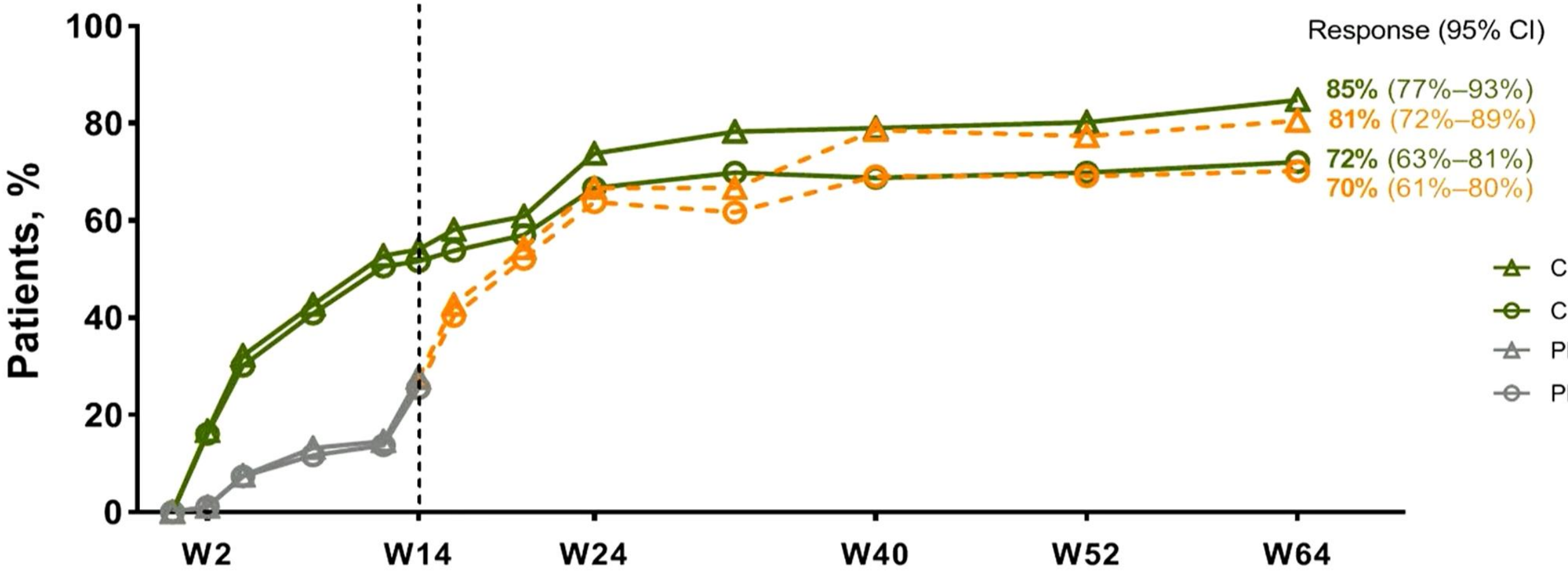
Efficacy and Safety of Upadacitinib in Patients With Active Ankylosing Spondylitis: 1-Year Results From a Randomized, Double-blind, Placebo-controlled Study With Open-label Extension

Atul Deodhar[1], Désirée van der Heijde[2], Joachim Sieper[3], Filip van den Bosch[4], Walter P Maksymowych[5], Tae-Hwan Kim[6], Mitsumasa Kishimoto[7], Andrew Ostor[8], Bernard Combe[9], Yunxia Sui[10], Alvina D Chu[10], In-Ho Song[10]

[1]Oregon Health & Science University, Portland, OR, United States; [2]Leiden University Medical Center, Leiden, the Netherlands; [3]Charité Universitätsmedizin Berlin, Berlin, Germany; [4]Ghent University Hospital, Ghent, Belgium; [5]University of Alberta, Edmonton, AB, Canada; [6]Hanyang University Hospital for Rheumatic Diseases, Seoul, Republic of Korea; [7]Kyorin University School of Medicine, Tokyo, Japan; [8]Cabrini Medical Center and Monash University, Melbourne, Australia; [9]CHU Montpellier, Montpellier University, Montpellier, France; [10]AbbVie Inc., North Chicago, IL, United States

- Upadacitinib, a JAK inhibitor, was efficacious and well tolerated during the first 14 weeks of the phase 2/3 SELECT-AXIS 1 study in patients with active ankylosing spondylitis (AS) who had an inadequate response to NSAIDs[1]
- The objective of this interim analysis was to report efficacy and safety of upadacitinib through 1 year

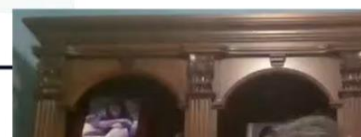
ASAS40



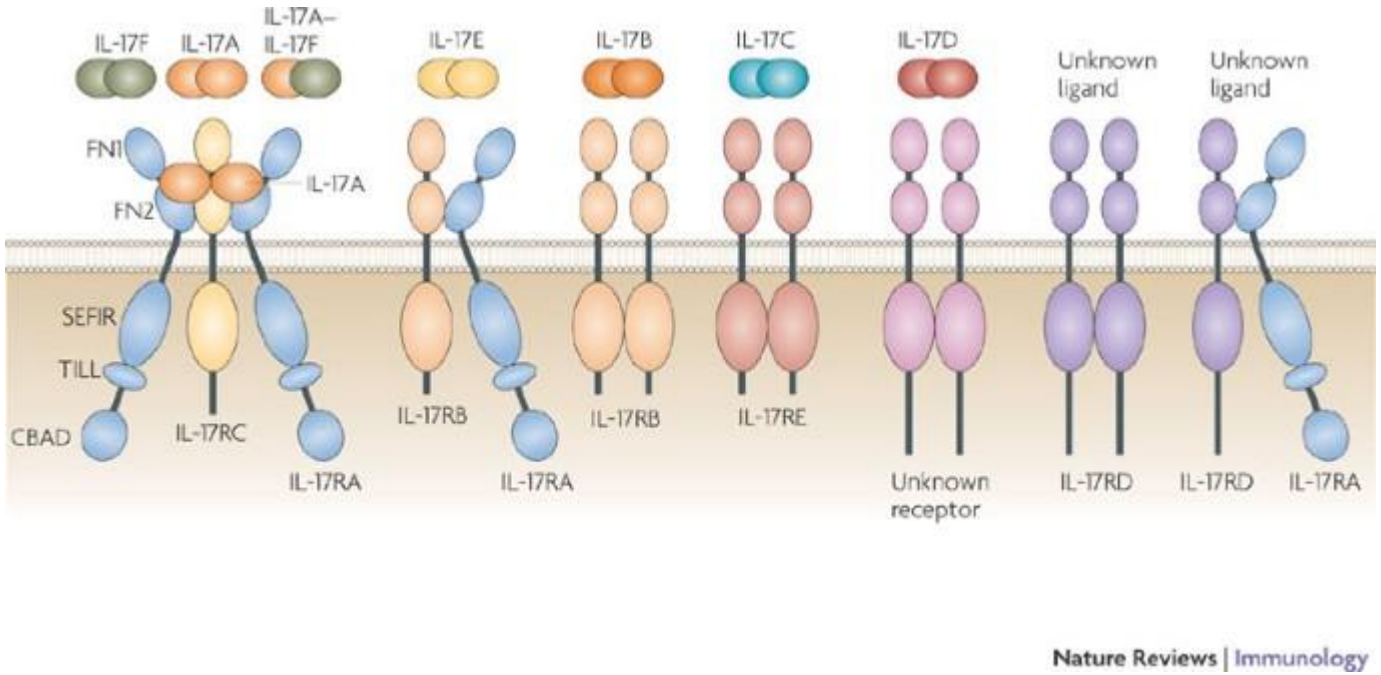
	W2	W14	W24	W40	W52	W64
D: % (n/N)	16.7 (15/90)	54.0 (47/87)	73.8 (62/84)	79.0 (64/81)	80.2 (65/81)	84.8 (67/79)
	1.1 (1/90)	27.6 (24/87)	66.7 (60/90)	78.6 (66/84)	77.4 (65/84)	80.5 (66/82)
NRI: %	16.1	51.6	66.7	68.8	69.9	72.0
	1.1	25.5	63.8	69.1	69.1	70.2

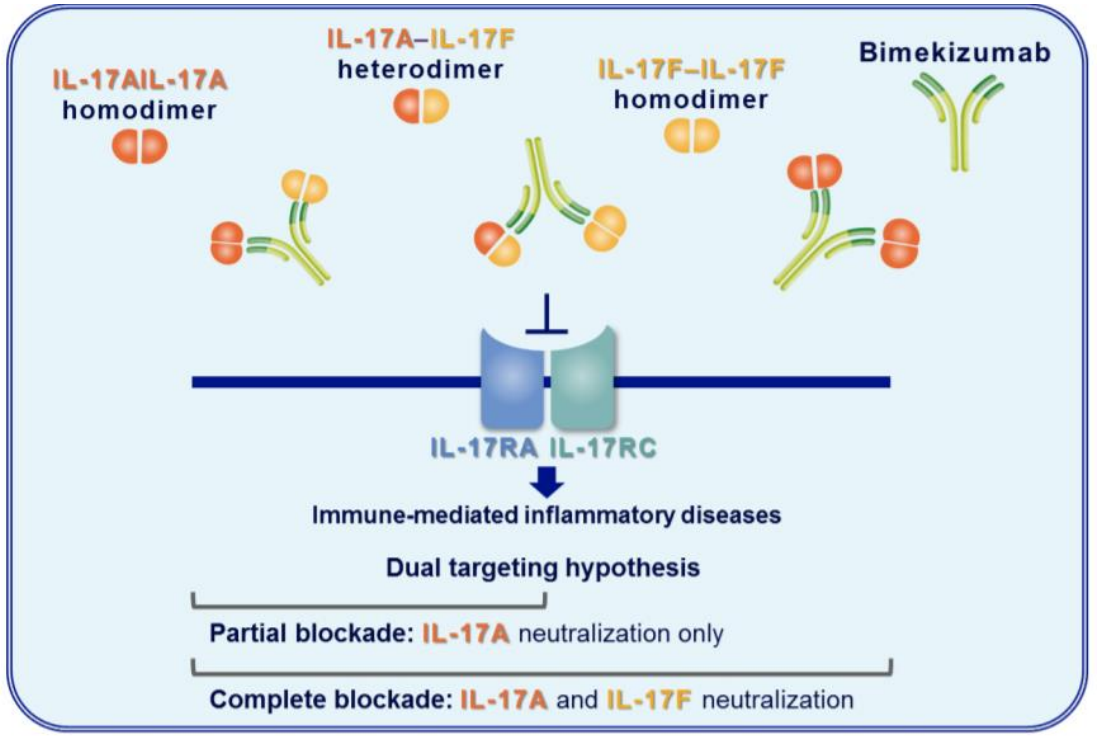
- No serious infections, active tuberculosis, venous thromboembolic events, major adverse cardiovascular events, gastrointestinal perforation, inflammatory bowel disease, renal dysfunction, or deaths were reported with upadacitinib treatment

AE, E (E/100 PY)	Upadacitinib 15 mg QD N = 182 (237.6 PY)
Any AE	618 (260.1)
Serious AE	14 (5.9)
AE leading to discontinuation	15 (6.3)
Infections	205 (86.3)
Opportunistic infection	2 (0.8)
Herpes zoster*	5 (2.1)
Creatine phosphokinase elevation†	28 (11.8)
Hepatic disorder‡	24 (10.1)
Neutropenia	7 (2.9)
Anemia	3 (1.3)
Lymphopenia	2 (0.8)
Malignancy§	1 (0.4)
Death	0



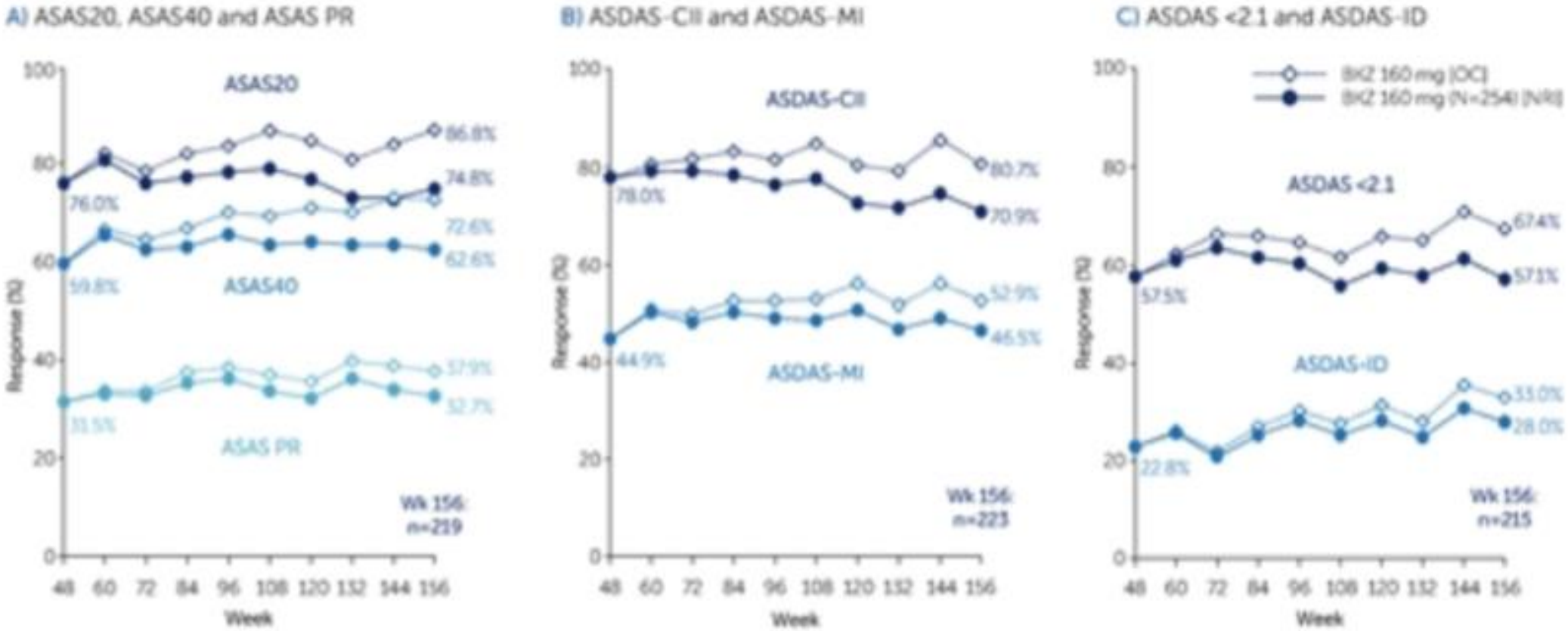
Η IL17 δεν είναι μόνο η IL17A….





Bimekizumab Long-Term Safety and Efficacy in Patients with Ankylosing Spondylitis: 3-Year Results from a Phase 2b Study

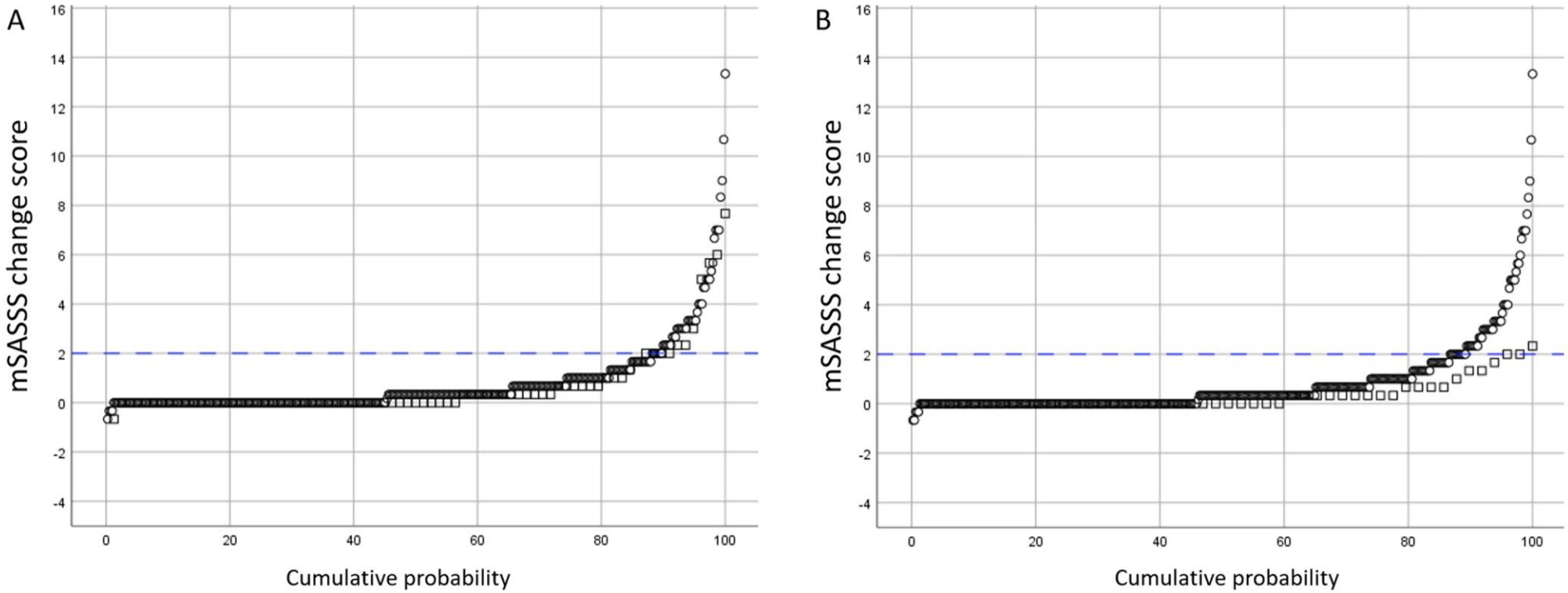
Figure 2 Efficacy responses from Week 48 to Week 156 (NRI and OC)



A Time-Shifted Effect of Tumor Necrosis Factor Inhibitors on Radiographic Spinal Progression in Patients With Axial Spondyloarthritis:

Long-term Results From the German Spondyloarthritis Inception Cohort

Denis Poddubnyy, Valeria Rios Rodriguez, Murat Torgutalp, Ani Dilbaryan, Maryna Verba, Mikhail Protopopov, Fabian Proft, Judith Rademacher, Hildrun Haibel, Joachim Sieper, Martin Rudwaleit



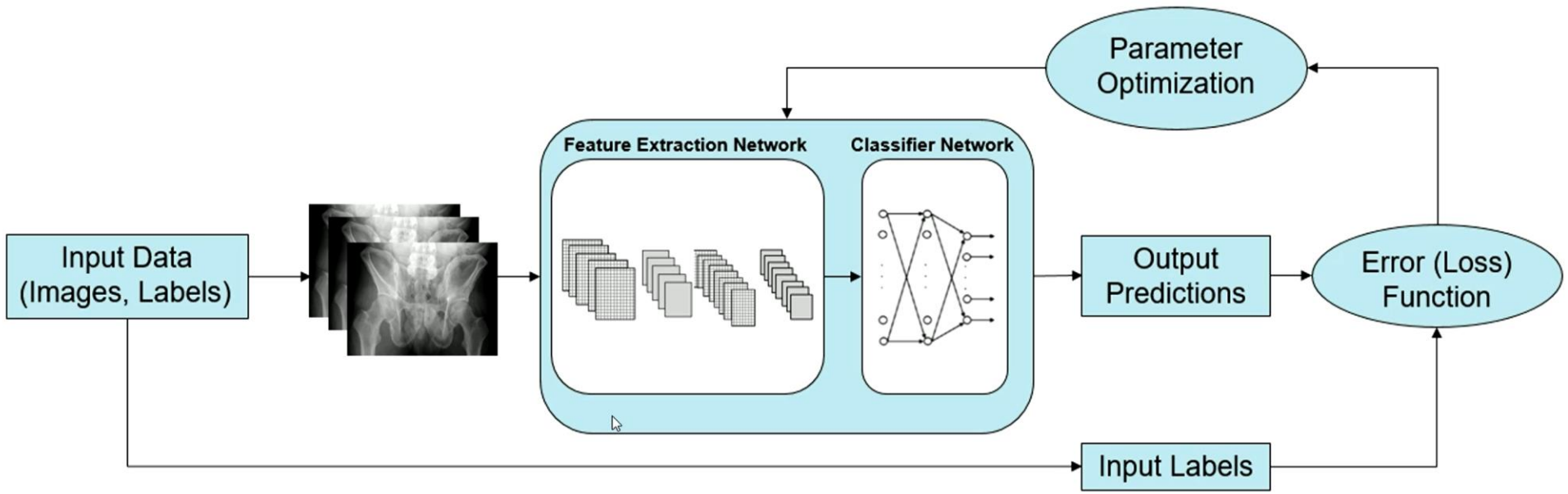
□ TNFi for ≥12 months in the current 2-year interval
○ No TNFi for ≥12 months in the current 2-year interval

□ TNFi for ≥12 months in the previous 2-year interval
○ No TNFi for ≥12 months in the previous 2-year interval

An artificial neural network for the detection of definite radiographic sacroiliitis with high specificity in the diagnostic setting

Janis L. Vahldiek, Keno-Kyrill Bressem, Kay-Geert Hermann, Stefan Niehues, Lisa Adams, Laura Spiller, Mikhail Protopopov, Valeria Rios Rodriguez, Burkhard Muche, Judith Rademacher, Hildrun Haibel, Murat Torgutalp, Fabian Proft, Denis Poddubnyy

Artificial Convolutional Neural Network (CNN)



Results

Clinical diagnosis	CNN's prediction	
	Radiographic sacroiliitis present	Radiographic sacroiliitis absent
Radiographic axial SpA (n=61)	48/61 (78.7%)	13/61 (21.3%)
Non-radiographic axial SpA (n=49)	4/49 (8.2%)	45/49 (91.8%)
No axial SpA (n=230)	14/230 (6.1%)	216/230 (93.9%)

- Sensitivity for the detection of r-axSpA: 78.7%
- Specificity: 93.9%
- Absolute agreement on the classification as r- or nr-axSpA: 85%
- ROC AUC for the prediction of the presence of definite radiographic sacroiliitis: 0.88

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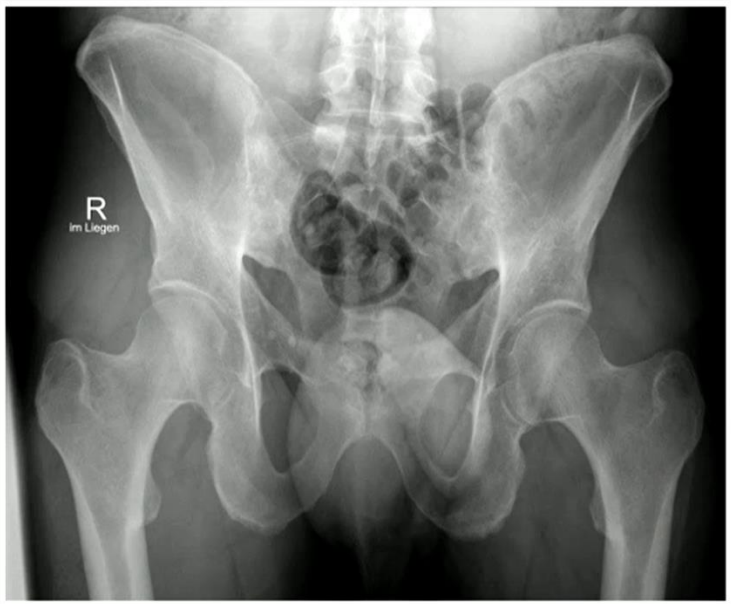
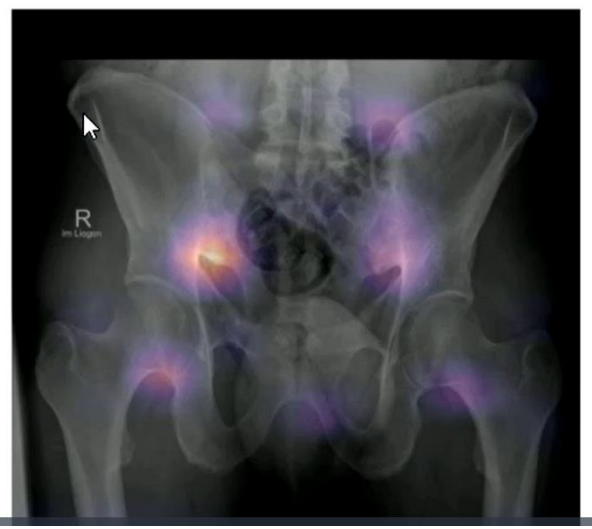


Prediction:

Definite radiographic sacroiliitis according to the modified New York (mNY) criteria is ***present***.

The balanced cutoff of 0.724 for the probability value was applied for classification. This cutoff has a sensitivity of 88% and a specificity of 95% for the presence of definite radiographic sacroiliitis.

Probability value for definite radiographic sacroiliitis according to the mNY criteria: 0.90119



https://rad-ai.charite.de/spa

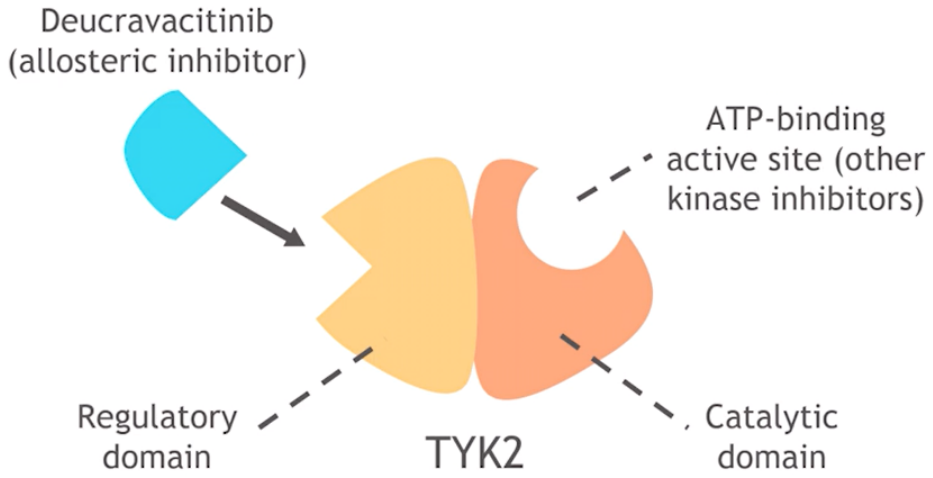
Κλινικά δεδομένα-PsA

Efficacy of Deucravacitinib, an Oral, Selective Tyrosine Kinase 2 Inhibitor, in Musculoskeletal Manifestations of Active Psoriatic Arthritis in a Phase 2, Randomized, Double-Blind, Placebo-Controlled Trial

Philip J Mease,[1] Atul Deodhar,[2] Désirée van der Heijde,[3] Frank Behrens,[4] Alan J Kivitz,[5] Thomas Lehman,[6] Lan Wei,[6] Marleen Nys,[7] Subhashis Banerjee,[6] Miroslawa Nowak[6]

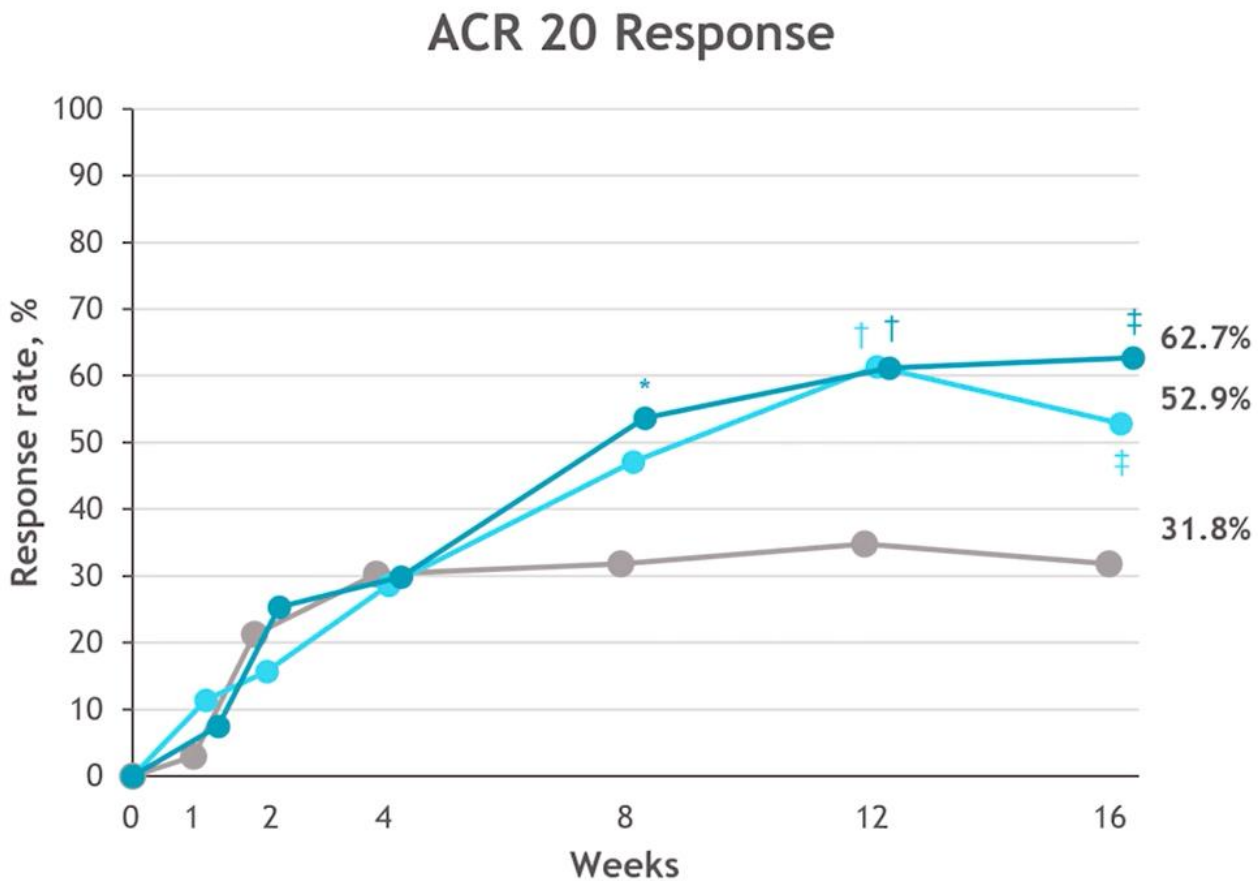
Deucravacitinib

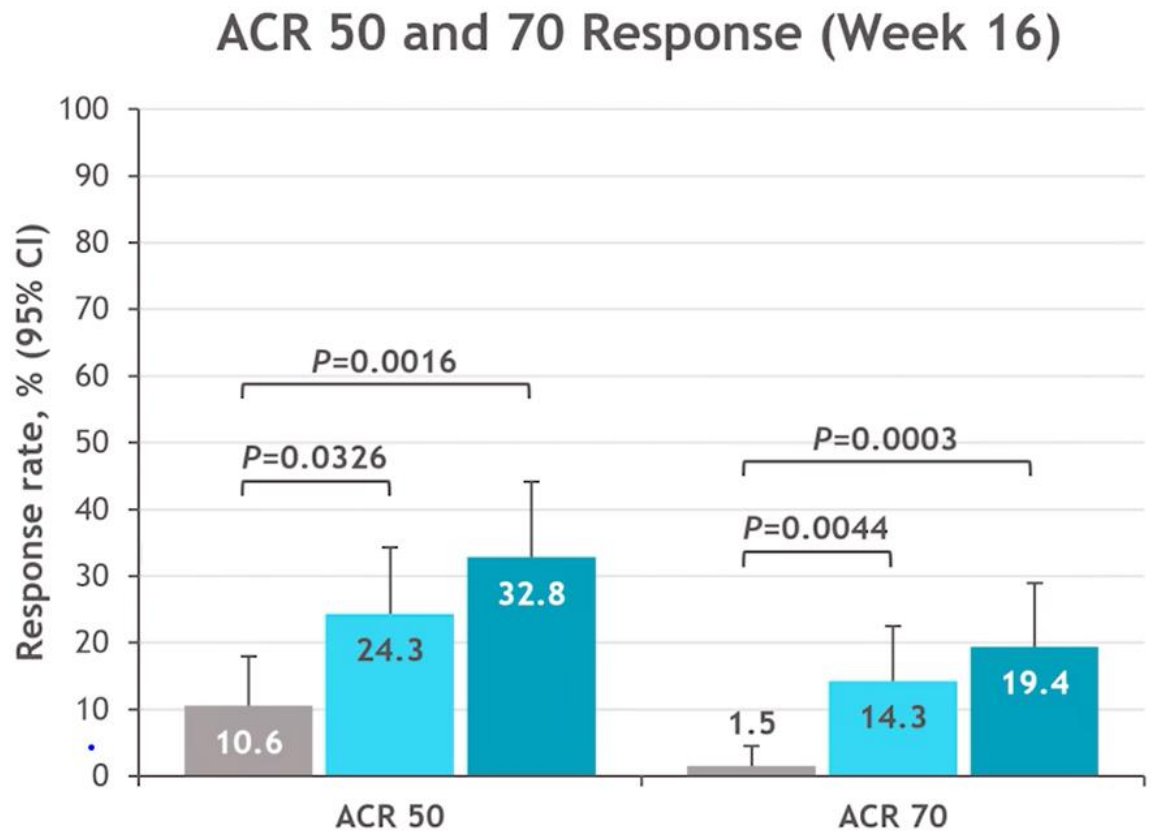
- Novel, oral, selective TYK2 inhibitor with a unique mechanism of action distinct from JAK1/2/3 inhibitors[1]
- Binds the TYK2 regulatory domain with high selectivity and inhibits TYK2 via an allosteric mechanism[1]
- Inhibits key cytokines involved in psoriasis and PsA (eg, IL-23)[1]
- Does not inhibit cytokines and mediators involved in metabolic or hematopoietic pathways[1]



- Showed superior efficacy in two Phase 3 trials in moderate to severe plaque psoriasis[2] (*POS1042*)
- Showed superior efficacy in a Phase 2 trial in PsA[3] (*POS0198; poster tour: 04 June 2021, 11:50-13:30 CEST*)
- **This analysis explores improvement in musculoskeletal disease domains from the Phase 2 trial in PsA**

ACR 20, ACR 50, and ACR 70 responses, NRI





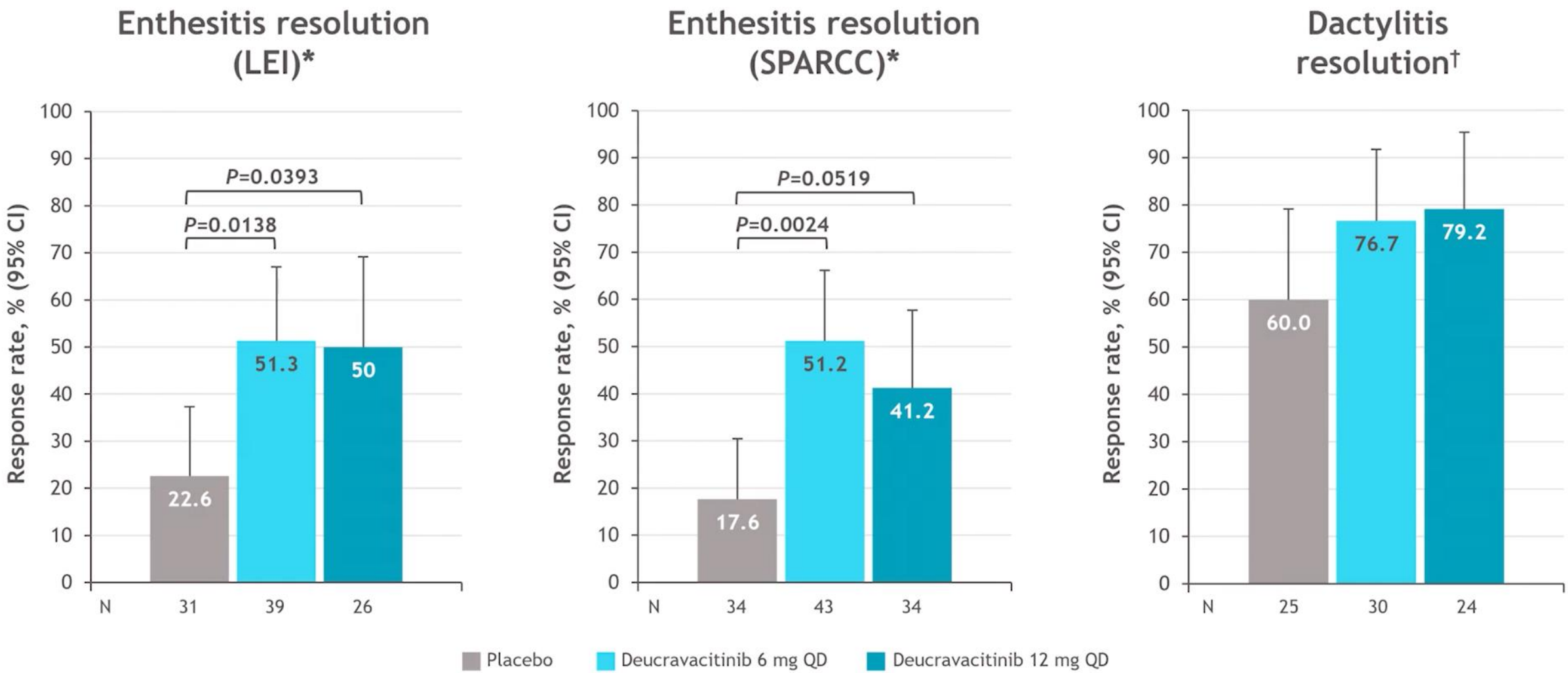
*P=0.0108 (12 mg). †P=0.0021 (6 mg); P=0.0021 (12 mg). ‡P=0.0134 (6 mg); P=0.0004 (12 mg).

Placebo Deucravacitinib 6 mg QD Deucravacitinib 12 mg QD

Nominal P values for pairwise comparison versus placebo. P values in time course are for odds ratios obtained using a stratified Cochran-Mantel-Haenszel (CMH) test with stratification factors (body weight and prior TNFi use) per randomization. ITT population.

ACR, American College of Rheumatology; ITT, intent-to-treat; NRI, nonresponder imputation; QD, once daily; TNFi, tumor necrosis factor inhibitor.

Enthesitis and dactylitis resolution at Week 16



Overall safety summary

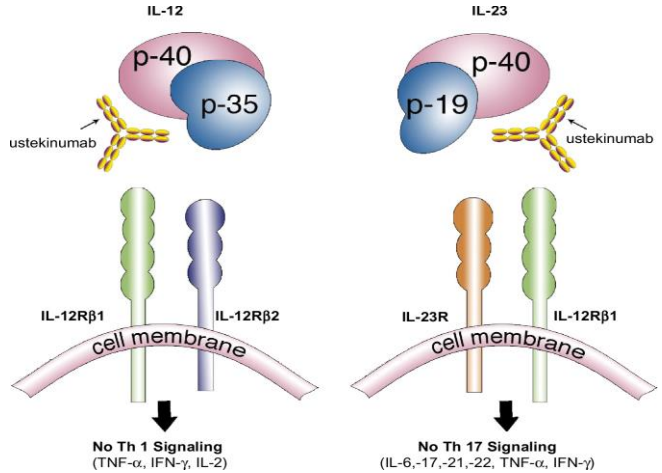
Patients, n (%)	Placebo (n=66)	Deucravacitinib 6 mg QD (n=70)	Deucravacitinib 12 mg QD (n=67)
Deaths	0	0	0
Serious adverse events	1 (1.5)	0	0
Treatment-related adverse events	6 (9.1)	22 (31.4)	17 (25.4)
Discontinued treatment due to adverse events	1 (1.5)	3 (4.3)	4 (6.0)
Most frequent adverse events (≥5%)			
Nasopharyngitis	5 (7.6)	4 (5.7)	12 (17.9)
Sinusitis	0	0	5 (7.5)
Headache	3 (4.5)	5 (7.1)	1 (1.5)
Rash	0	3 (4.3)	4 (6.0)
Upper respiratory tract infection	0	4 (5.7)	1 (1.5)
Bronchitis	1 (1.5)	4 (5.7)	0
Diarrhea	0	4 (5.7)	0

- No serious AEs, including serious infections, were reported in deucravacitinib-treated patients. There were no thrombotic events in the deucravacitinib groups
- There were no occurrences of herpes zoster infections, opportunistic infections, or malignancies observed in any deucravacitinib treatment group

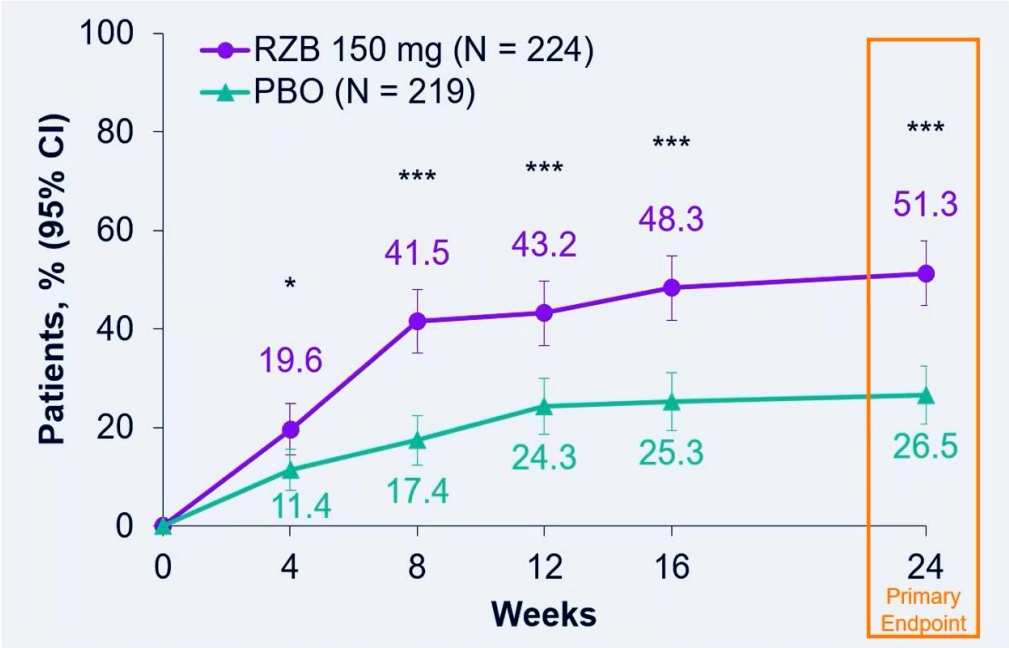
OP02

Efficacy and Safety of Risankizumab for Active Psoriatic Arthritis, Including Patients With Inadequate Response or Intolerance to Biologic Therapies: 24-Week Results From the Phase 3, Randomized, Double-blind, KEEPsAKE 2 Trial

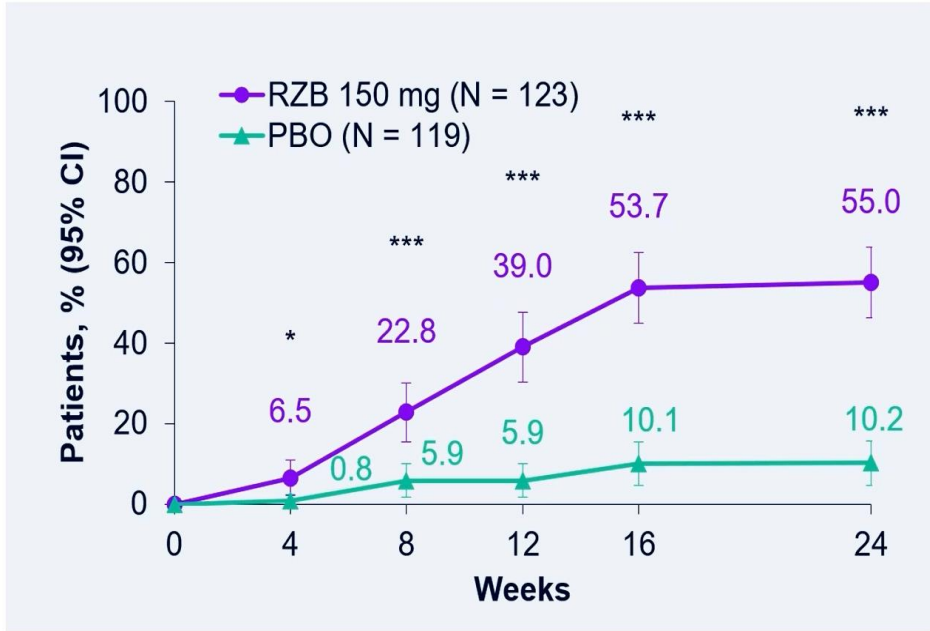
Andrew Östör,[1] Filip Van den Bosch,[2] Kim Papp,[3] Cecilia Asnal,[4] Ricardo Blanco,[5] Jacob Aelion,[6] Gabriela Alperovich,[7] Ying Zhang,[8] Zailong Wang,[8] Ahmed M Soliman,[8] Ann Eldred,[8] Lisa Barcomb,[8] Alan Kivitz[9]



Primary Endpoint: ACR20 Response



PASI 90[a] Response Over Time



Safety: Overview and Adverse Events of Special Interest

Patients, n (%)	RZB 150 mg N = 224	PBO N = 219
TEAE	124 (55.4)	120 (54.8)
COVID-19–related TEAE	1 (0.4)[a]	0
Serious TEAE	9 (4.0)	12 (5.5)
Severe TEAE	6 (2.7)	7 (3.2)
TEAE leading to discontinuation of study drug	2 (0.9)	5 (2.3)
Death	0	0
AEs of Special Interest		
Serious Infection	2 (0.9)[b]	5 (2.3)
Herpes zoster	0	1 (0.5)
Malignancy	1 (0.4)	1 (0.5)
Injection site reaction	3 (1.3)[c]	1 (0.5)
MACE	1 (0.4)[d]	0

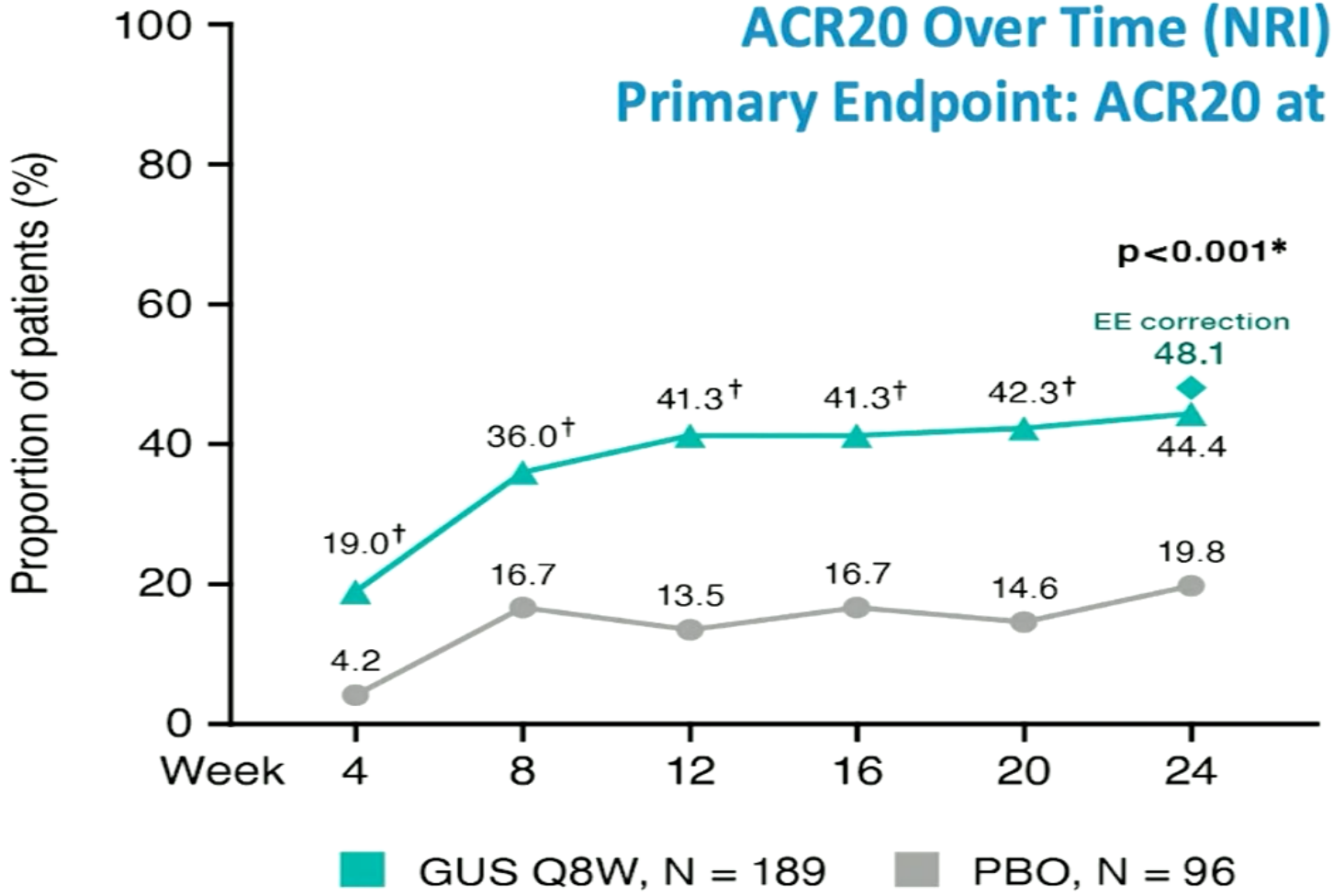
- Except for upper respiratory tract infection, no TEAE was reported for ≥ 5% of patients in either group
- There were no reports of active tuberculosis or other opportunistic infection in either treatment group

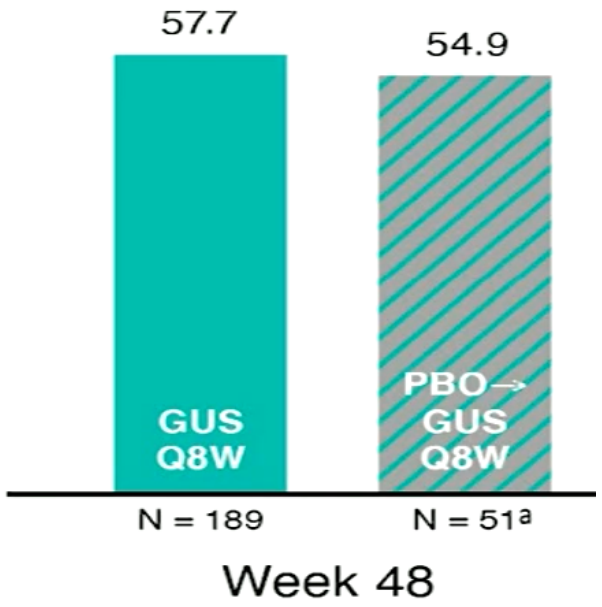
Significantly Higher ACR20 Response Rate Achieved With Guselkumab vs. Placebo at Week 24; ACR20 Response Rates Increased at 1 Year

Efficacy and Safety of Guselkumab in Patients With Active Psoriatic Arthritis who Demonstrated Inadequate Response to Tumor Necrosis Factor Inhibition: Results of a Phase 3b, Randomized, Controlled Study

Laura C. Coates[1], Laure Gossec[2], Elke Theander[3], Paul Bergmans[4], Marlies Neuhold[5], Chetan S. Karyekar[6], May Shawi[6], Wim Noël[5], Georg Schett[7], Iain B. McInnes[8]

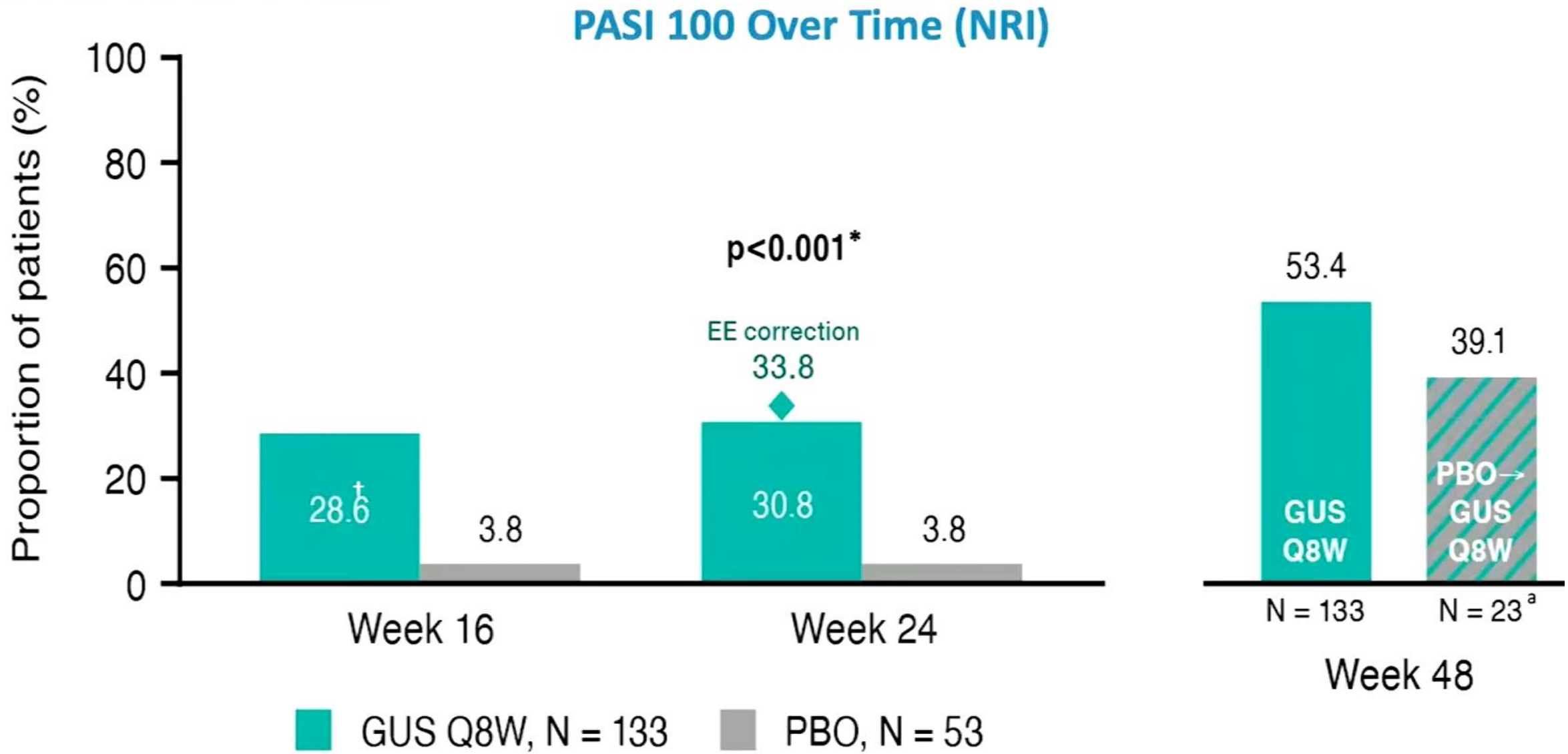
ACR20 Over Time (NRI)
Primary Endpoint: ACR20 at W24





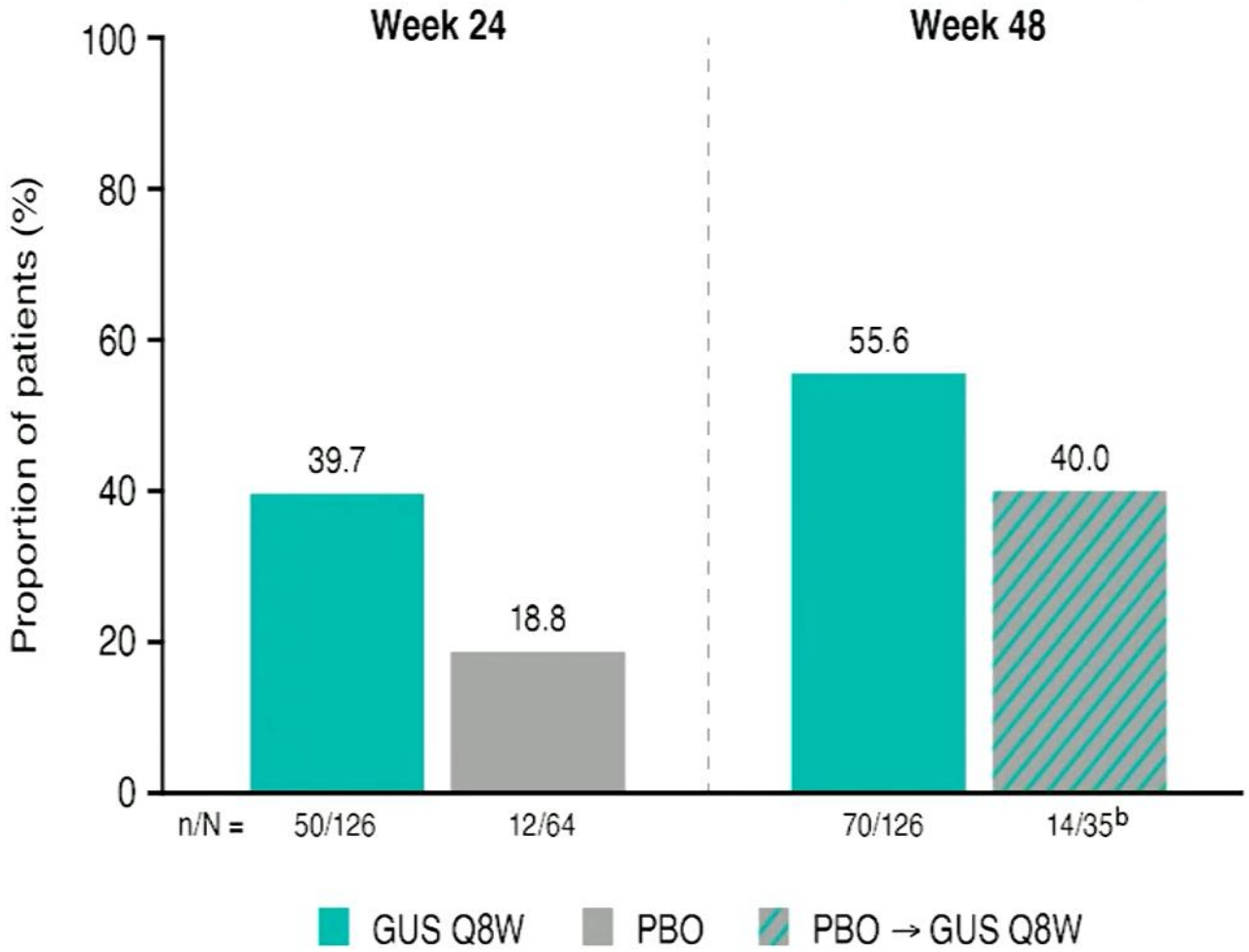
- GUS separated from PBO for achievement of ACR20 response as early as W4
- Sensitivity analyses supported the results of the Primary analysis

Significantly Higher PASI 100 Response Rate Achieved With Guselkumab vs. Placebo at Week 24; PASI 100 Response Rates Increased at 1 Year

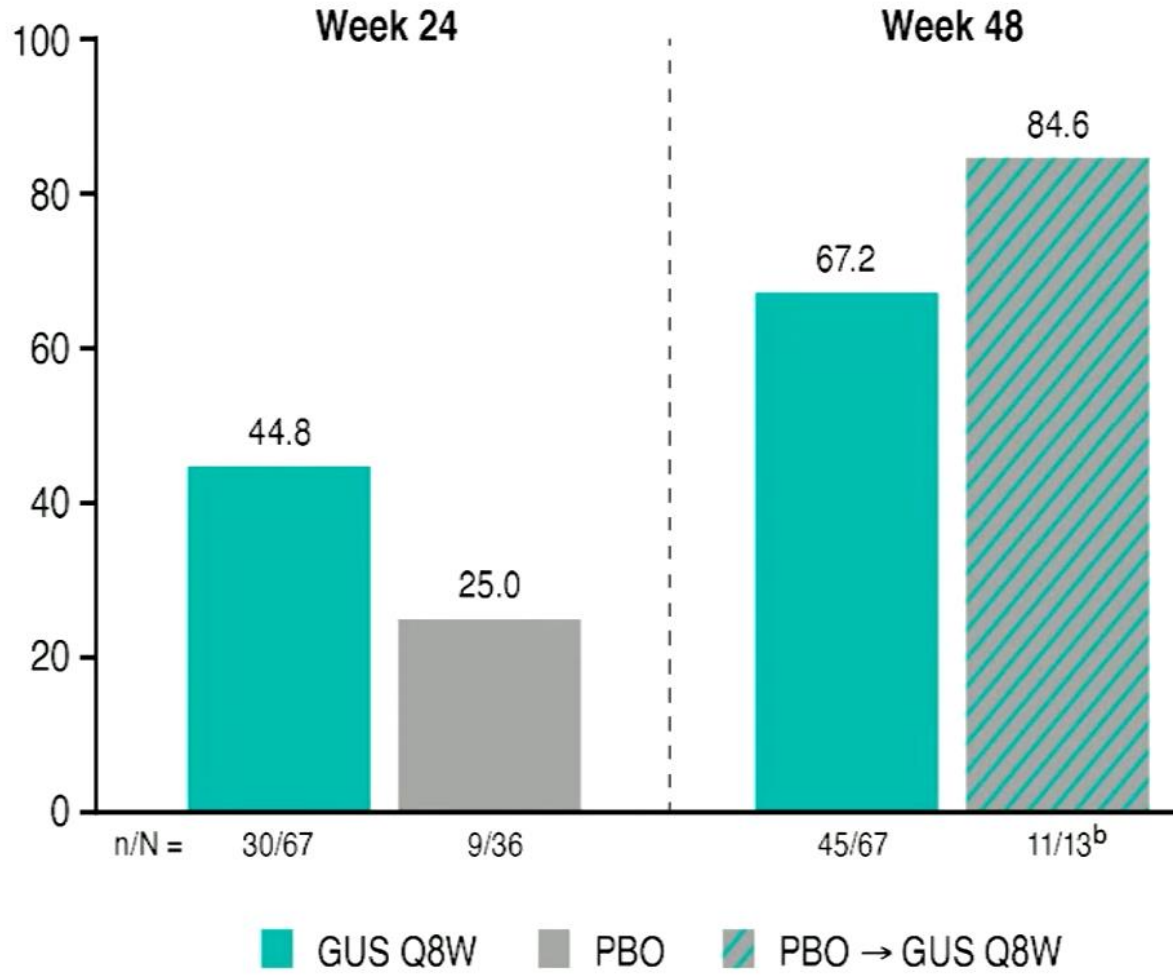


Higher Enthesitis and Dactylitis Resolution[a] Rates Achieved With Guselkumab vs. Placebo at Week 24; Resolution Rates Increased at 1 Year

Enthesitis Resolution (LEI=0; NRI)



Dactylitis Resolution (DSS=0; NRI)

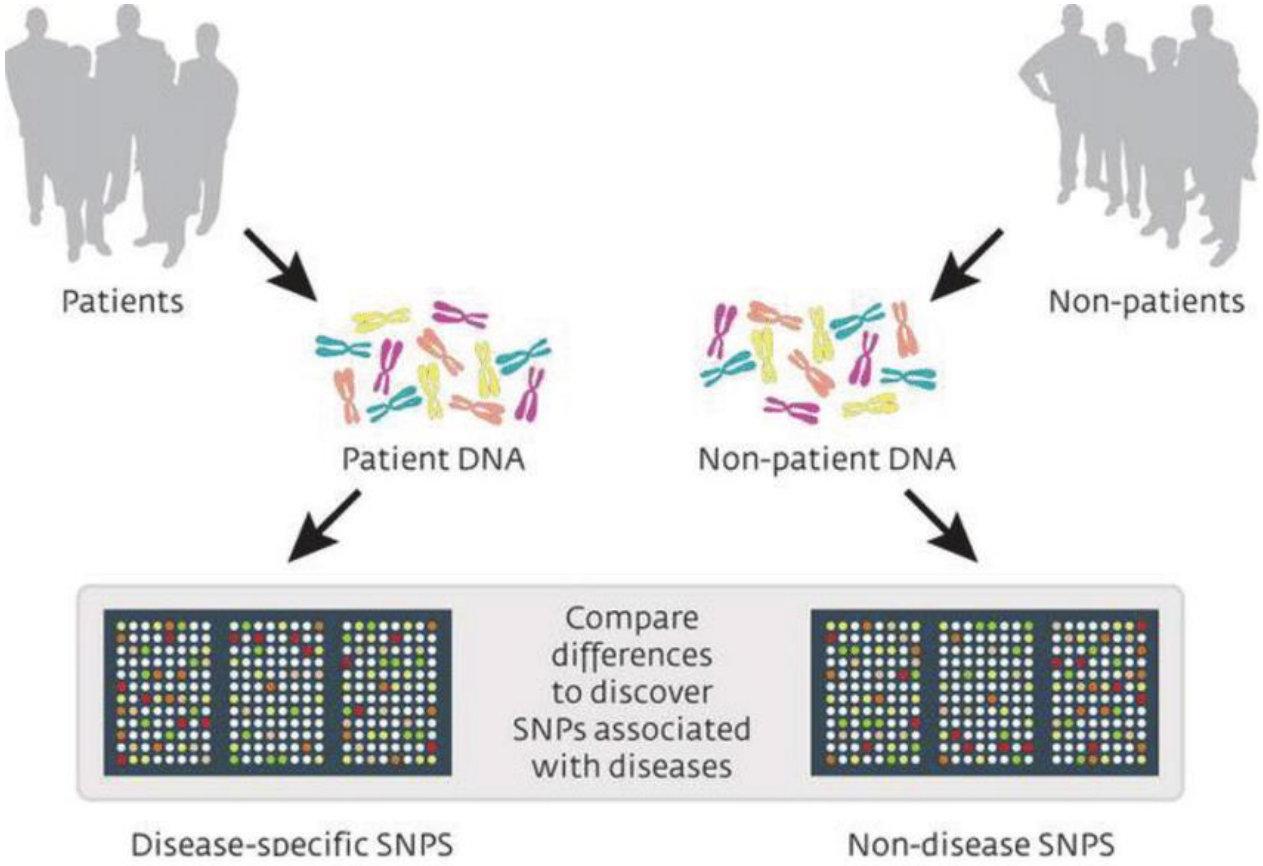


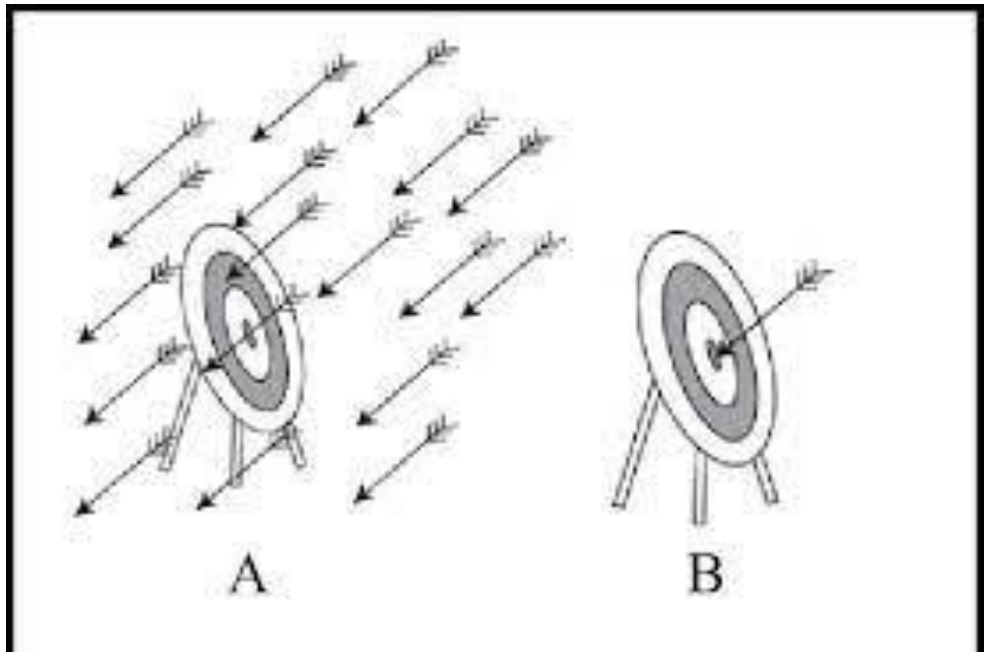
Guselkumab Demonstrated a Favorable Benefit-Risk Profile Through Week 56

Events/100 PY	PBO[a] (W0-24)	PBO → GUS Q8W (W16-56)[b]	PBO → GUS Q8W (W24-56)[c]	Randomized to GUS Q8W[d] (W0-24)	Randomized to GUS Q8W[d] (W0-56)
Pts, N	96	45	45	189	189
Total PY of follow-up	36.7	32.9	27.1	87.7	194.2
AEs					
Events/100 PY	283.7	127.5	143.7	229.2	149.3
95% CI	(231.8, 343.8)	[91.9, 172.4]	[102.2, 196.5]	[198.6, 263.2]	[132.7, 167.6]
SAEs					
Events/100 PY	8.2	6.1	7.4	8.0	6.2
95% CI	(1.7, 23.9)	[0.7, 21.9]	[0.9, 26.6]	[3.2, 16.5]	[3.2, 10.8]
AEs leading to study agent discontinuation					
Events/100 PY	5.5	0	0	4.6	3.6
95% CI	(0.7, 19.7)	-	-	[1.2, 11.7]	[1.5, 7.4]
Infections					
Events/100 PY	76.4	30.4	29.5	63.9	39.7
95% CI	(50.8, 110.4)	[14.6, 55.9]	[12.7, 58.1]	[48.2, 82.9]	[31.3, 49.6]
Serious infections					
Events/100 PY	0	0	3.7	1.1	0.5
95% CI	-	-	[0.1, 20.5]	[0.03, 6.4]	[0.01, 2.9]

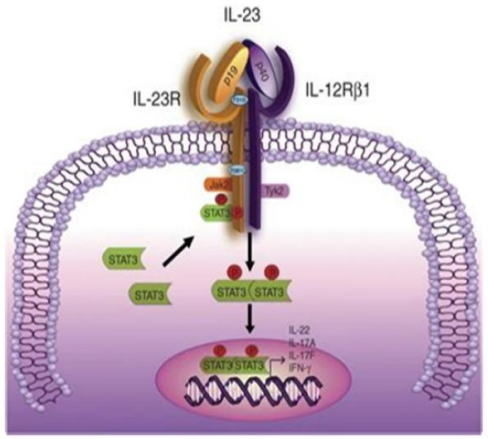
- **No opportunistic infection, active TB, anaphylactic/serum sickness-like reaction, confirmed IBD, or death**
- **No increase in AE rates through 1 year of GUS**

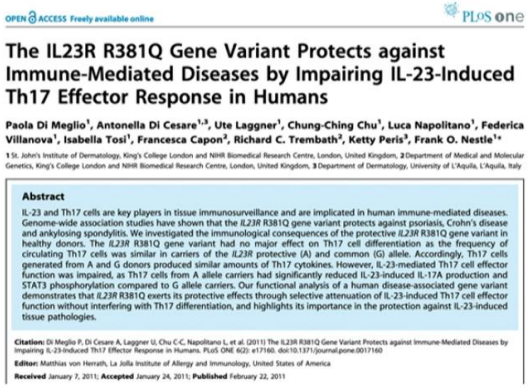
Αλλαγές στην μεθοδολογία της βασικής έρευνας τα τελευταία χρόνια….





IL23R





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PLoS one

The IL23R R381Q Gene Variant Protects against Immune-Mediated Diseases by Impairing IL-23-Induced Th17 Effector Response in Humans

Paola Di Meglio[1], Antonella Di Cesare[1,3], Ute Laggner[1], Chung-Ching Chu[1], Luca Napolitano[1], Federica Villanova[1], Isabella Tosi[1], Francesca Capon[2], Richard C. Trembath[2], Ketty Peris[3], Frank O. Nestle[1]*

1 St. John's Institute of Dermatology, King's College London and NIHR Biomedical Research Centre, London, United Kingdom, 2 Department of Medical and Molecular Genetics, King's College London and NIHR Biomedical Research Centre, London, United Kingdom, 3 Department of Dermatology, University of L'Aquila, L'Aquila, Italy

Abstract

IL-23 and Th17 cells are key players in tissue immunosurveillance and are implicated in human immune-mediated diseases. Genome-wide association studies have shown that the *IL23R* R381Q gene variant protects against psoriasis, Crohn's disease and ankylosing spondylitis. We investigated the immunological consequences of the protective *IL23R* R381Q gene variant in healthy donors. The *IL23R* R381Q gene variant had no major effect on Th17 cell differentiation as the frequency of circulating Th17 cells was similar in carriers of the *IL23R* protective (A) and common (G) allele. Accordingly, Th17 cells generated from A and G donors produced similar amounts of Th17 cytokines. However, IL-23-mediated Th17 cell effector function was impaired, as Th17 cells from A allele carriers had significantly reduced IL-23-induced IL-17A production and STAT3 phosphorylation compared to G allele carriers. Our functional analysis of a human disease-associated gene variant demonstrates that *IL23R* R381Q exerts its protective effects through selective attenuation of IL-23-induced Th17 cell effector function without interfering with Th17 differentiation, and highlights its importance in the protection against IL-23-induced tissue pathologies.

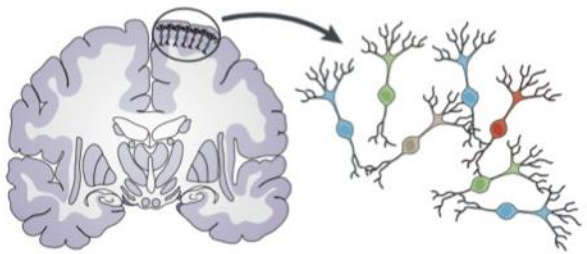
Citation: Di Meglio P, Di Cesare A, Laggner U, Chu C-C, Napolitano L, et al. (2011) The IL23R R381Q Gene Variant Protects against Immune-Mediated Diseases by Impairing IL-23-Induced Th17 Effector Response in Humans. PLoS ONE 6(2): e17160. doi:10.1371/journal.pone.0017160

Editor: Matthias von Herrath, La Jolla Institute of Allergy and Immunology, United States of America

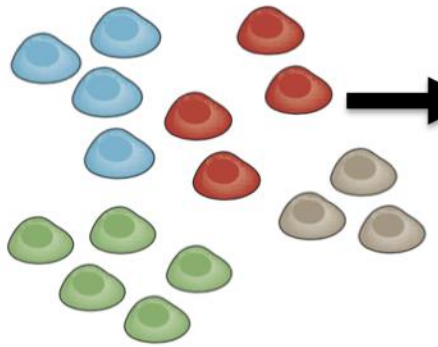
Received January 7, 2011; **Accepted** January 24, 2011; **Published** February 22, 2011

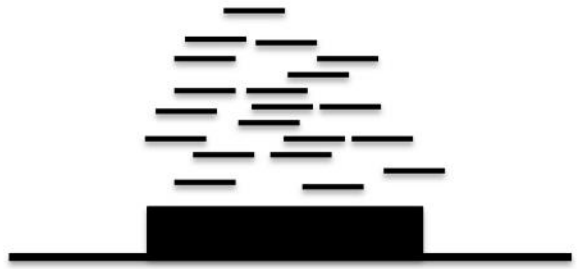
Single-cell RNA-Seq (scRNA-Seq)

Tissue (e.g. tumor)



Isolate and sequence individual cells



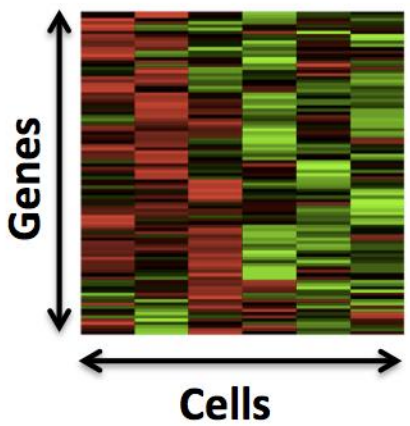


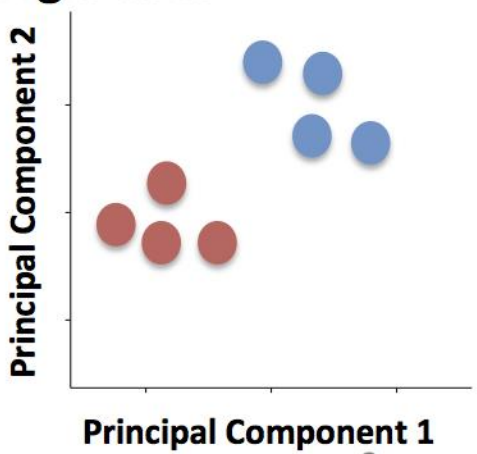
Gene 1
Cell 1

Read Counts

	Cell 1	Cell 2	…
Gene 1	18	0	
Gene 2	1010	506	
Gene 3	0	49	
Gene 4	22	0	
…			

Compare gene expression profiles of single cells



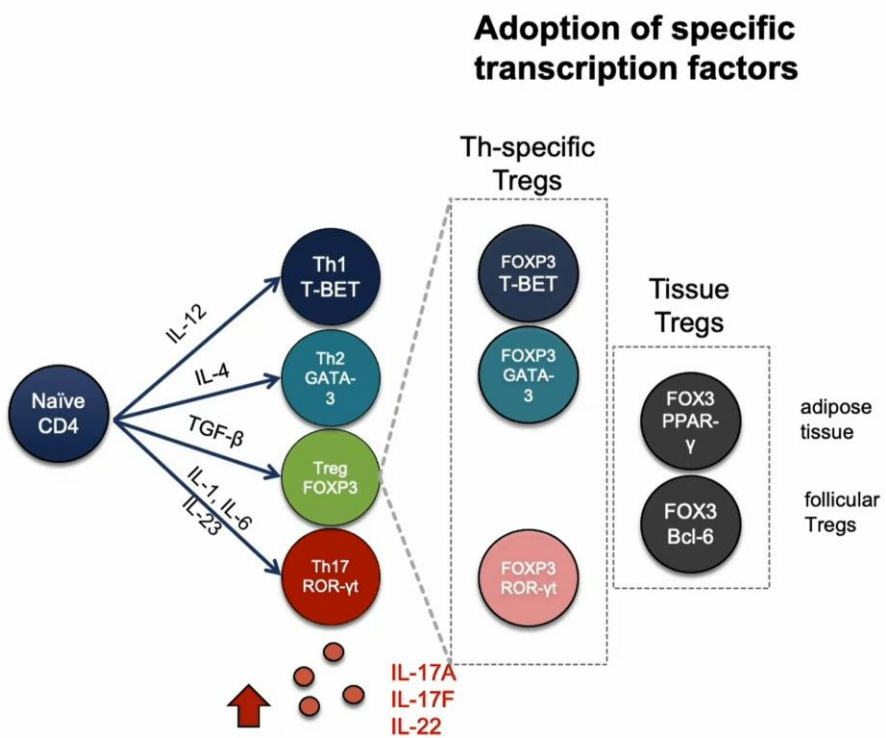


DAVIDE SIMONE, FRANK PENKAVA, ANNA RIDLEY, STEPHEN SANSOM,
HUSSEIN AL MOSSAWI, PAUL BOWNESS

NDORMS, UNIVERSITY OF OXFORD, UNITED KINGDOM

SINGLE CELL ANALYSIS OF SPONDYLOARTHRITIS TREGS IDENTIFIES DISTINCT SYNOVIAL GENE EXPRESSION PATTERNS AND CLONAL FATES

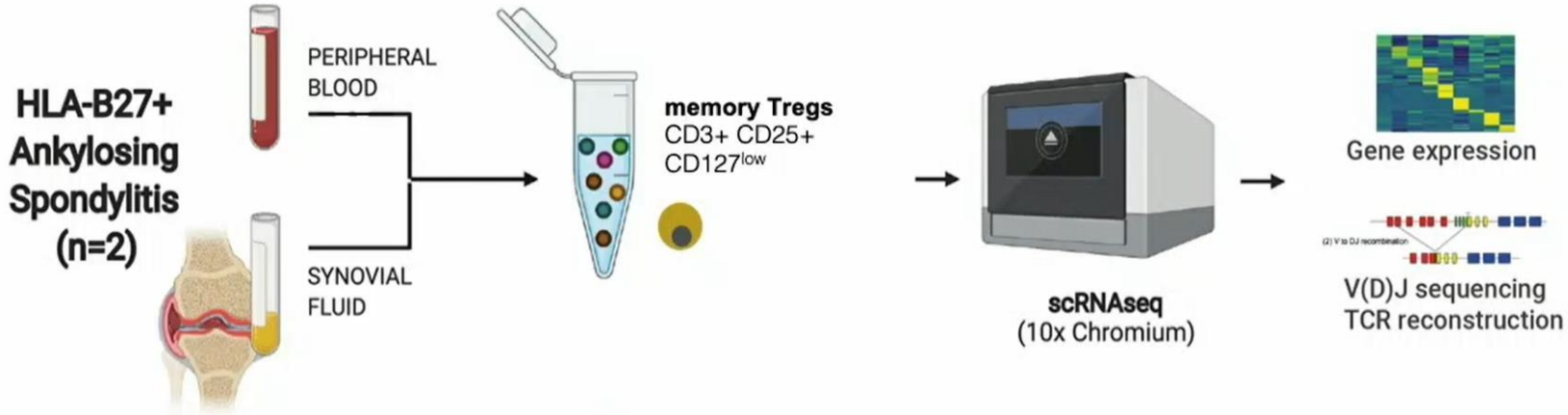
heterogeneity of regulatory T cells

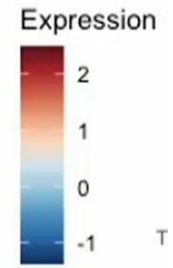


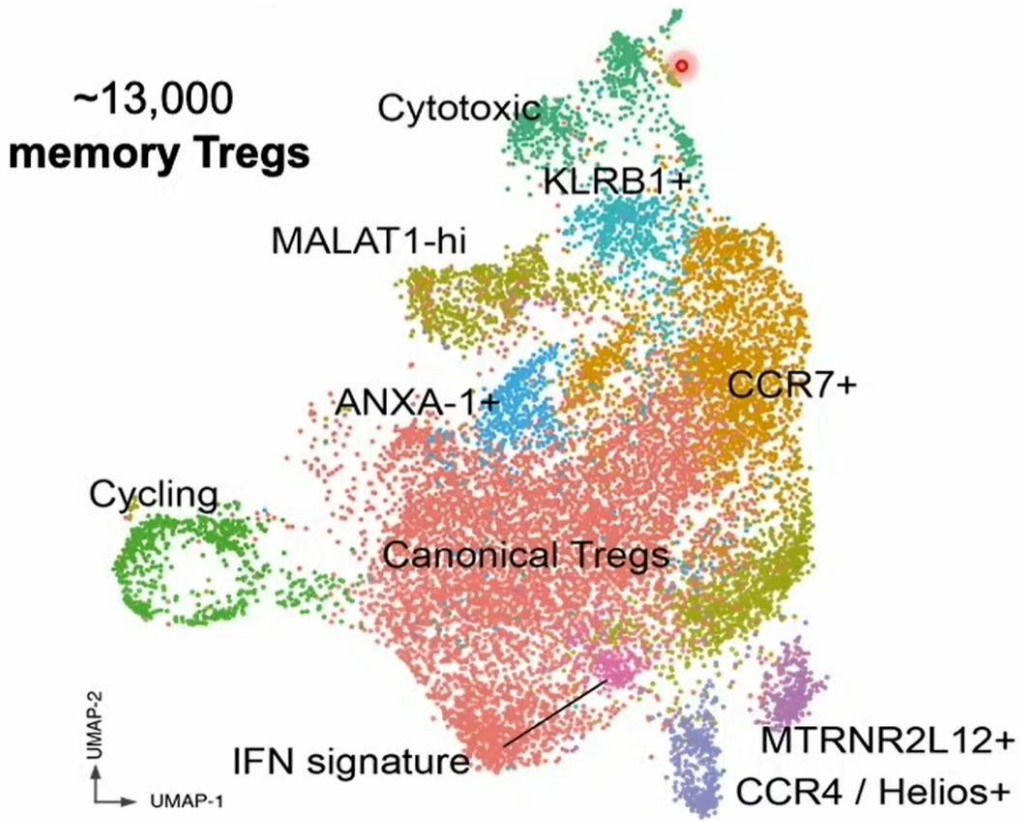
Diverse mechanisms of suppression

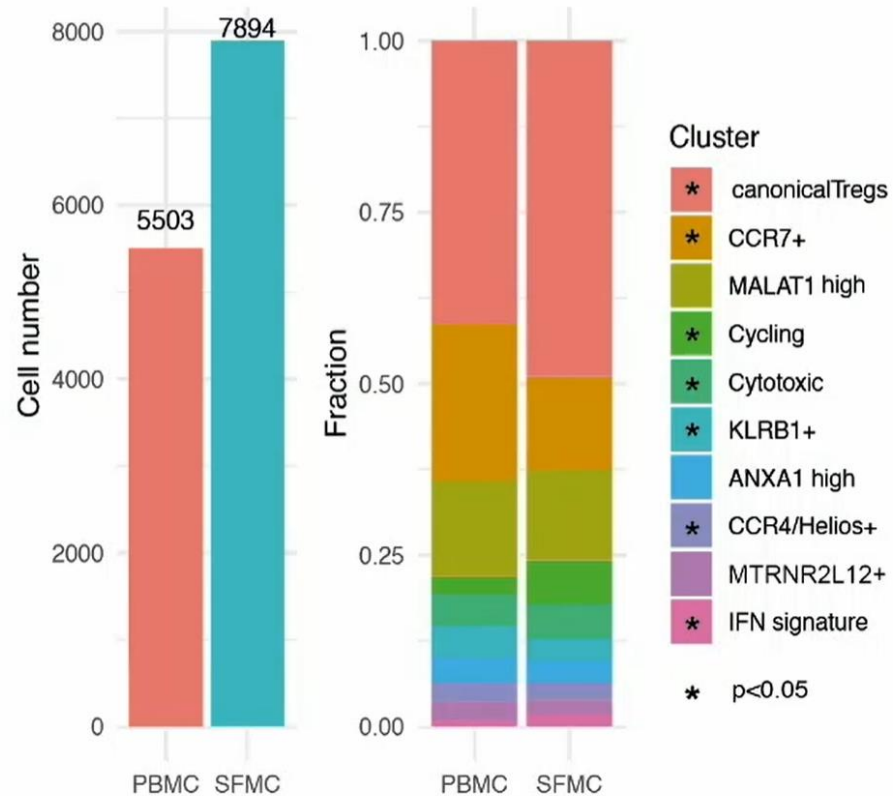
CTLA-4	CD39
IL-10	TIGIT
TGF-β	LAG-3
	TIM-3

Describing Treg heterogeneity and gene regulation, in particular at inflammatory sites, could guide the development of novel treatments

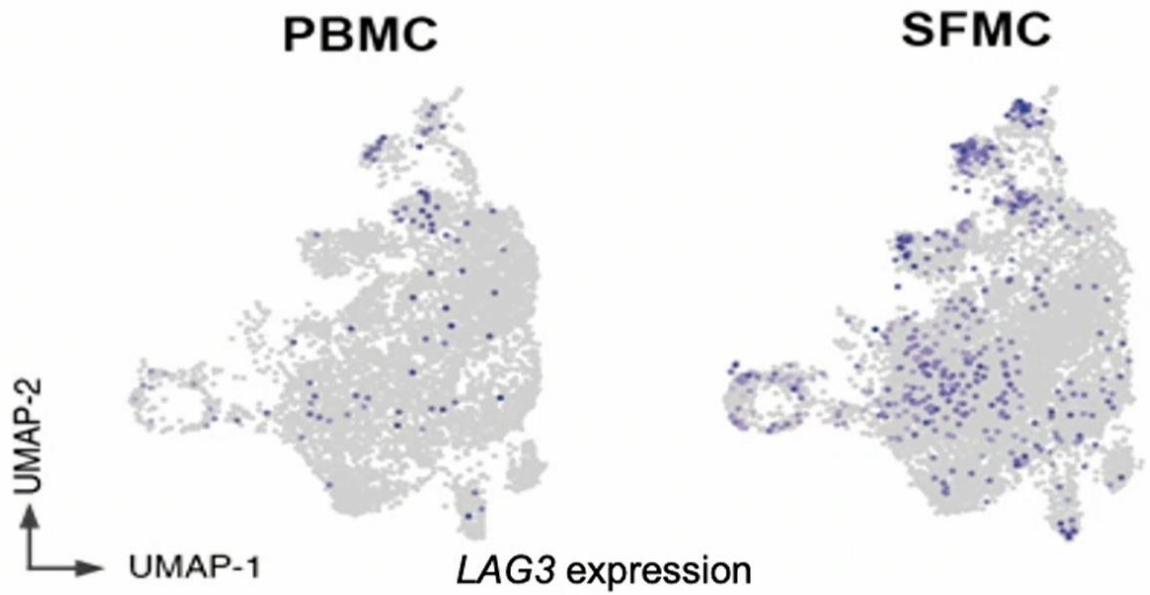

HLA-B27+
Ankylosing
Spondylitis
(n=2)
PERIPHERAL
BLOOD
SYNOVIAL
FLUID
memory Tregs
CD3+ CD25+
CD127low
scRNAseq
(10x Chromium)
Gene expression
V(D)J sequencing
TCR reconstruction

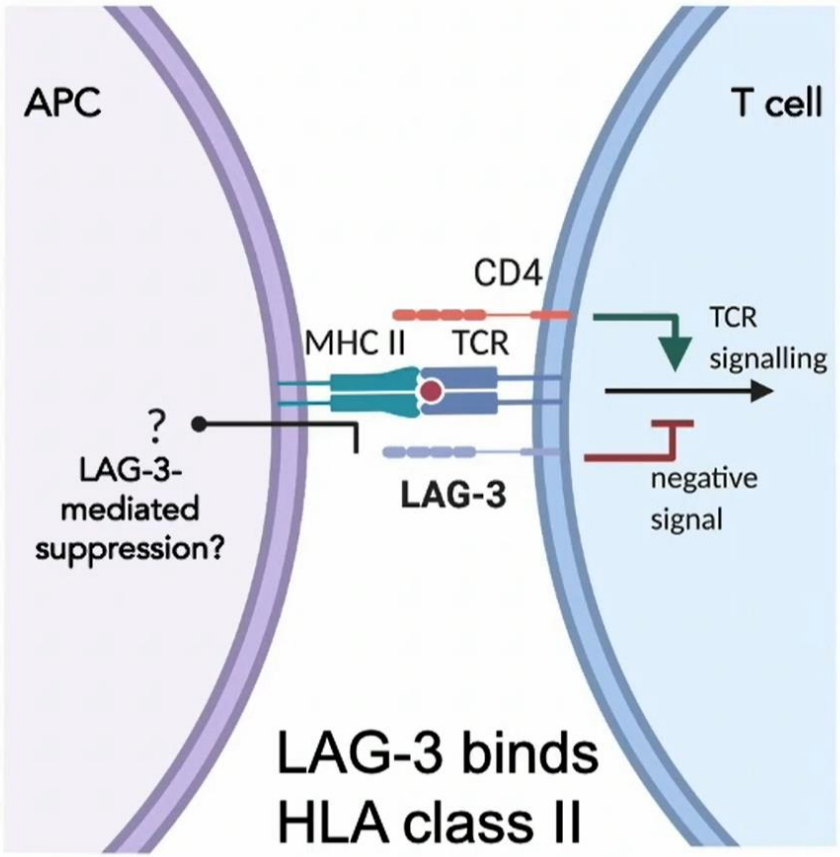

Expression
2
1
0
-1


~13,000
memory Tregs
Cytotoxic
KLRB1+
MALAT1-hi
ANXA-1+
CCR7+
Cycling
Canonical Tregs
IFN signature
MTRNR2L12+
CCR4 / Helios+
UMAP-2
UMAP-1


8000
6000
4000
2000
0
Cell number
5503
7894
PBMC
SFMC
1.00
0.75
0.50
0.25
0.00
Fraction
PBMC
SFMC
Cluster
canonicalTregs
CCR7+
MALAT1 high
Cycling
Cytotoxic
KLRB1+
ANXA1 high
CCR4/Helios+
MTRNR2L12+
IFN signature
p<0.05

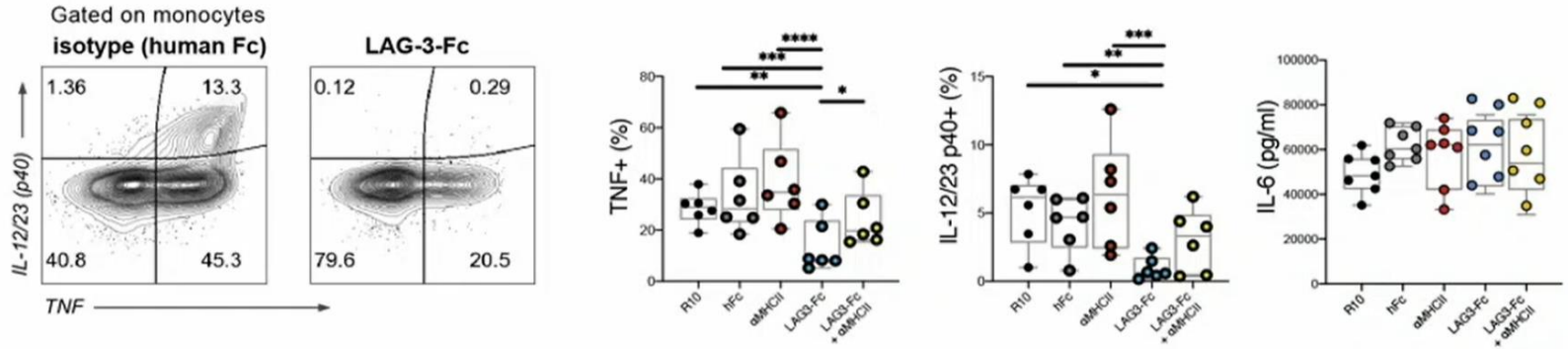
CD8 and CD161+ Tregs express the checkpoint inhibitor LAG-3



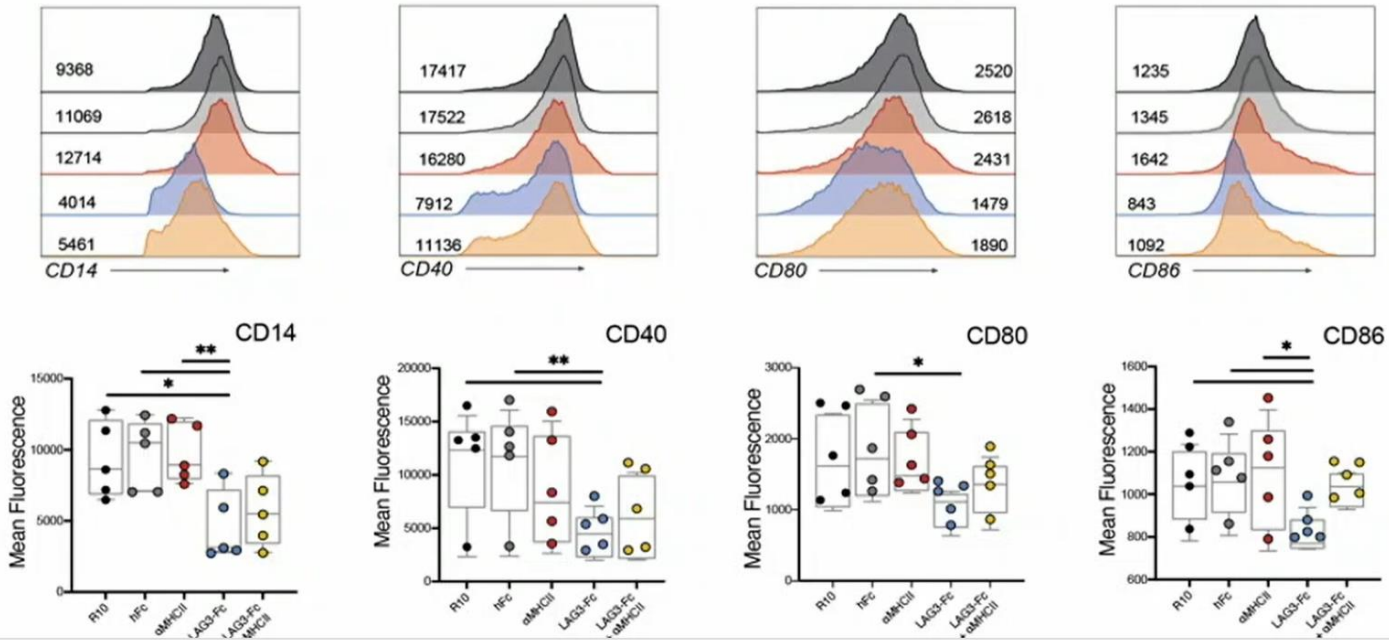


LAG-3 suppresses SpA monocyte TNF and IL-12/23 production and costimulatory molecule expression

LPS-activated AS monocytes + LAG-3/Fc fusion protein



Cytokine production

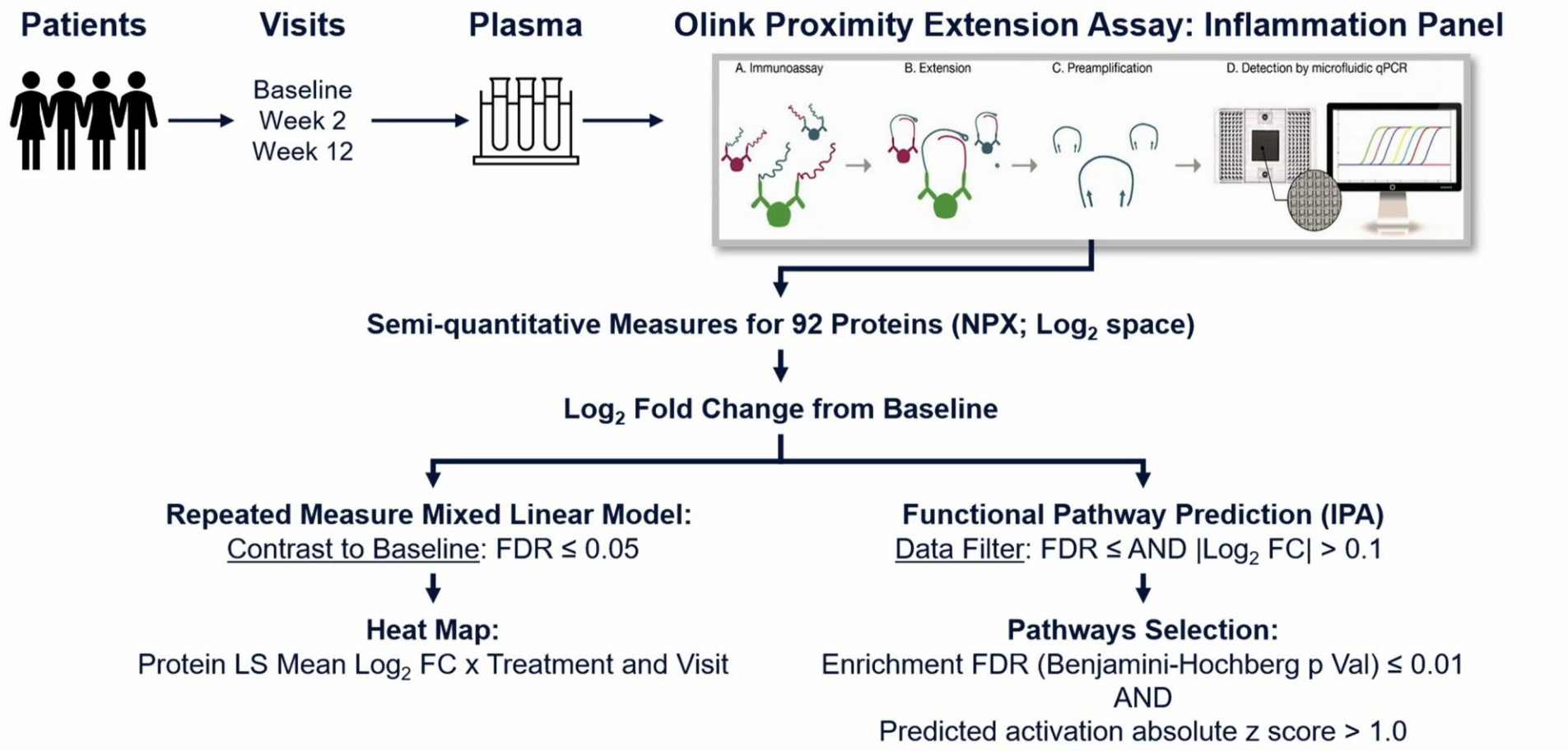


Expression of costimulatory molecule

Βασική έρευνα

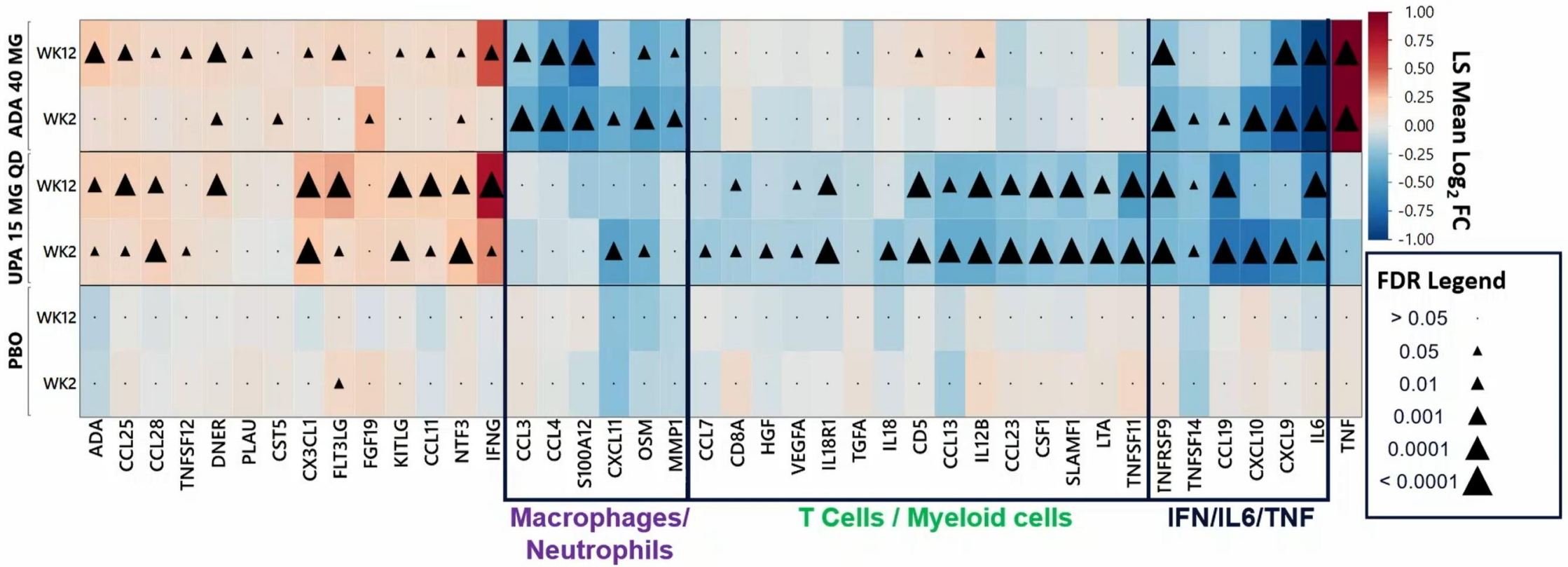
OP0030

Treatment of Non-biologic-DMARD-IR PsA Patients with Upadacitinib or Adalimumab Results in the Modulation of Distinct Functional Pathways: Proteomics Analysis of the SELECT-PsA 1 Phase 3 Study



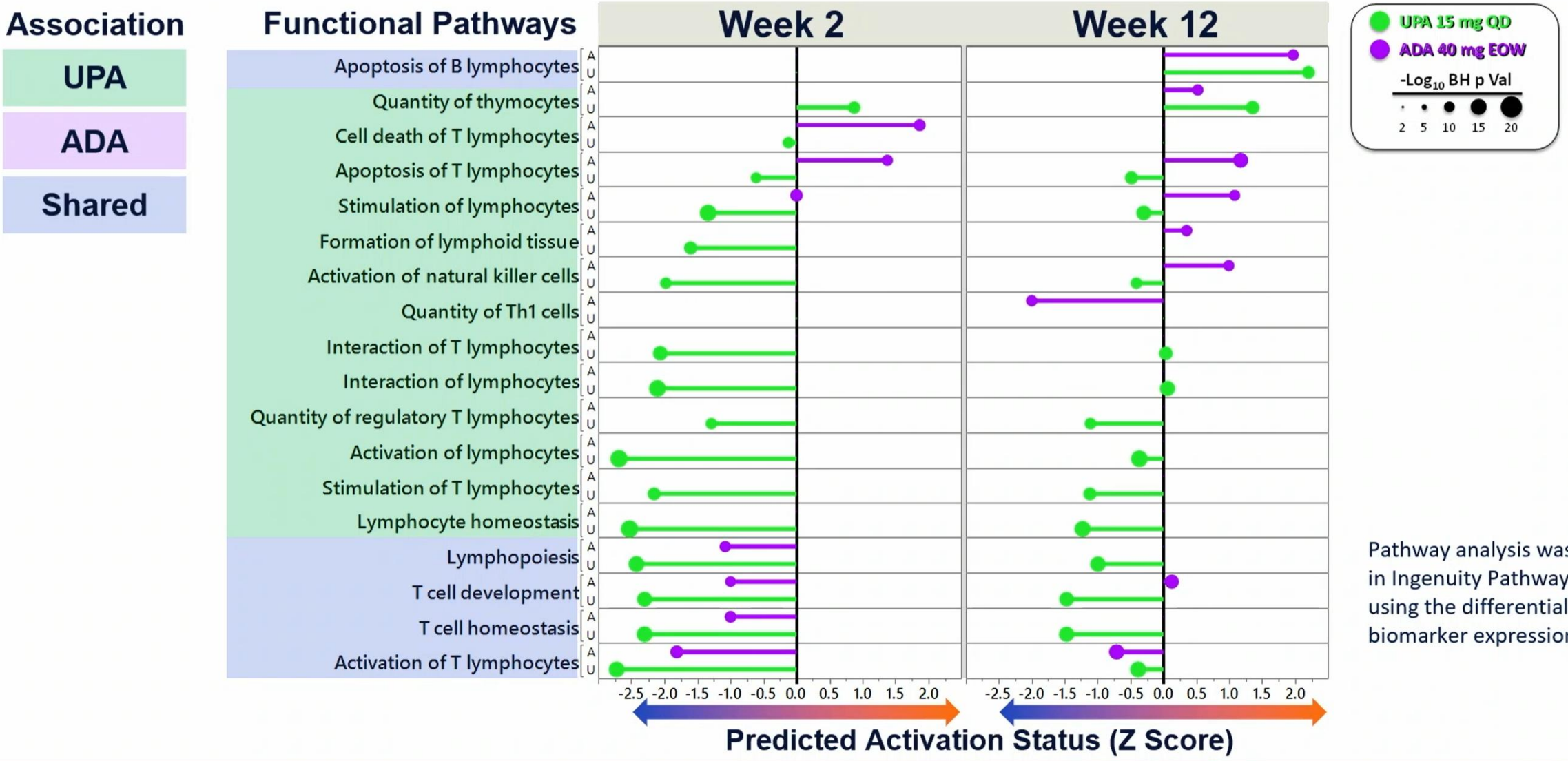
At the single protein biomarker level, treatment with UPA and ADA in non-biologic-DMARD-IR PsA patients demonstrate down modulation of inflammation

- **UPA** down modulated biomarkers associated with **T cells** and **myeloid cells** that was not observed with **ADA**
- **ADA** down modulated biomarkers associated with **Macrophages and neutrophils**, that was not observed with **UPA**
- Both treatments down modulated CCL19, CXCL9, CXCL10, IL6, TNFRSF19, and TNSF14 suggesting common activity on the core pathways related to IFN, IL6, and TNF



Treatment with UPA is predicted to down modulate the activity of T cells to a greater extent than treatment with ADA

Prediction of the effect of UPA and ADA on functional pathways associated with T, B, and NK cells



Pathway analysis was conducted in Ingenuity Pathway Analysis® using the differential protein biomarker expression data


ευχαριστώ!
Email: jimdaoussis@hotmail.com

Leiden University Medical Center

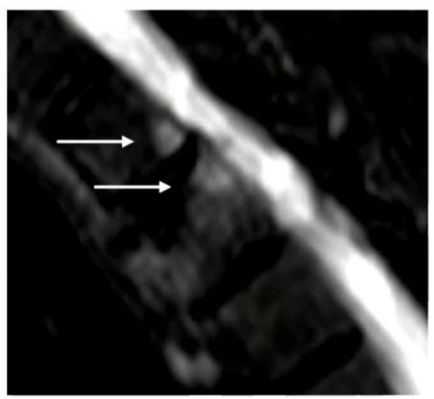
MRI vertebral corner inflammation and fat deposition are associated with whole spine low dose CT detected syndesmophytes: a multilevel analysis

Rosalinde Stal[1], Xenofon Baraliakos[2], Alexandre Sepriano[1], Floris van Gaalen[1], Sofia Ramiro[1], Rosaline van den Berg [1], Monique Reijnierse[3], Jürgen Braun[2], Robert Landewé[4], Désirée van der Heijde[1]

[1] Leiden University Medical Center, Rheumatology, Leiden, The Netherlands
[2] Rheumazentreum Ruhrgebiet, Rheumatology, Herne, Ruhr-University Bochum, Germany
[3] Leiden University Medical Center, Radiology, Leiden, The Netherlands
[4] Amsterdam University Medical Center, Rheumatology, Amsterdam, The Netherlands

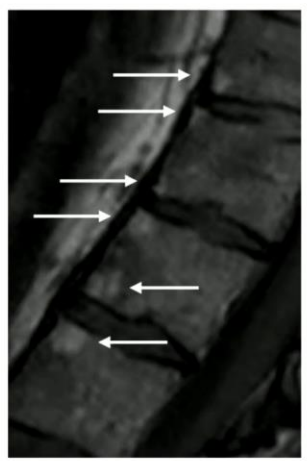
Spinal lesions in radiographic axial spondyloarthritis

Vertebral corner inflammation (VCI)



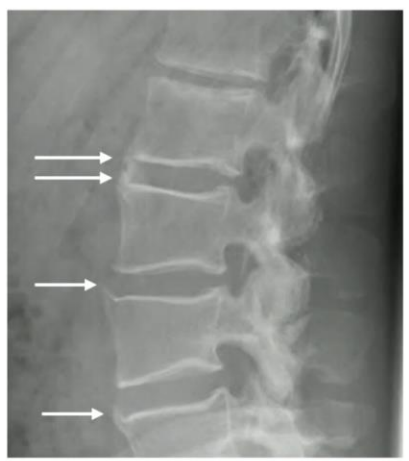
MRI – STIR sequence

Vertebral corner fat deposition (VCFD)



MRI – T1 sequence

Syndesmophytes



Conventional radiography

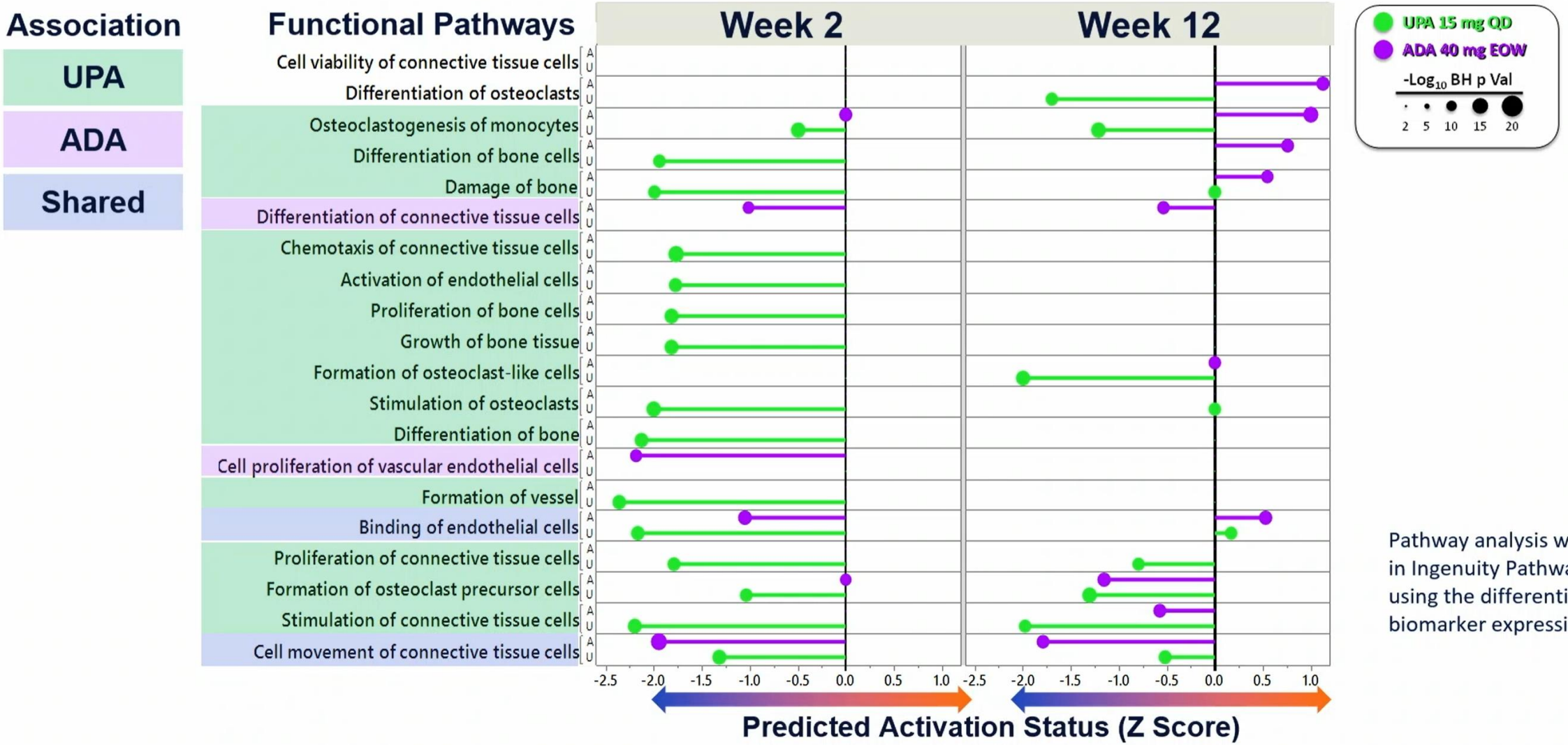
Results – effects of VCI and VCFD on syndesmophyte formation/growth

Pattern	Odds ratio (95% CI)
1. VCI at any timepoint, irrespective of VCFD	**2.4 (1.5 - 3.8)**
2. VCFD at any timepoint, irrespective of VCI	**2.6 (2 - 3.4)**
3. VCI at any timepoint and absence of VCFD on all timepoints	**1.9 (1.1 - 3.1)**
4. VCFD at any timepoint and absence of VCI on all timepoints	**1.9 (1.4 - 2.5)**
5. VCI precedes VCFD	2.2 (0.8 - 5.9)
6. VCI precedes or coincides with VCFD	**2.3 (1.5 - 3.7)**
7. Absence of VCI and VCFD on all timepoints	**0.3 (0.2 - 0.5)**

Of all corners with bone formation, 44% - 47% had absence of VCI and VCFD on all timepoints

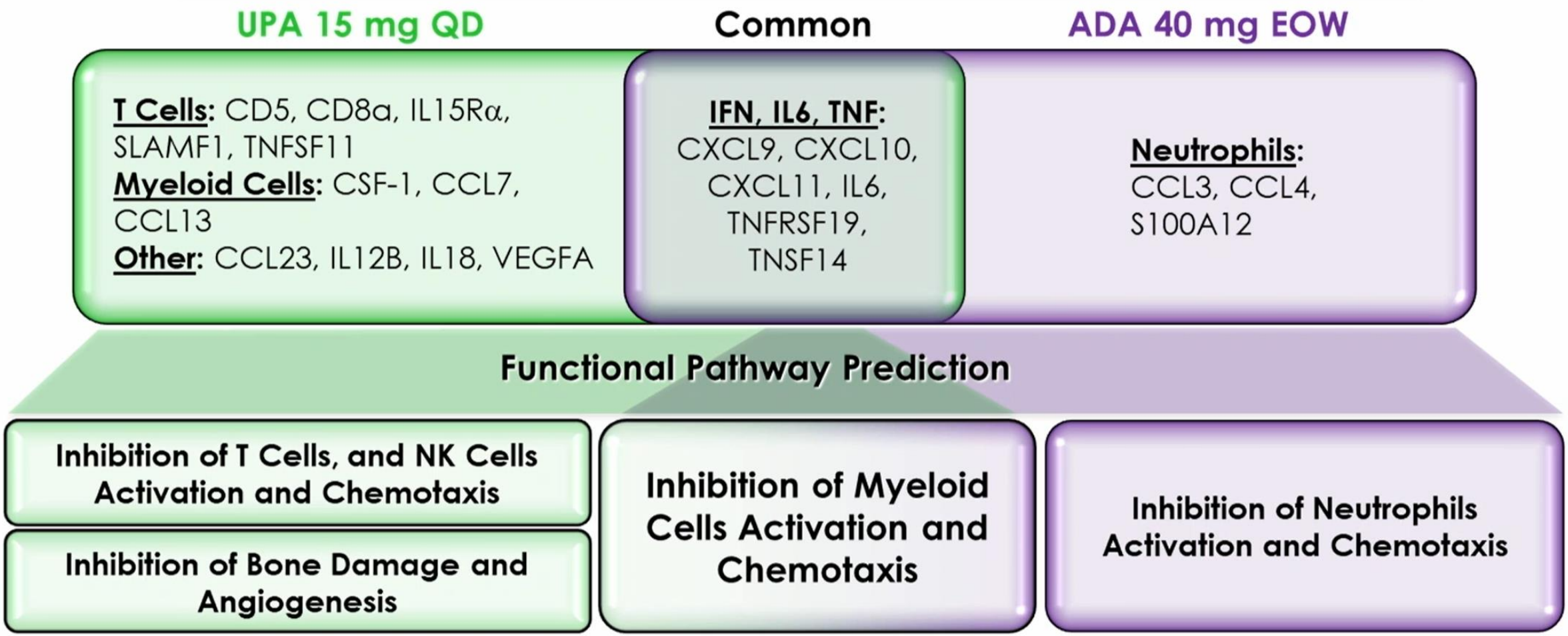
Treatment with UPA preferentially inhibited pathways related to tissue damage and angiogenesis, as compared to the predicted effect of treatment with ADA

Prediction of the effect of UPA and ADA on functional pathways associated with Vascular, Connective Tissue, and Bone

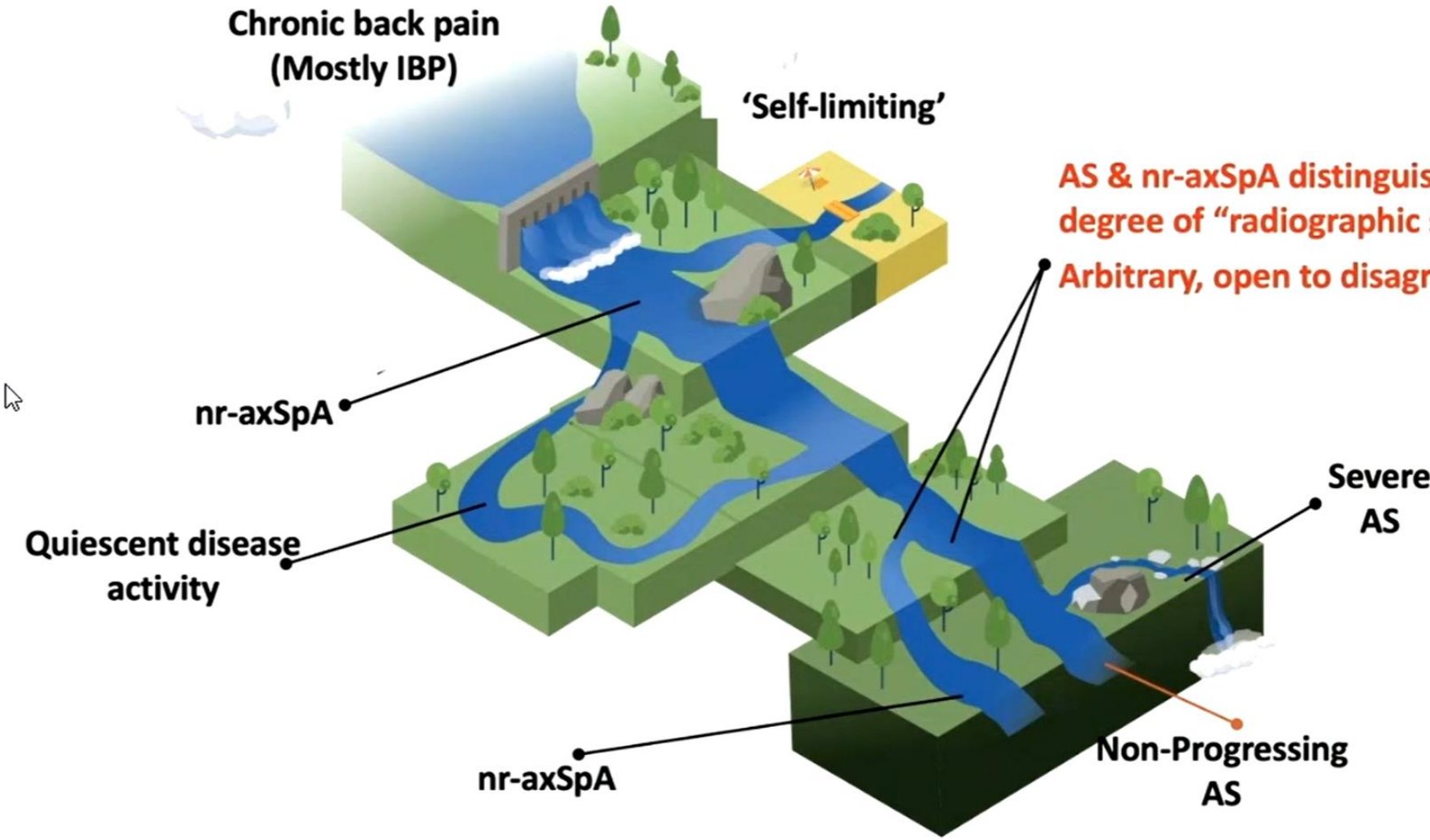


Pathway analysis was conducted in Ingenuity Pathway Analysis® using the differential protein biomarker expression data

Biomarkers Modulated in UPA and ADA in DMARD-IR PsA Patients



Axial SpA Spectrum: nr-axSpA and r-axSpA



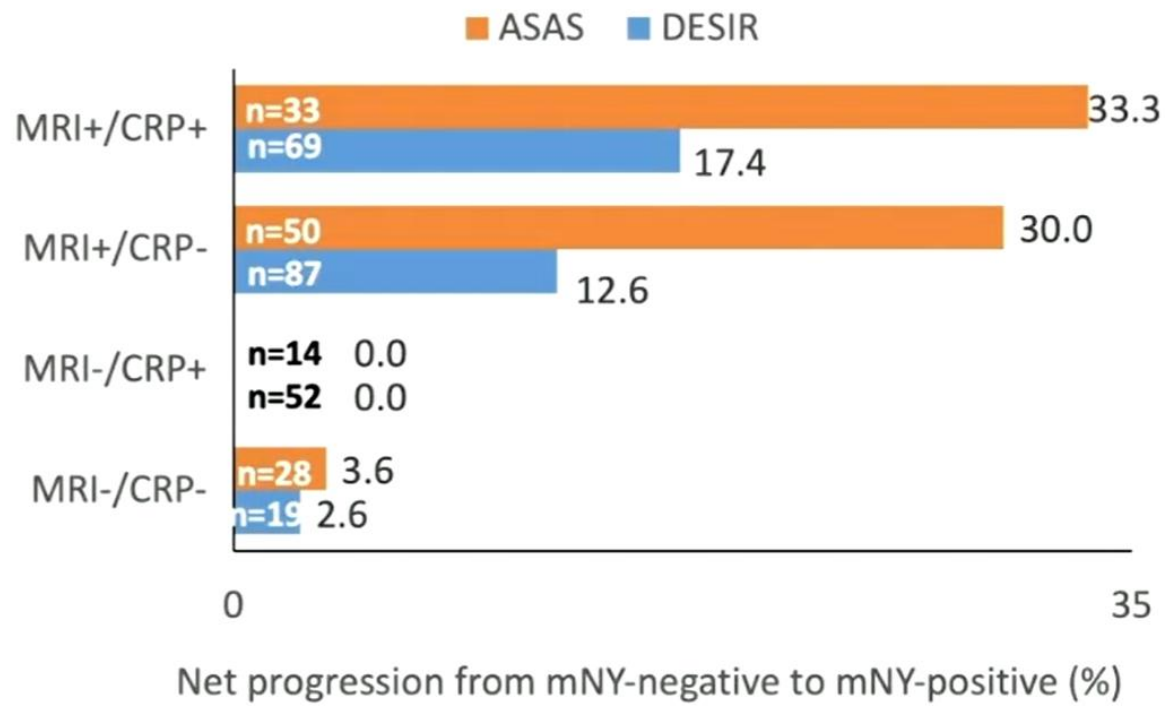
Garg N et al. *Best Pract Res Clin Rheumatol.* 2014;28(5):663-672.

Predictors for radiographic progression in nr-axSpA

Predictors of progression from nr-axSpA to r-axSpA

- Baseline structural damage on x-rays and on MRI[1]
- HLA-B27 positivity[1,4]
- Cigarette smoking[4]
- Younger age[5]
- Male sex[6]

Data from ASAS & DESIR cohorts showed MRI-SI joint inflammation & CRP predicted development of radiographic damage



1. Protopopov M and Poddubnyy D. Expert Rev Clin Immunol. 2018;14(6):525–533.
2. Sepriano A et al. Rheumatology. 2018; 77(Suppl2):628. Abstract FRI0172.
3. Sepriano A et al. Ann Rheum Dis 2018; 77(Suppl2):172. Abstract OP0246.
4. Navarro-Compán V and Machado PM. Nat Rev Rheumato. 2016;12:380–382.
5. Protopopov M et al. Arthritis Rheumatol. 2018; 70 (suppl 10). Abstract 660.
6. Rudwaleit M et al. Arthritis Rheum. 2009;60(3):717–727.

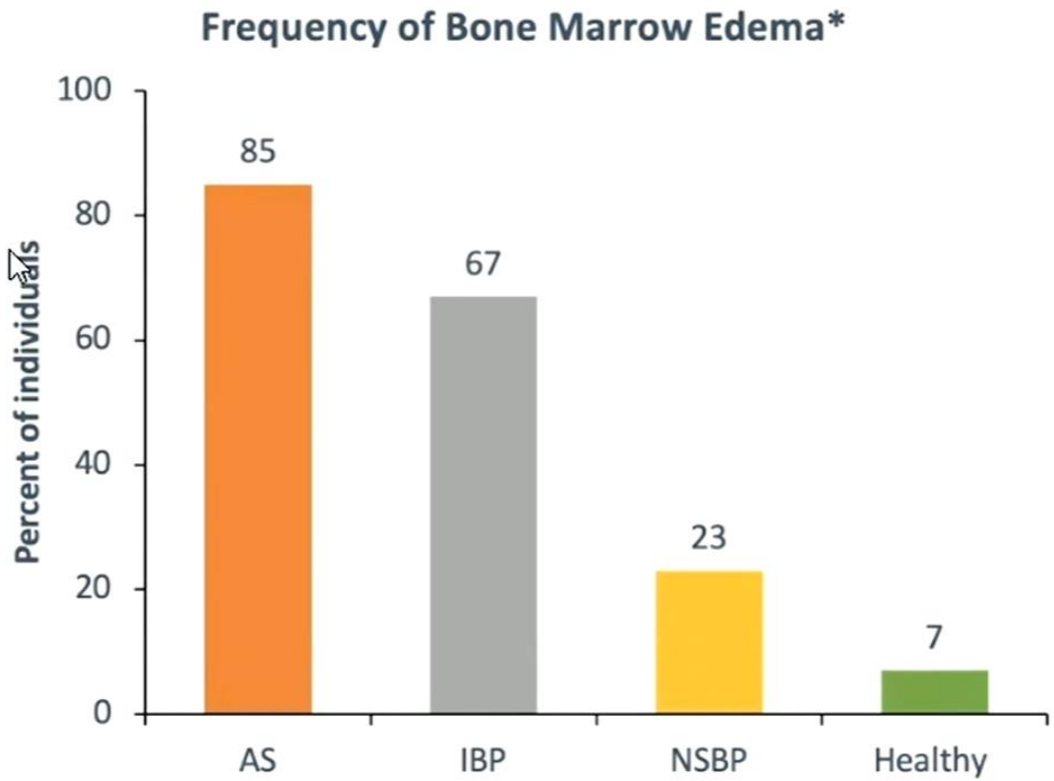
What constitutes a positive MRI for *classification* of axial spondyloarthritis: a consensual approach

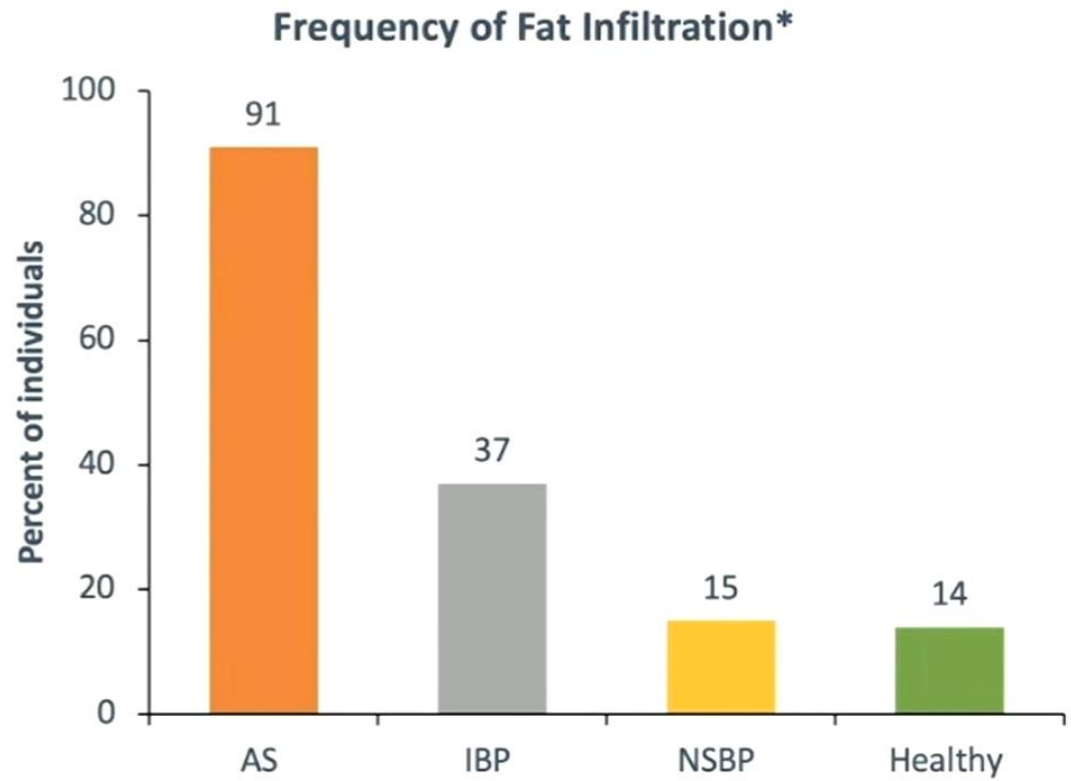
- Positive MRI definition is based on active inflammatory SIJ lesions
- Subchondral or periarticular bone marrow edema (BME) highly suggestive of sacroiliitis
- ≥2 BME lesions on a single SIJ slice and/or ≥1 BME lesion on 2 consecutive slices
- "Classification criteria" should not be used to make a diagnosis
- Inappropriate use of this definition has led to erroneous diagnosis of "nr-axSpA" in patients having "two white spots" on SIJ MRI

Rudwaleit M. et al. Ann Rheum Dis 2009; 68: 1520-7
Deodhar A. Arthritis Rheumatol. 2016 Apr;68(4):775-8

Bone Marrow Edema Occurs in Healthy, Asymptomatic Individuals

Diagnostic utility study of MRI, images from 187 individuals (AS, IBP, NSBP, and healthy)





*Meeting ASAS criteria for positive MRI.

Weber U et al. *Arthritis Rheumatol.* 2010;62(10):3048-3058.

RHEUMATOLOGY

Rheumatology 2021;00:1–12
doi:10.1093/rheumatology/keab099
Advance access publication 1 February 2021

Original article

Data-driven definitions for active and structural MRI lesions in the sacroiliac joint in spondyloarthritis and their predictive utility

Walter P. Maksymowych [1,2], Robert G. Lambert[3,4], Xenofon Baraliakos[5], Ulrich Weber[6,7], Pedro M. Machado [8,9,10], Susanne J. Pedersen[11], Manouk de Hooge[12,13], Joachim Sieper[14], Stephanie Wichuk[1], Denis Poddubnyy [14], Martin Rudwaleit[15,16], Désirée van der Heijde[17], Robert Landewe[18,19], Iris Eshed [20] and Mikkel Ostergaard[11,21]

- Definite active lesion typical of axSpA: 4 SI joint quadrants with BME at any location or at the same location in 3 consecutive slices
- Definite structural lesion: Any one of 3 SI joint quadrants with erosion or 5 with fat lesions, erosion at same location for 2 consecutive slices, fat lesions at same location for 3 consecutive slices, or presence of a deep (i.e. >1 cm depth) fat lesion
- PPVs $\geq$ 95% for clinical diagnosis of axSpA

Non-Radiographic or Radiographic axial SpA: Does it Matter

Making the Diagnosis

It doesn't matter:

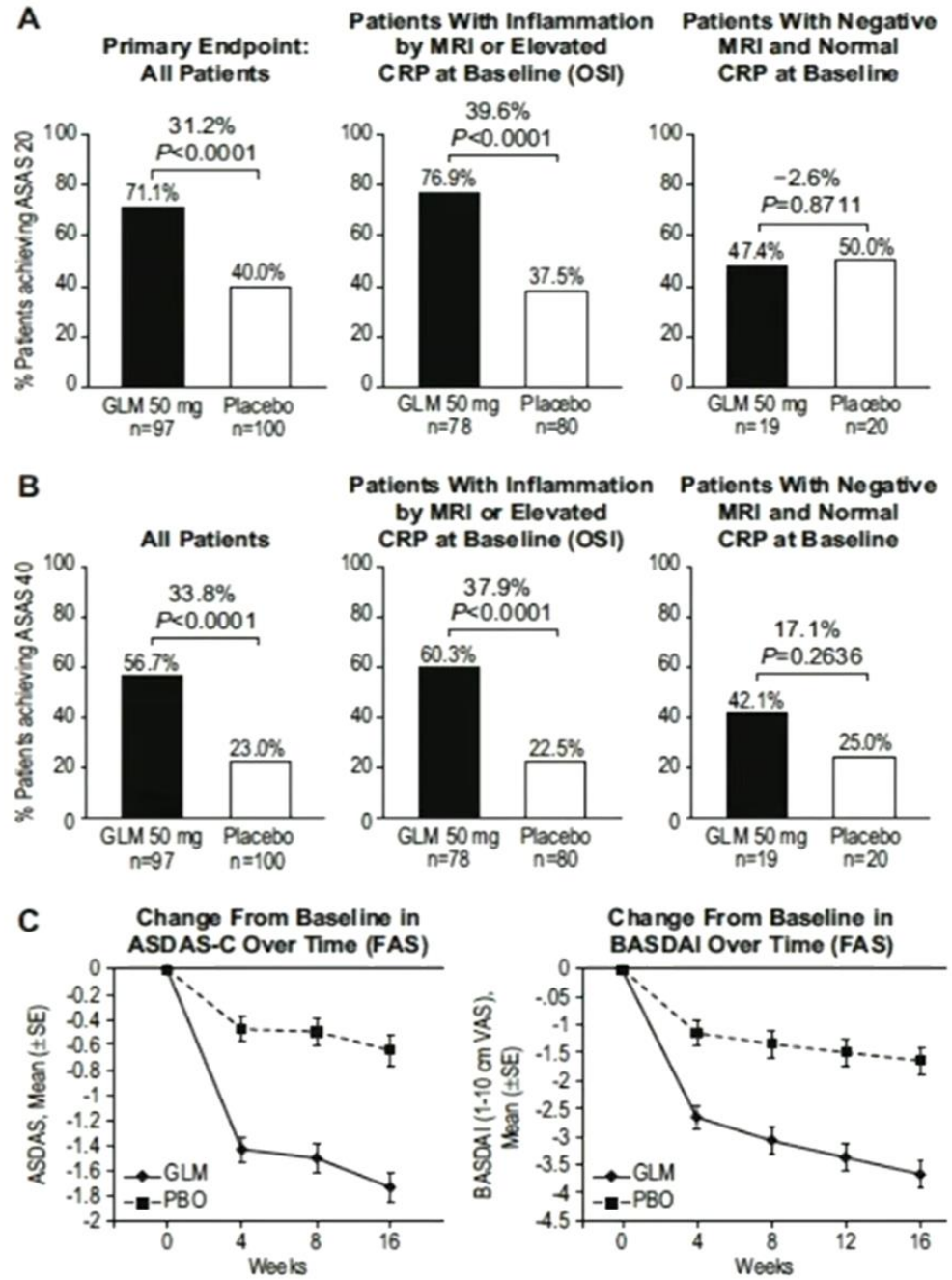
- The distinction is arbitrary: based on the degree of sacroiliitis: Just call it "axSpA"

It matters:

- Patients' perspective:
  - Nr-axSpA may be somewhat reassuring: not "ankylosing", 'early stage', 'irreversible damage has not occurred'
  - May be motivating to not smoke to prevent progression
- Rheumatologists' perspective:
  - Nr-axSpA is a challenging diagnosis to make, may need to revisit, & reconsider if no treatment response

Objective evidence of inflammation is required for treatment success in nr-axSpA

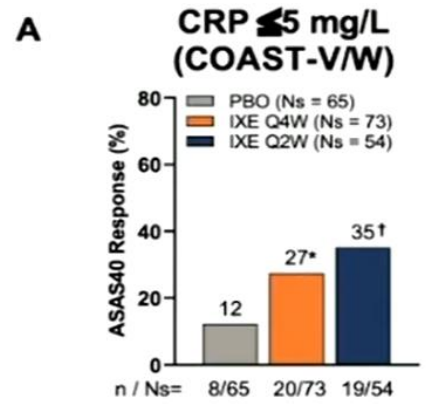
- Almost all RCTs in nr-axSpA require 'objective evidence of inflammation
- Golimumab in nr-axSpA: GO-AHEAD Trial
- DBRPCT in 'active' nr-axSpA patients (18-45 yrs) S/C Gol 50 mg vs PL Q4W n=197
- 1^0 endpoint: ASAS20 @ Wk16
- 1^0 end point achieved 71% vs 40%; p <0.0001
- In patients with negative MRI & normal CRP 47.4% vs 50%, p=0.87

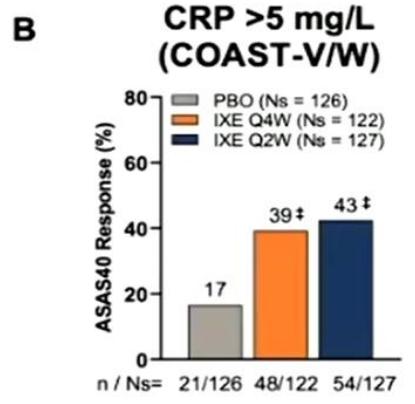


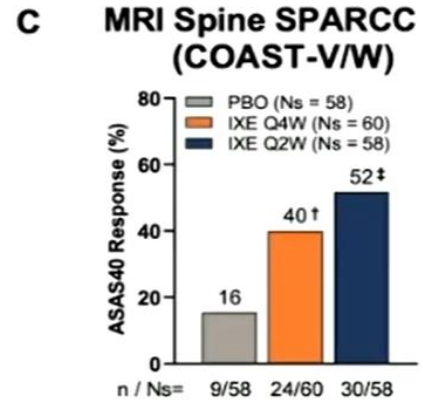
Sieper J. et al. Arthritis Rheumatol 2015;67:2702-12

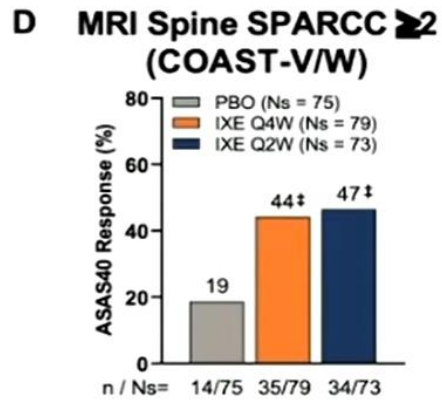
Should we treat a r-axSpA patient without objective signs of inflammation?

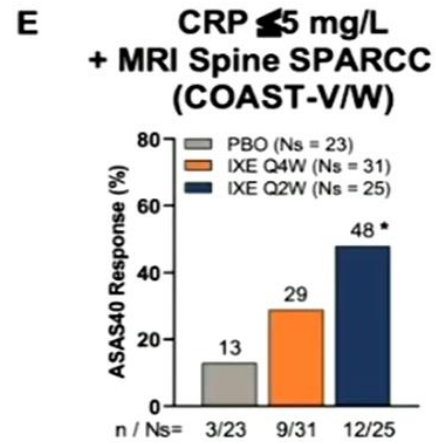
- There is a reluctance to treat AS patients with biologics if they don't have objective signs of inflammation
- In bDMARD-naive and TNFi-experienced populations, ixekizumab demonstrated efficacy (ASAS40 response) even in the absence of elevated CRP and MRI scores

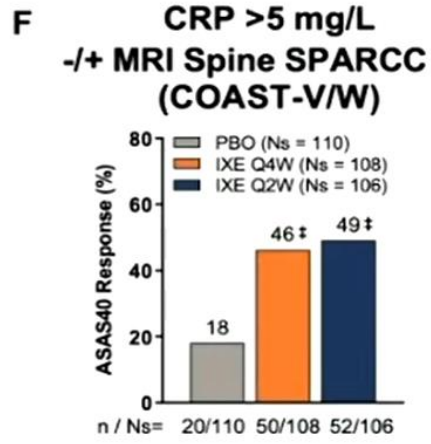






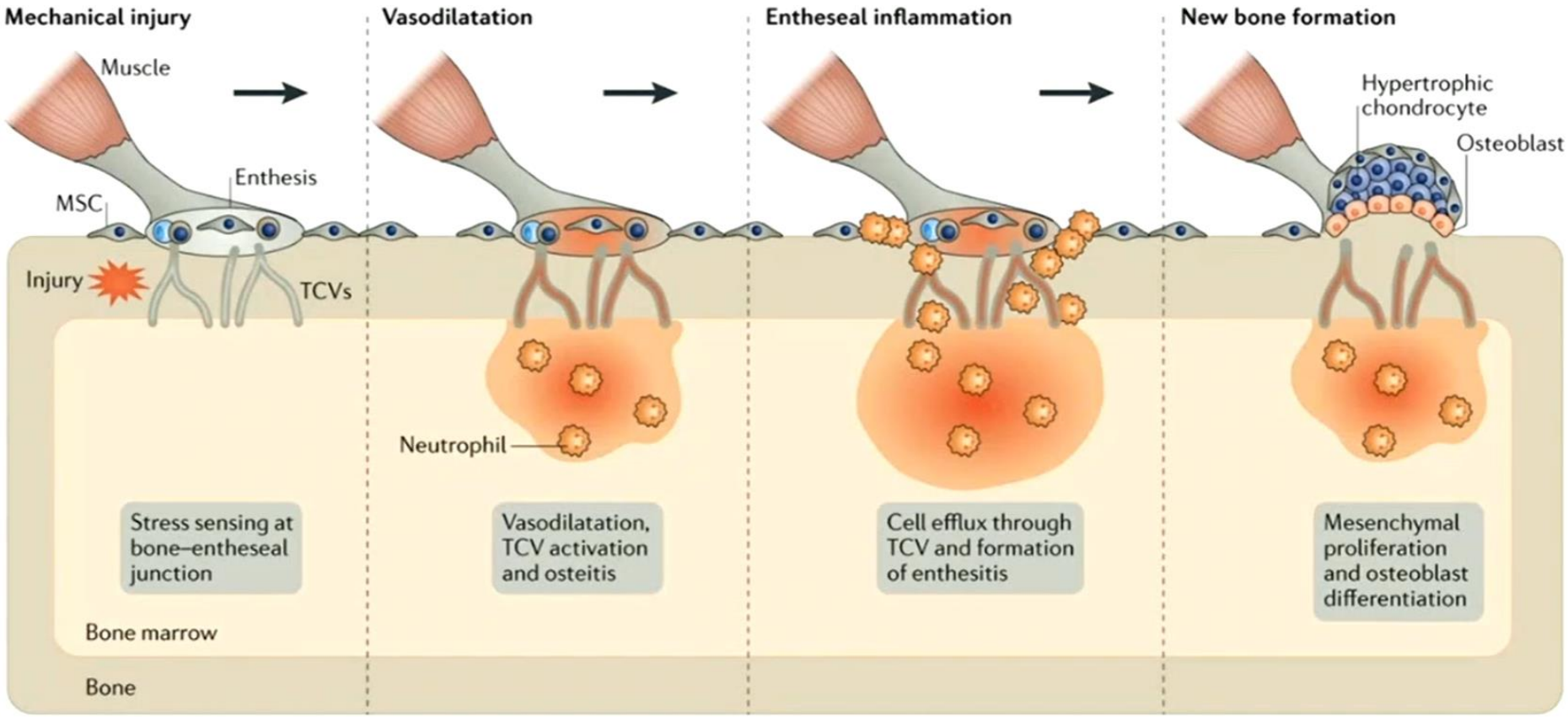






Maksymowych W, et al. Submitted 2021

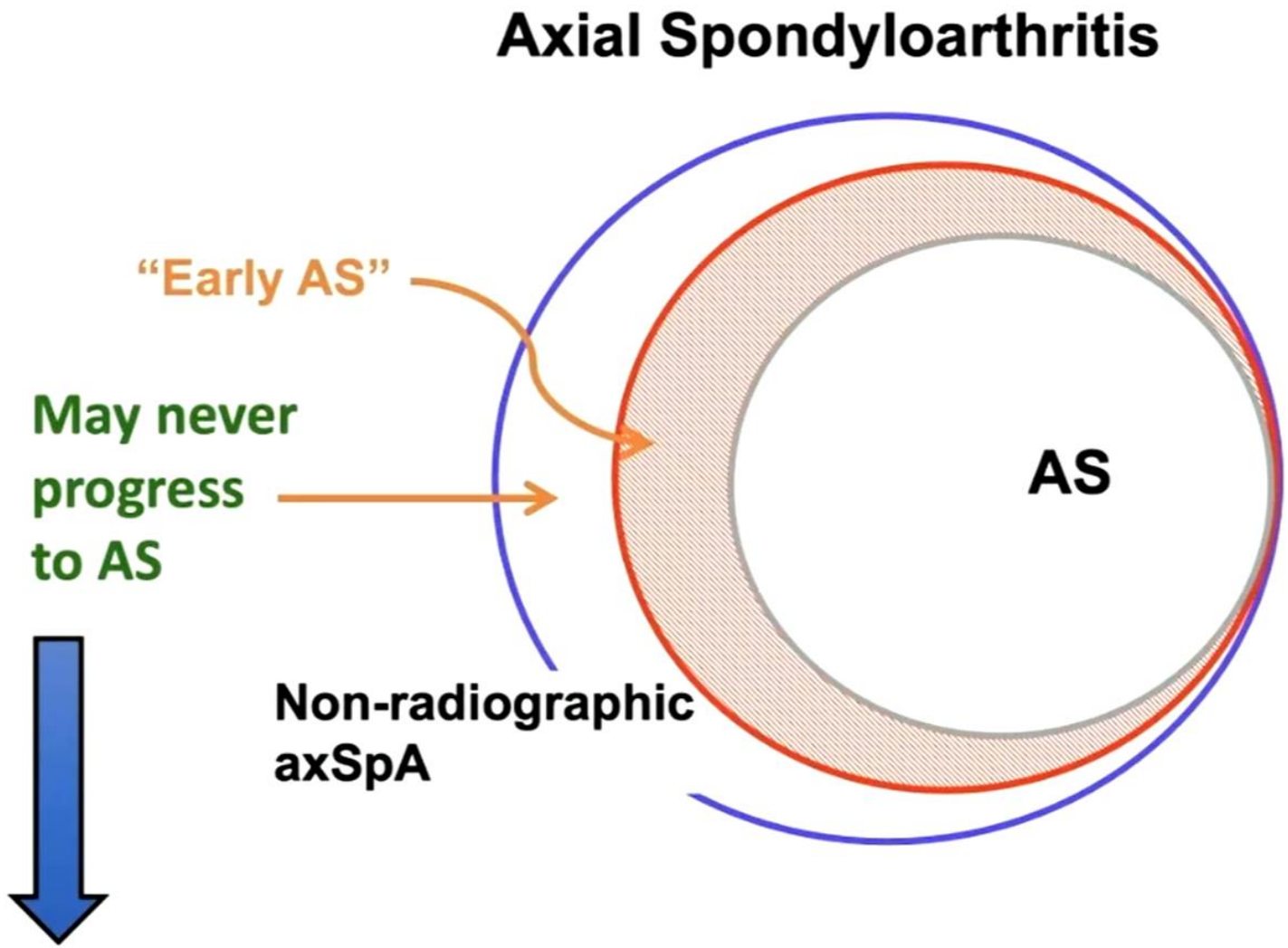
Nr-axSpA vs R-axSpA: Does it matter in Research?
Pathophysiology of Osteogenesis



Mechanical Trauma → Neutrophilic Inflammation → Excessive Repair: Osteogenesis

Gravallese EM, Schett G. Nat Rev Rheumatol. 2018 Nov;14(11):631-640.

Implications of the Concept of Axial Spondyloarthritis



What happens to these patients over long-term? Do they still have the same disease as someone with the other extreme: bamboo spine?

AxSpA patients can have *very different* clinical phenotypes

57-yr-Male Bamboo Spine

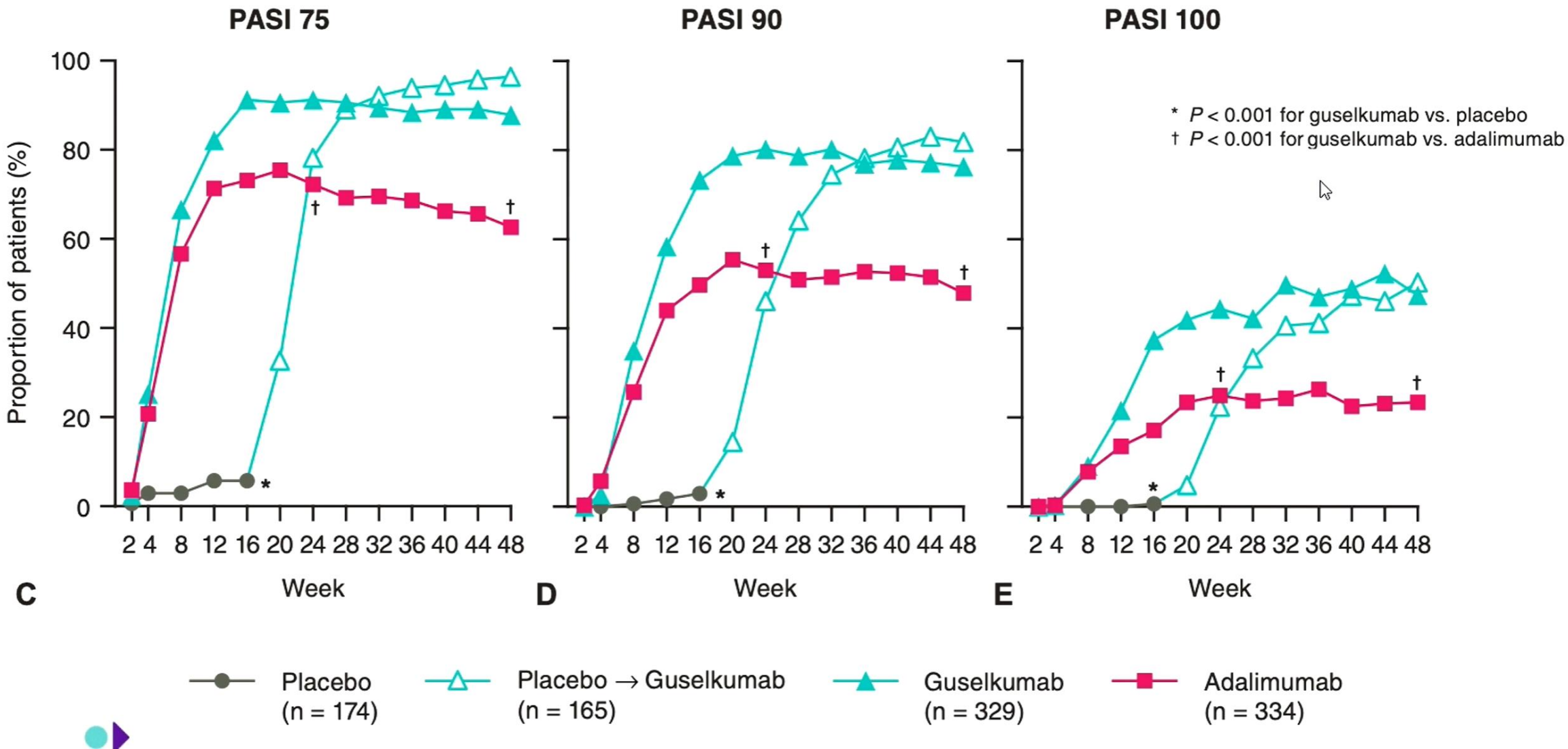
AS

57-yr-Female Normal SIJ & spine after 25 yrs of symptoms

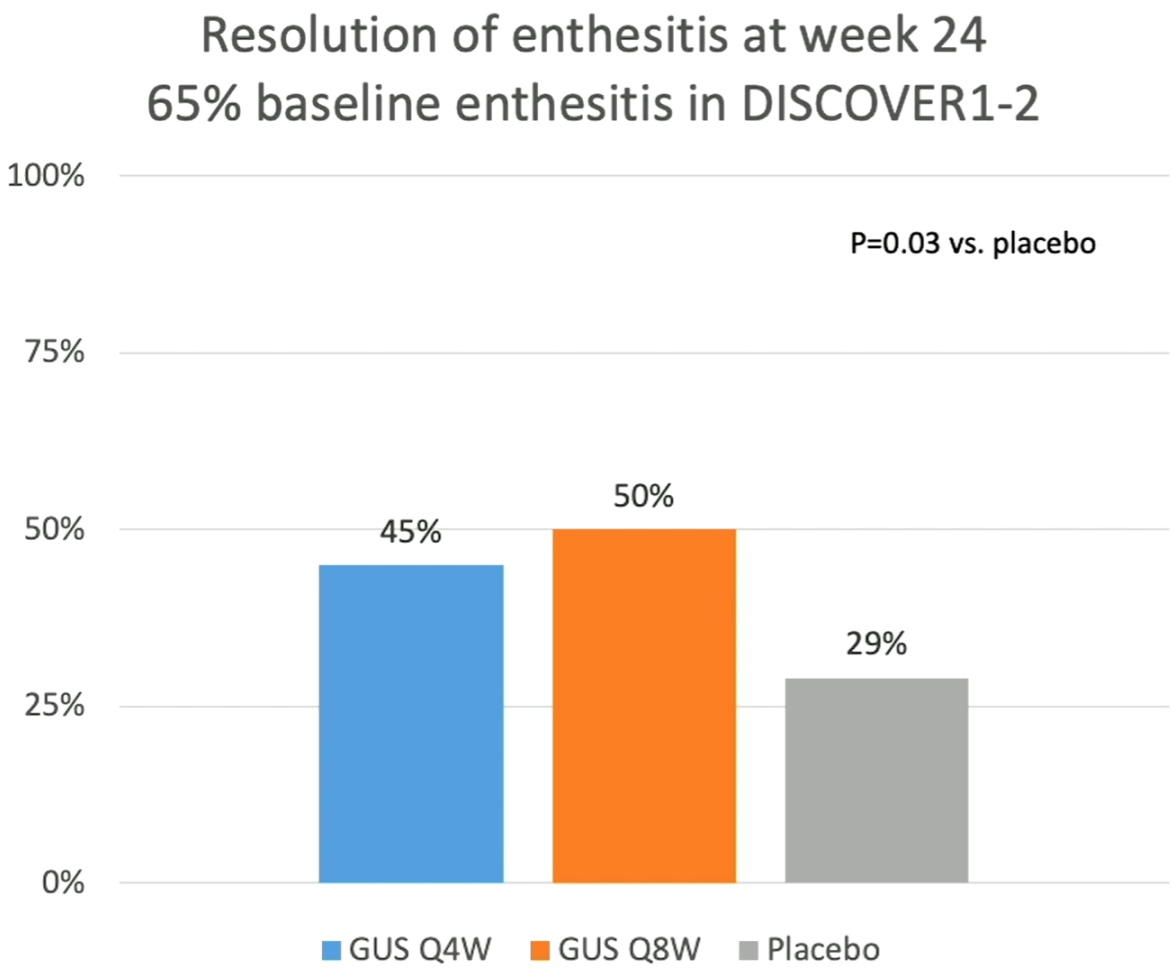
Nr-axSpA

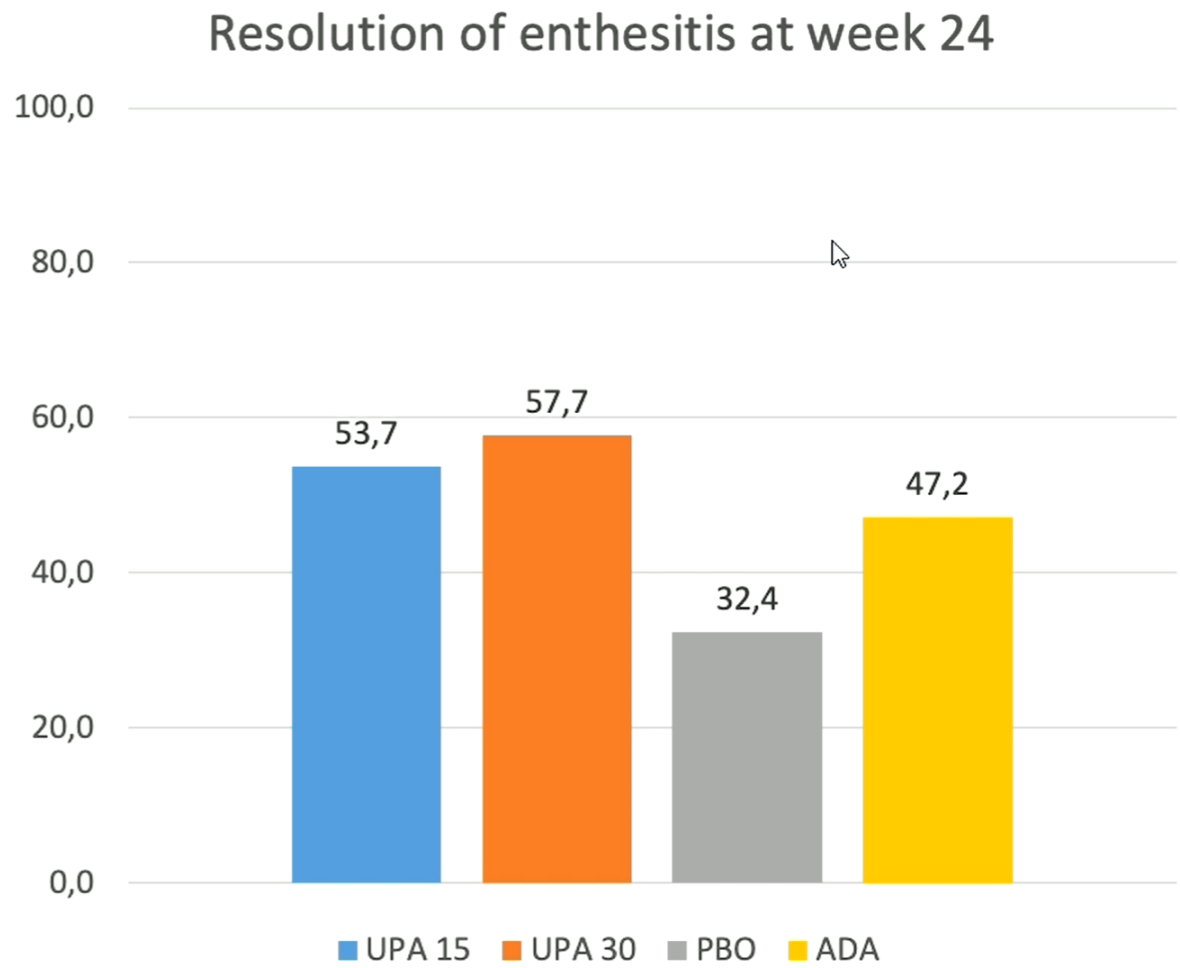
- Do these two patients really have the same disease?
- Is it possible that genes for bone destruction and new bone formation are not being expressed in the nr-axSpA patient that hasn't progressed after 25 years of disease?
- In future will we be able to distinguish those who will develop structural damage, from those who will not have radiographic progression by gene expression profiles?

Psoriasis: Guselkumab vs. Adalimumab
In dermatology high hurdle endpoints improved …



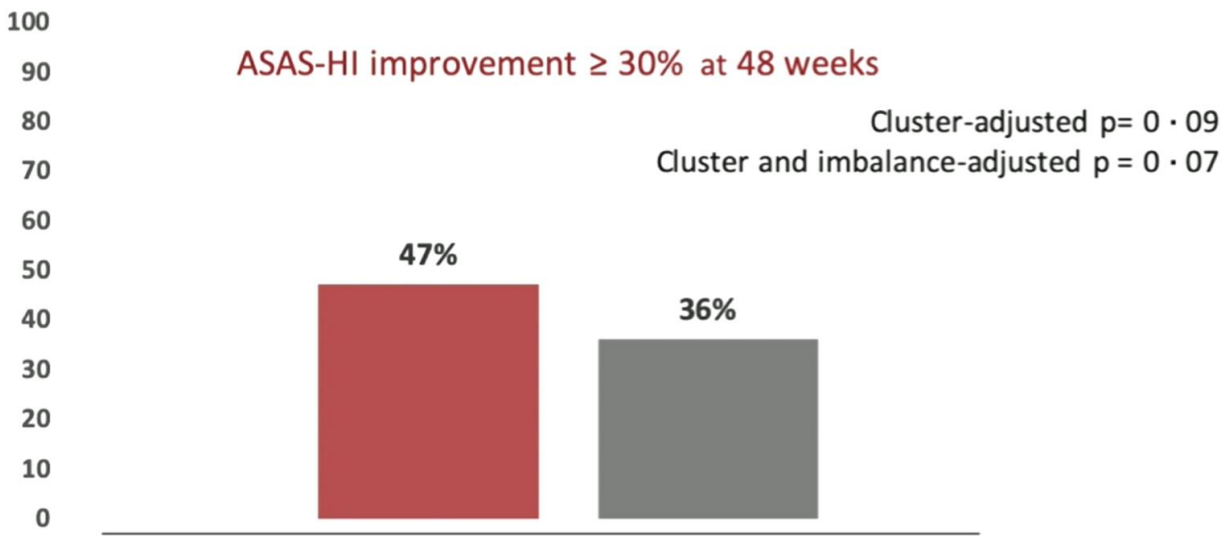
Remission / Resolution of Enthesitis Results for Guselkumab and Upadacitinib

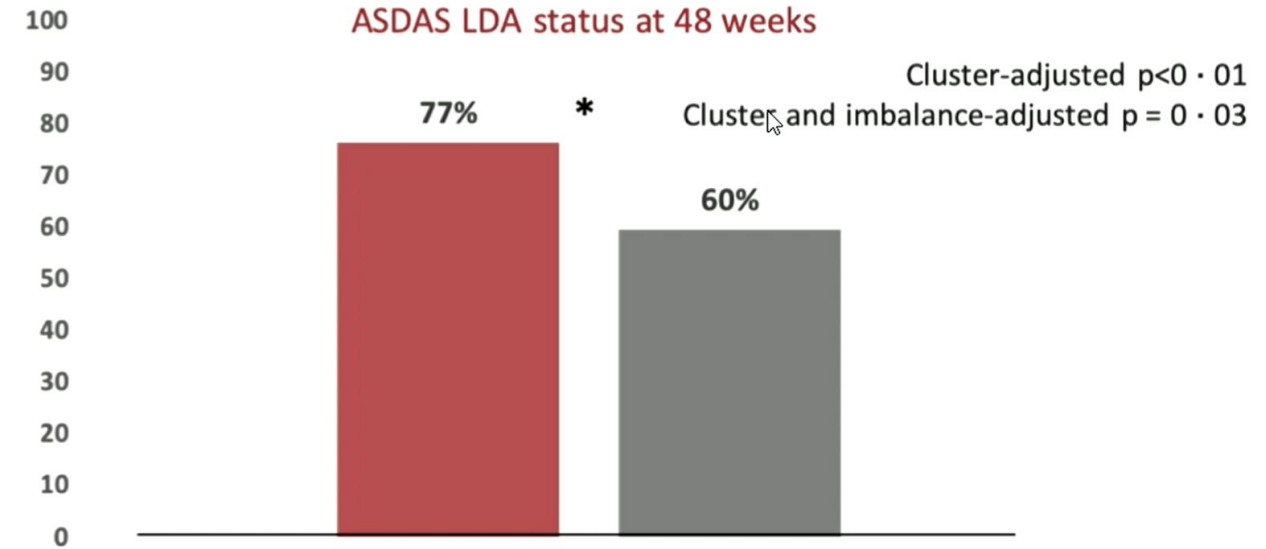




McGonagle D, et al. Rheumatology (Oxford) 2021 Apr 6: online ahead o

T2T/TC in Axial Spondyloarthritis





Strategy 4:
The “DEER” Treatment Approach!

“Dedicated Empathic and Educated Rheumatologist” Treatment Approach

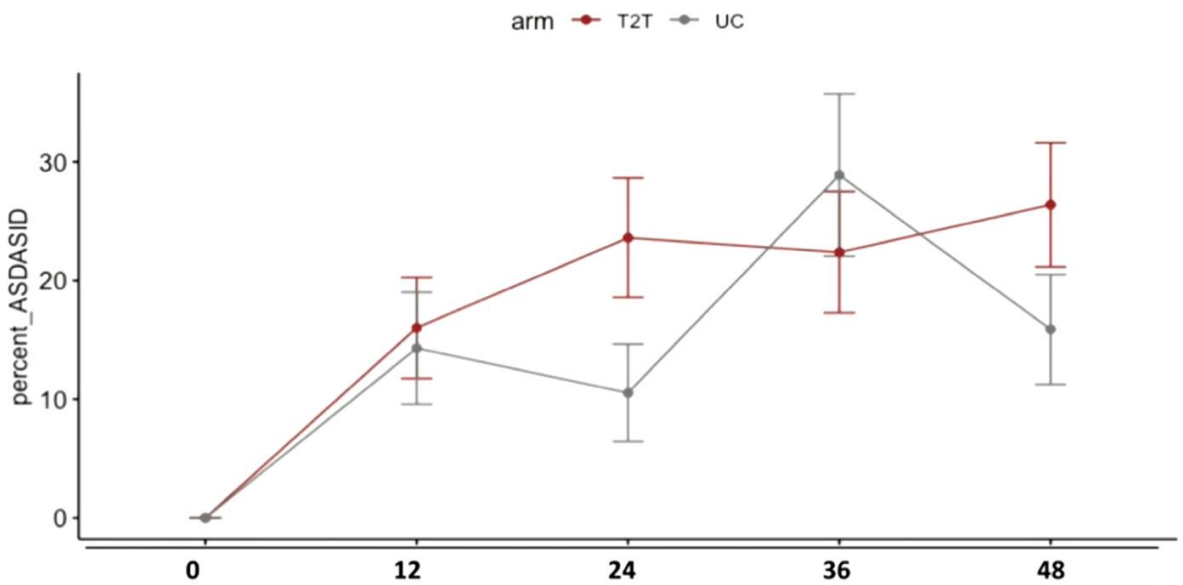
… aka …

“Usual (Good) Care”

The “DEER” Approach in TICOSPA

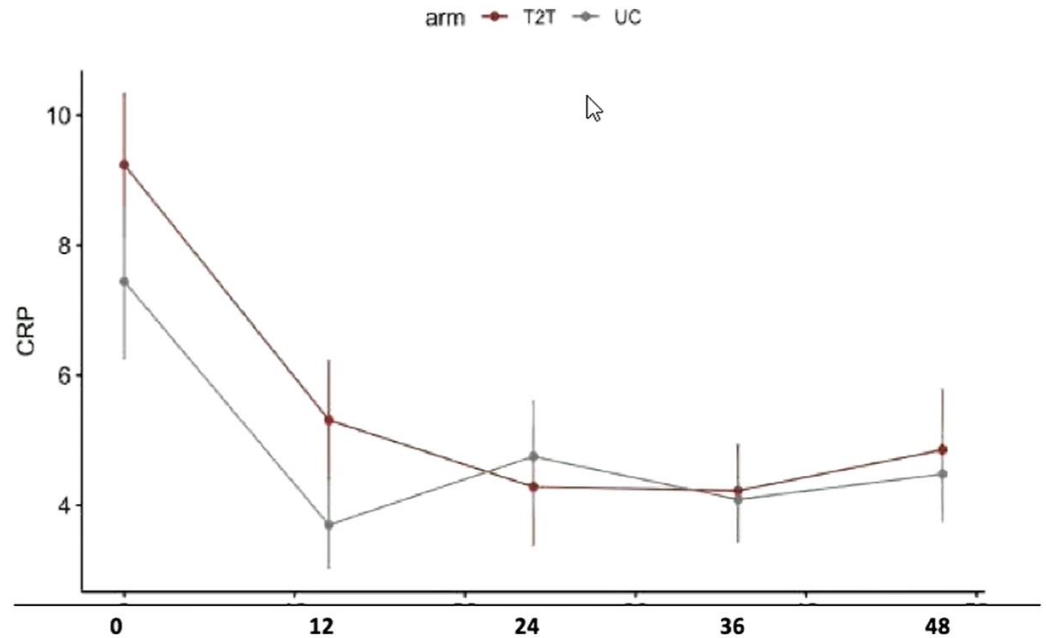
TICOSPA
TIGHT CONTROL IN SPONDYLOARTHRITI

ASDAS Inactive Disease (<1.3)



ASDAS ID (% patients)	T2T (n=80)	UC (n=80)	T2T (n=75)	UC (n=72)	T2T (n=72)	UC (n=69)	T2T (n=68)	UC (n=59)	T2T (n=72)	UC (n=72)
	0%	0%	16.0%	14.3%	23.6%	10.5%	22.4%	28.9 %	26.4 %	15.9 %

CRP



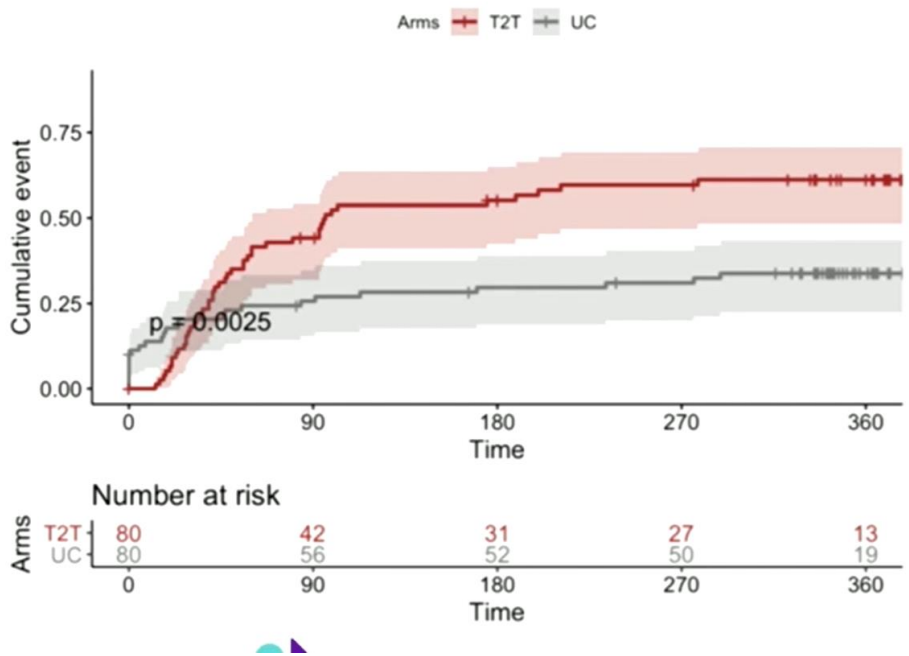
CRP (mg/L)	T2T (n=80)	UC (n=80)	T2T (n=75)	UC (n=72)	T2T (n=72)	UC (n=69)	T2T (n=68)	UC (n=59)	T2T (n=72)	UC (n=72)
	9.24 (9.75)	7.38 (10.5)	5.31 (7.89)	3.70 (5.02)	4.28 (7.59)	4.75 (6.62)	4.22 (5.77)	4.09 (4.35)	4.85 (7.86)	4.48 (5.85)

The “DEER” Approach in TICOSPA

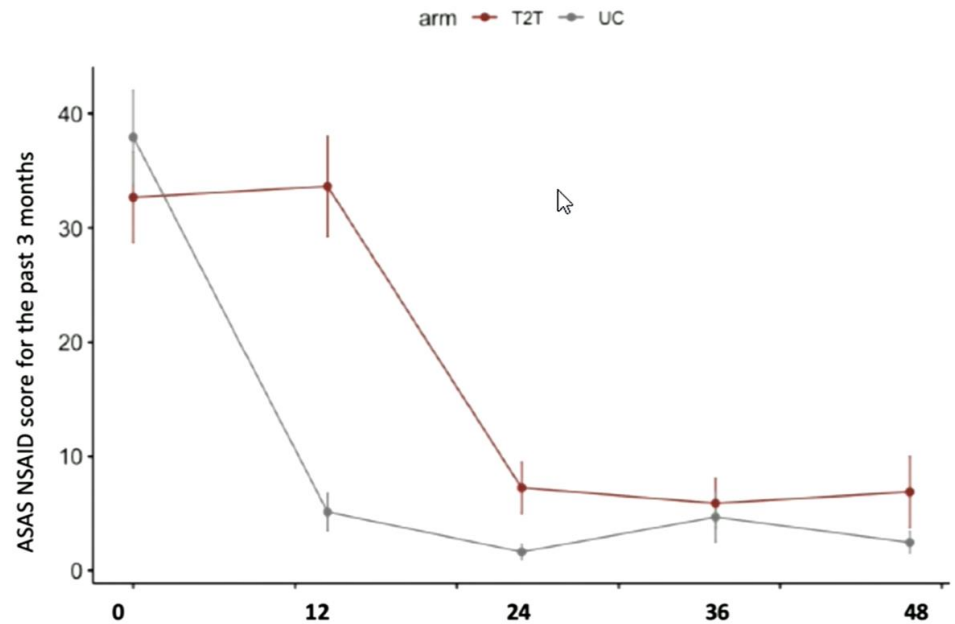
TICOSPA
TIGHT CONTROL IN SPONDYLOARTHRITIS

bDMARDs initiation

	0		12		24		36		48	
	T2T (n=80)	UC (n=80)	T2T (n=80)	UC (n=80)	T2T (n=80)	UC (n=80)	T2T (n=80)	UC (n=80)	T2T (n=80)	UC (n=80)
bDMARD	0 (0%)	0 (0%)	29 (36.2%)	19 (23.8%)	37 (46.2%)	21 (26.2%)	41 (51.2%)	14 (17.5%)	45 (56.2%)	22 (27.5%)



ASAS-NSAID score



	0		12		24		36		48	
	T2T (n=80)	UC (n=80)	T2T (n=75)	UC (n=72)	T2T (n=72)	UC (n=69)	T2T (n=68)	UC (n=59)	T2T (n=72)	UC (n=72)
Mean (SD)	32.70 (35.4)	37.50 (36.6)	33.60 (38.0)	5.13 (14.0)	7.24 (19.3)	1.64 (5.71)	5.90 (18.0)	4.68 (16.7)	6.88 (26.5)	2.47 (8.05)

TiCoPA
Tight Control of Psoriatic Arthriti

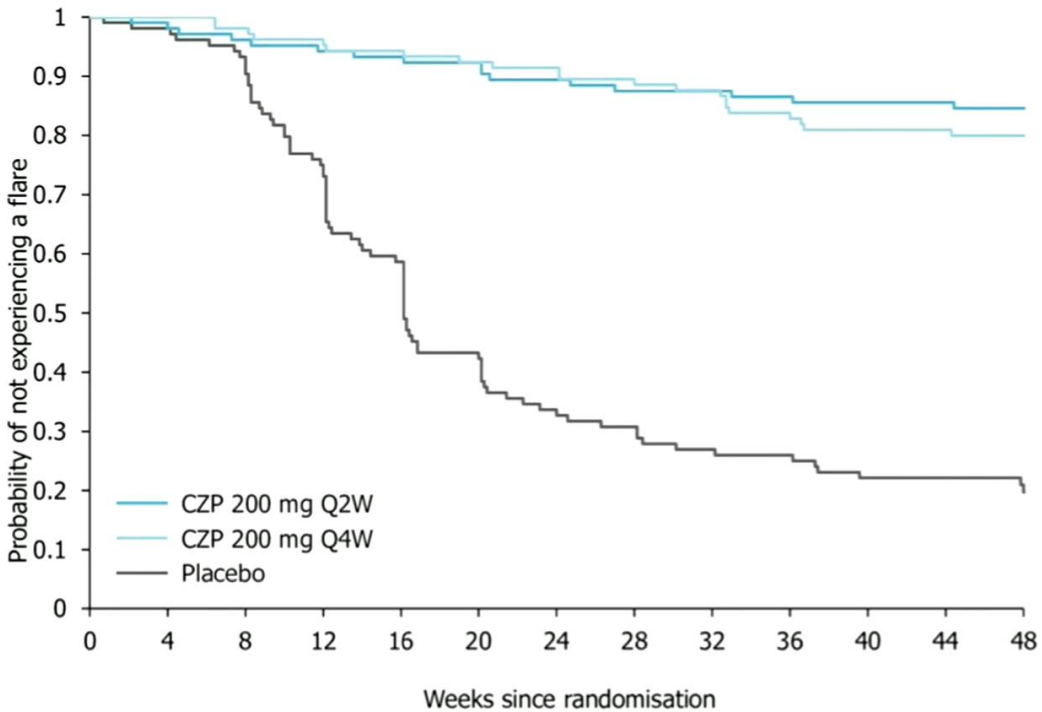
Long-term follow-up of patients in the TICOPA trial

- Case review approx. 5 years after completion of TICOPA: n=110
- Working definition of ”Low Disease Activity”: no tender or swollen joints, no dactylitis and enthesitis + no change in treatment required.

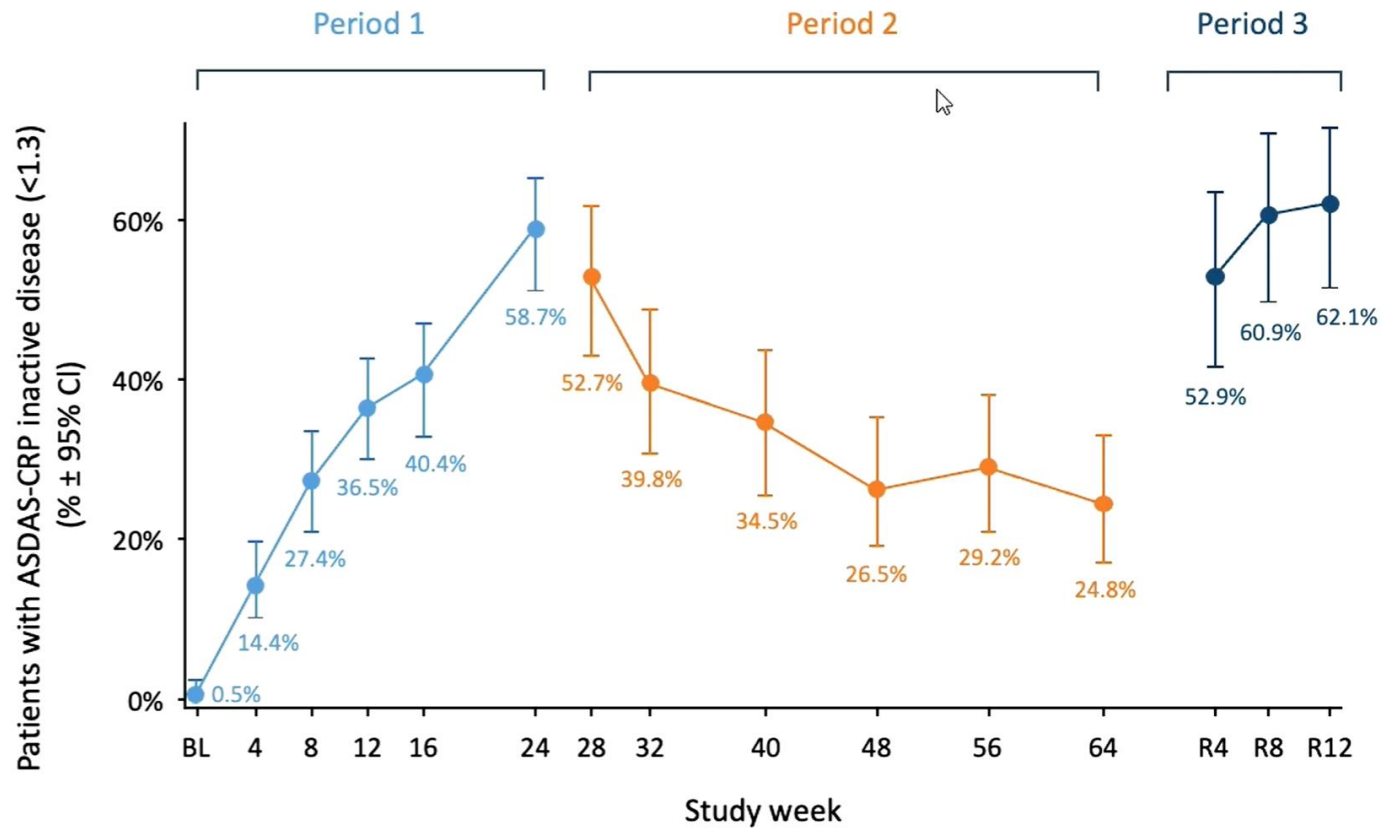
	Tight Control (n=54)	Standard of Care (n=56)
Current LDA	69%	76%
bDMARD use		
- End of TICOPA	39%	7%
- At 5-year Follow-up	54%	52%
Methotrexate use diminished in both groups over time		

Discontinuation or Tapering in (nr-)axSpA?

C-Optimise



Re-EMBARK

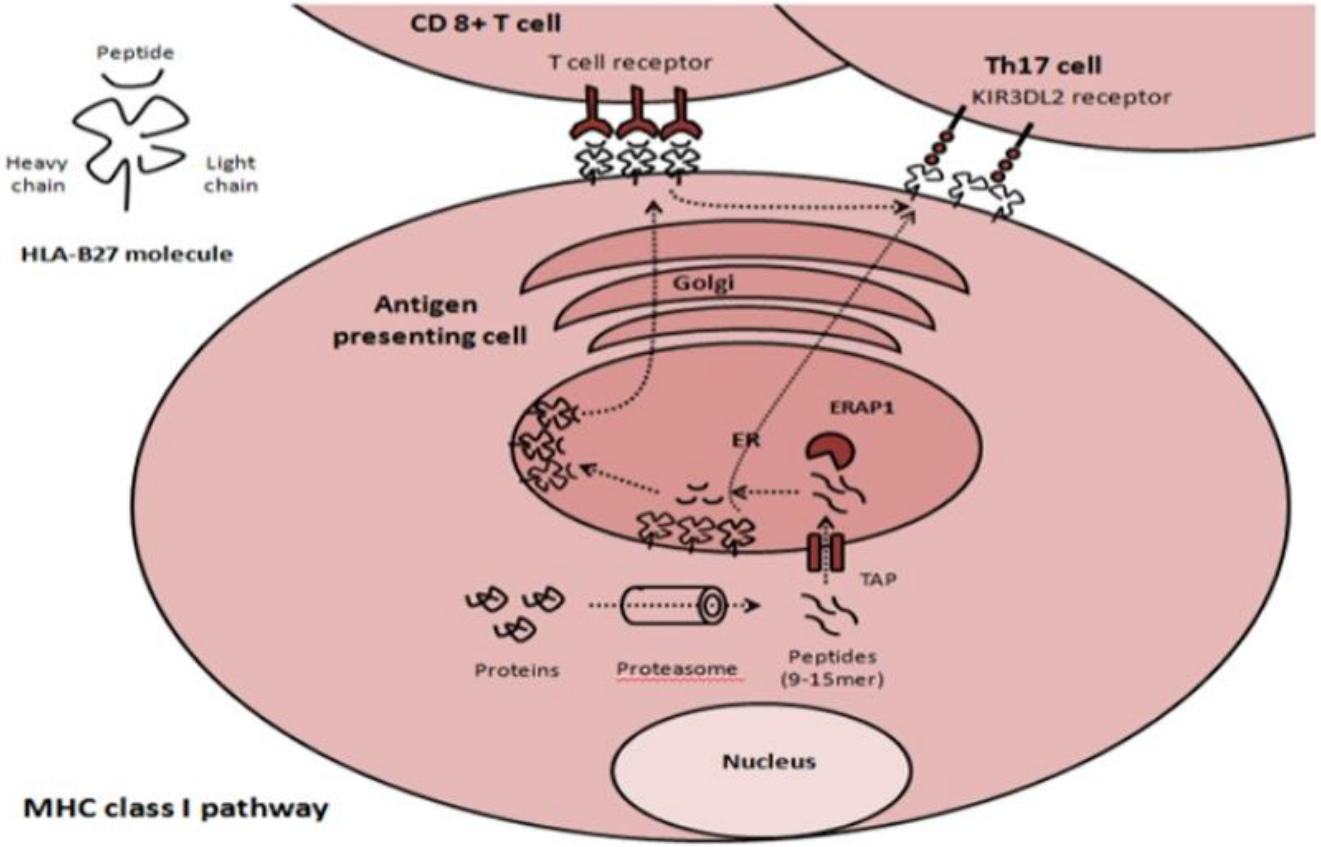


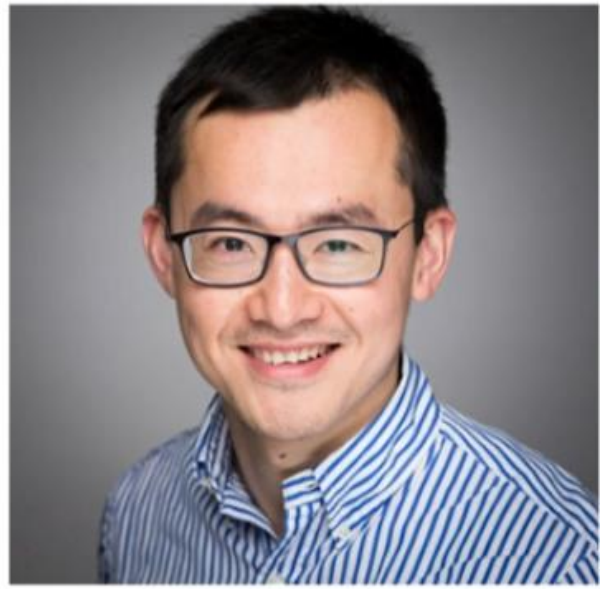
AS genetics reveals an epistatic interaction between HLA-B27 and ERAP-1

ERAP1 affects HLA-B27 presentation of viral peptides (to CD8 T cells)

ERAP1 affects cell surface HLA-B27 expression including free heavy chains

B27 FHC/dimers interact with KIR3DL2 to skew T cells towards Th17





Liye Chen ARD 2016, 2018

RESEARCH INTO INFLAMMATORY ARTHRITIS CENTRE VERSUS ARTHRITIS

Definition of a positive MRI of the spine in axial spondyloarthritis: a **consensual approach** by the ASAS/OMERACT MRI study group

Hermann et al. Ann Rheum Dis 2012;71: 1278- 88

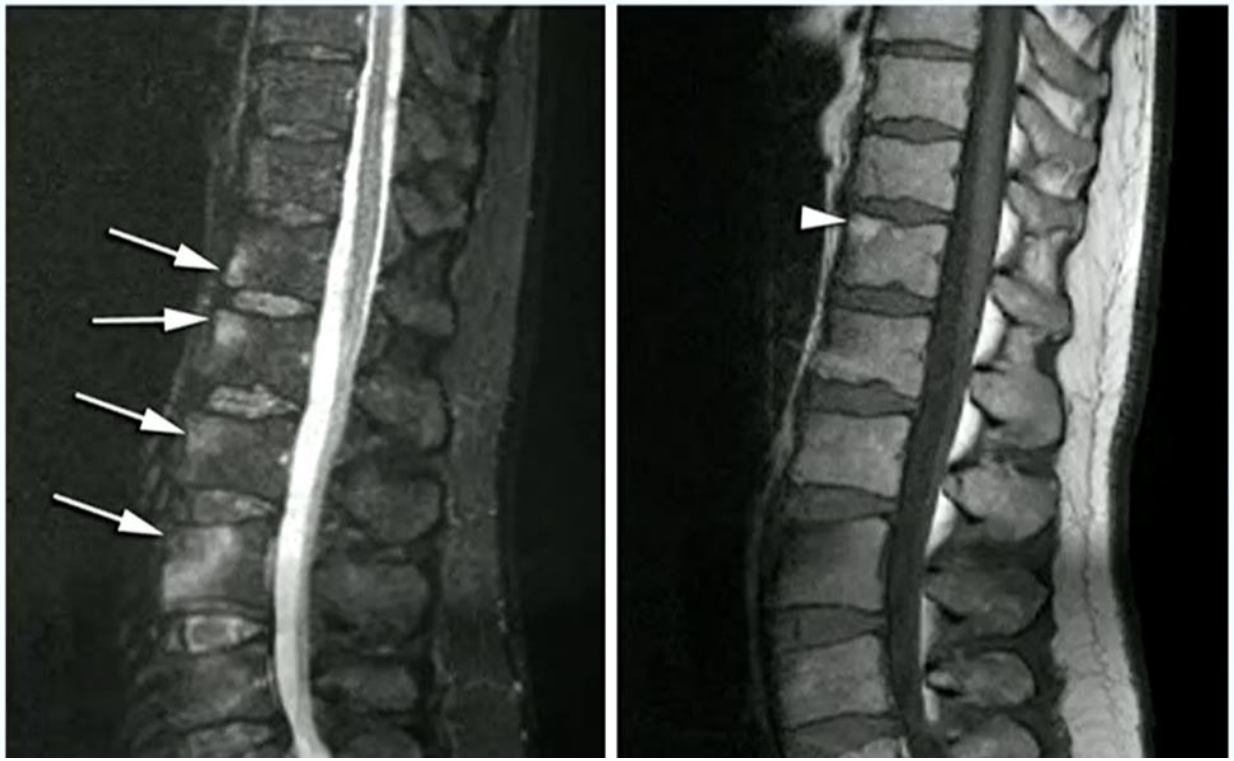


Figure. Anterior corner inflammation. (A) STIR image showing corner-related osteitis (white arrows) at T12 to L3. (B) The corresponding T1 image shows signal loss in the affected areas. In addition, there is fatty marrow infiltration at the upper endplate of T12 (white arrowhead). STIR, short τ inversion recovery.

"Evidence of anterior/posterior spondylitis in three or more sites is highly suggestive of axial SpA,

Diagnostic Utility of Spine Cut-offs for axSpA

Weber et al. Arthritis Rheumatol 2015;67:924-33

% with CIL at increasing cut-offs

	Nr-axSpA	AS	Nonspecific back pain	Healthy control
CIL≥1	63.2	69.4	50	43.8
CIL≥2	52.6	66.7	35.7	33.8
CIL≥3	43.4	61.1	25	17.5
CIL≥4	34.2	58.3	8.9	12.5
CIL≥5	31.6	58.3	5.4	5.0

RESULTS

Majority of readers (≥5/8) agreed as to the presence MRI findings consistent with axSpA

Cut-offs achieving ≥95% specificity

MRI cut-offs	Sensitivity (95%CI)	Specificity (95%CI)
BME in ≥1 vertebral corner	87.5(47.3 - 99.7)	83.3 (70.7 - 92.1)
BME in ≥2 vertebral corners	87.5 (47.3 - 99.7)	87.0 (75.1 - 94.6)
BME in ≥ 3 vertebral corners	87.5 (47.3 - 99.7)	94.4 (84.6 - 98.8)
BME in ≥4 vertebral corners	**75.0 (34.9 - 96.8)**	**98.2 (90.1 - 100.0)**
BME in ≥5 vertebral corners	62.5 (24.5 - 91.5)	98.2 (90.1 - 100.0)

RESULTS

Majority of readers (≥5/8) agreed as to the presence MRI findings consistent with axSpA

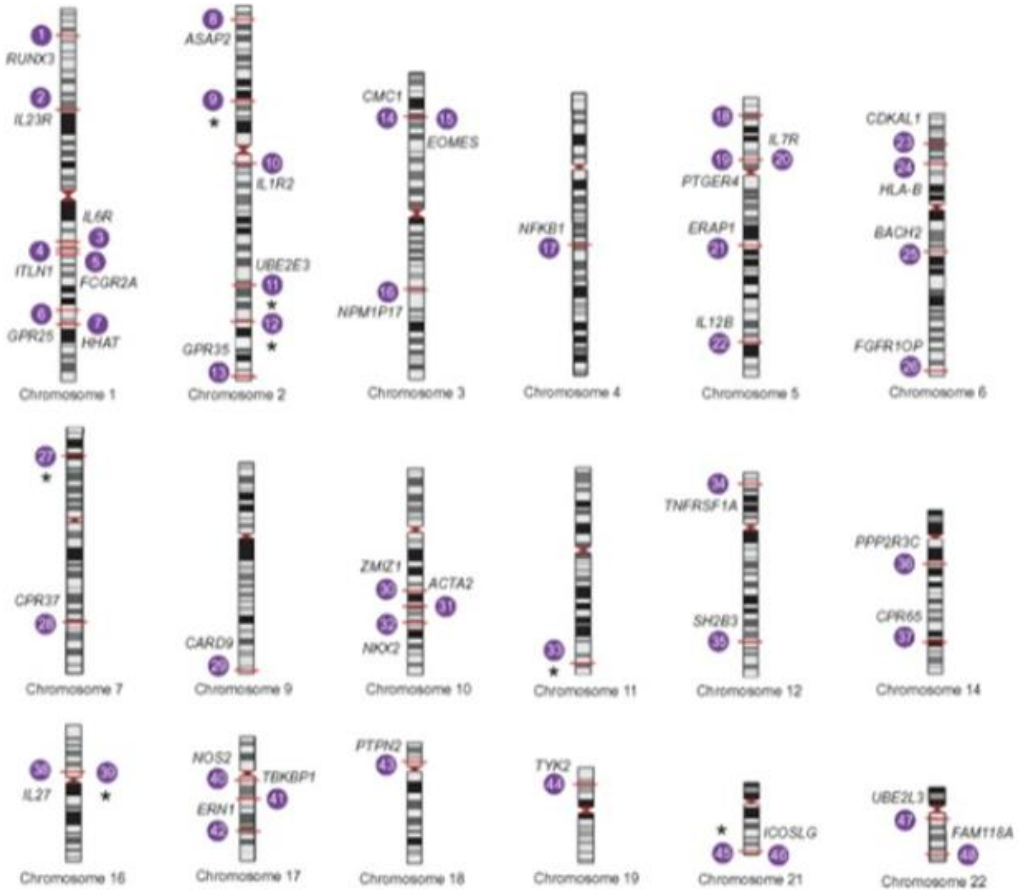
Cut-offs achieving ≥95% specificity

Cases with ≥2 vertebral corner fat lesions

MRI cut-offs	Sensitivity (95%CI)	Specificity (95%CI)
BME in ≥1 vertebral corner	**62.5 (24.5 - 91.5)**	**100.0 (93.4-100.0)**
BME in ≥2 vertebral corners	62.5 (24.5 - 91.5)	100.0 (93.4-100.0)
BME in ≥ 3 vertebral corners	50.0 (15.7 - 84.3)	100.0 (93.4-100.0)

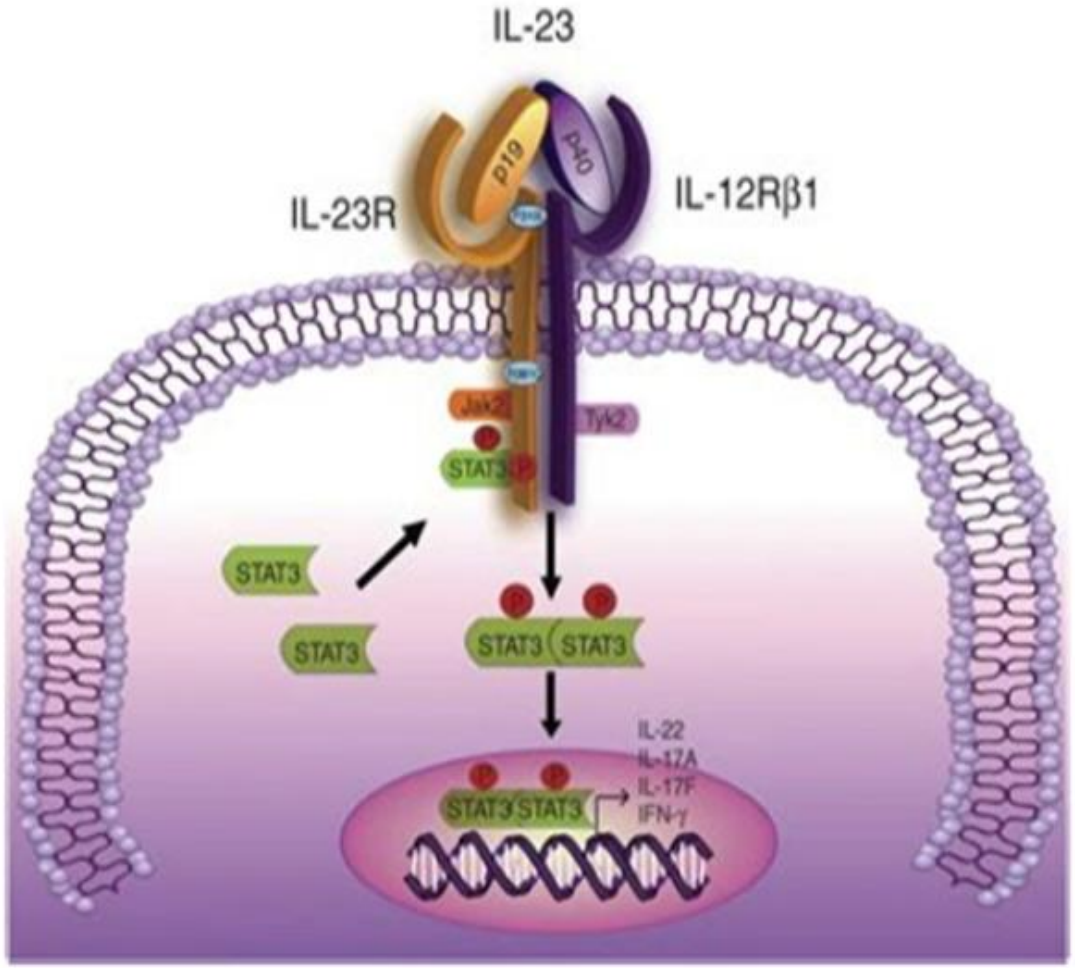
Introduction: AS Genetic risk

- AS is a highly heritable multi-trait disease (110 GWAS SNPs at 89 risk loci)
- HLA-B27 explains ~30% of AS genetics
- Several genetic associations point to the role of Th17 cells and antigen presentation (IL23R ERAP1, etc)
- **Majority of GWAS SNPs are in non-coding regions**



- Evans 2011 Nature Genetics
- Cortes 2013 Nature Genetics
- Ellinghaus 2016 Nature Genetics
- Jethwa and Bowness 2015 J Trans Imm
- Osgood and Knight 2018 Brief Fun Gen

IL23R



OPEN ACCESS Freely available online

PLoS one

The IL23R R381Q Gene Variant Protects against Immune-Mediated Diseases by Impairing IL-23-Induced Th17 Effector Response in Humans

Paola Di Meglio[1], Antonella Di Cesare[1,3], Ute Laggner[1], Chung-Ching Chu[1], Luca Napolitano[1], Federica Villanova[1], Isabella Tosi[1], Francesca Capon[2], Richard C. Trembath[2], Ketty Peris[3], Frank O. Nestle[1]*

1 St. John's Institute of Dermatology, King's College London and NIHR Biomedical Research Centre, London, United Kingdom, **2** Department of Medical and Molecular Genetics, King's College London and NIHR Biomedical Research Centre, London, United Kingdom, **3** Department of Dermatology, University of L'Aquila, L'Aquila, Italy

Abstract

IL-23 and Th17 cells are key players in tissue immunosurveillance and are implicated in human immune-mediated diseases. Genome-wide association studies have shown that the *IL23R* R381Q gene variant protects against psoriasis, Crohn's disease and ankylosing spondylitis. We investigated the immunological consequences of the protective *IL23R* R381Q gene variant in healthy donors. The *IL23R* R381Q gene variant had no major effect on Th17 cell differentiation as the frequency of circulating Th17 cells was similar in carriers of the *IL23R* protective (A) and common (G) allele. Accordingly, Th17 cells generated from A and G donors produced similar amounts of Th17 cytokines. However, IL-23-mediated Th17 cell effector function was impaired, as Th17 cells from A allele carriers had significantly reduced IL-23-induced IL-17A production and STAT3 phosphorylation compared to G allele carriers. Our functional analysis of a human disease-associated gene variant demonstrates that *IL23R* R381Q exerts its protective effects through selective attenuation of IL-23-induced Th17 cell effector function without interfering with Th17 differentiation, and highlights its importance in the protection against IL-23-induced tissue pathologies.

Citation: Di Meglio P, Di Cesare A, Laggner U, Chu C-C, Napolitano L, et al. (2011) The IL23R R381Q Gene Variant Protects against Immune-Mediated Diseases by Impairing IL-23-Induced Th17 Effector Response in Humans. PLoS ONE 6(2): e17160. doi:10.1371/journal.pone.0017160

Editor: Matthias von Herrath, La Jolla Institute of Allergy and Immunology, United States of America

Received January 7, 2011; **Accepted** January 24, 2011; **Published** February 22, 2011

An example of functional genomics at the single gene level:

Basic and translational research

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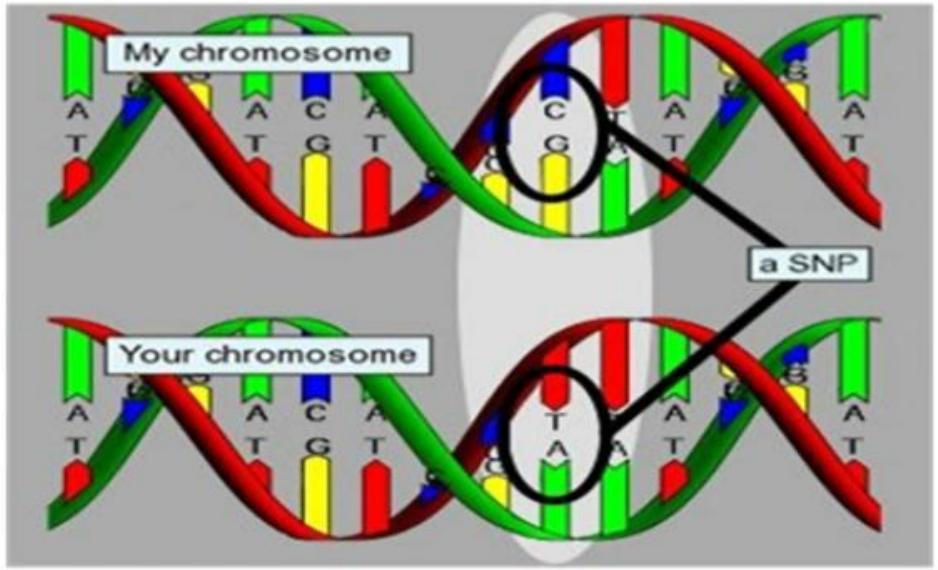
EXTENDED REPORT

The genetic association of *RUNX3* with ankylosing spondylitis can be explained by allele-specific effects on IRF4 recruitment that alter gene expression

Matteo Vecellio,[1,2,3] Amity R Roberts,[1,2,3] Carla J Cohen,[1,2,3] Adrian Cortes,[4,5] Julian C Knight,[5] Paul Bowness,[1,2,3] B Paul Wordsworth[1,2,3]

RUNX3 has a role in the development, number and function of CD8 T cells

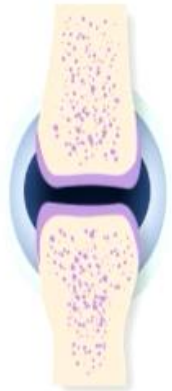
AS SNP rs4648889



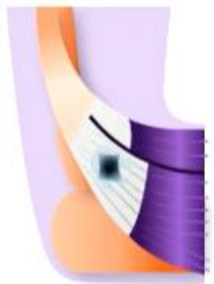
G is protective

A = risk of AS

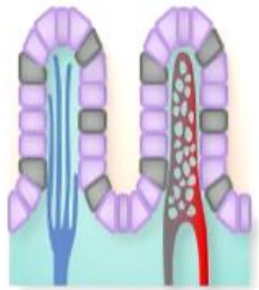
Take home message :
Tissue dependent cytokine involvement in SpA



Joint
TNF
IL-17, IL-23
IFN-γ

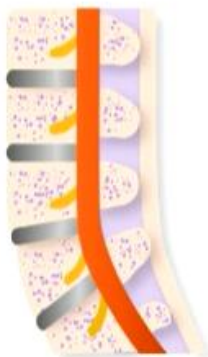


Enthesis
TNF
IL-17
IL-22
IL-23



Gut
TNF
IL-23

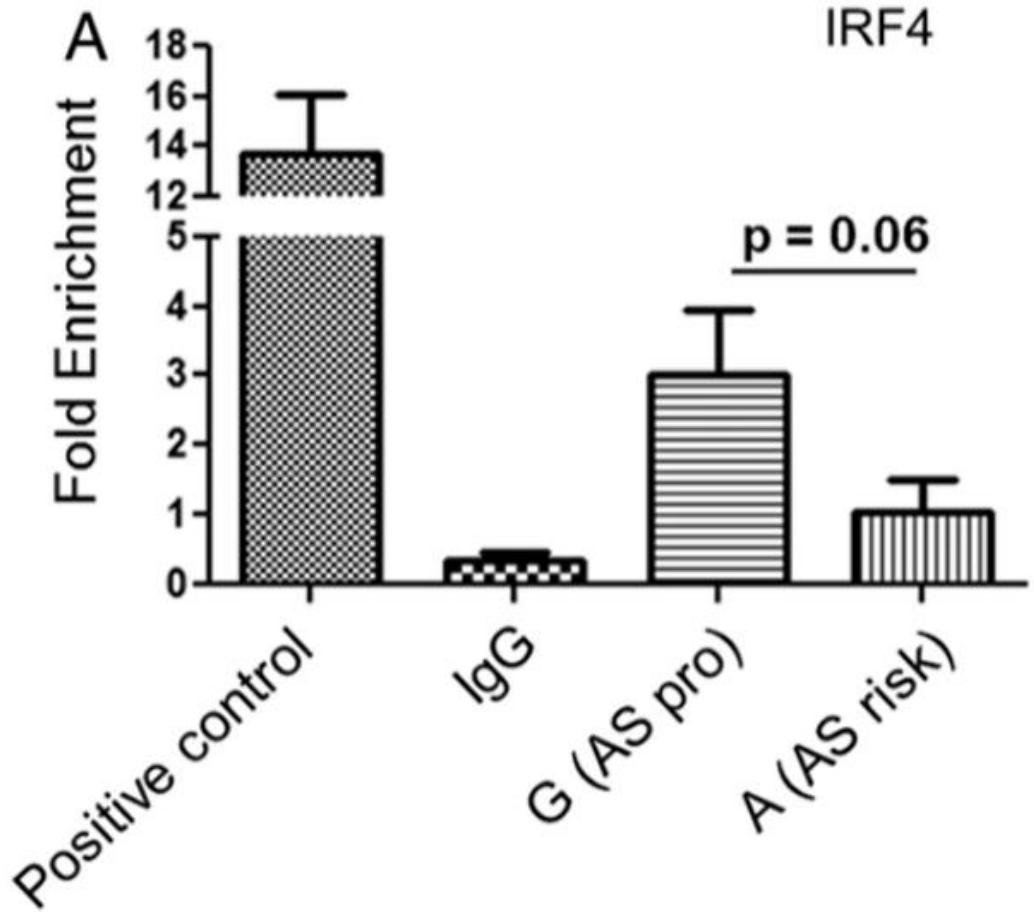
Skin and nails
TNF
IL-2, IL-17, IL-22,
IL-23
IFN-γ



Axial skeleton
TNF
IL-17

Uveitis
TNF
IFN-γ
IL-1, IL-6, IL-17, IL-22,
IL-23

The transcription factor IRF4 binds more strongly to the protective (G) allele than the risk allele (A)



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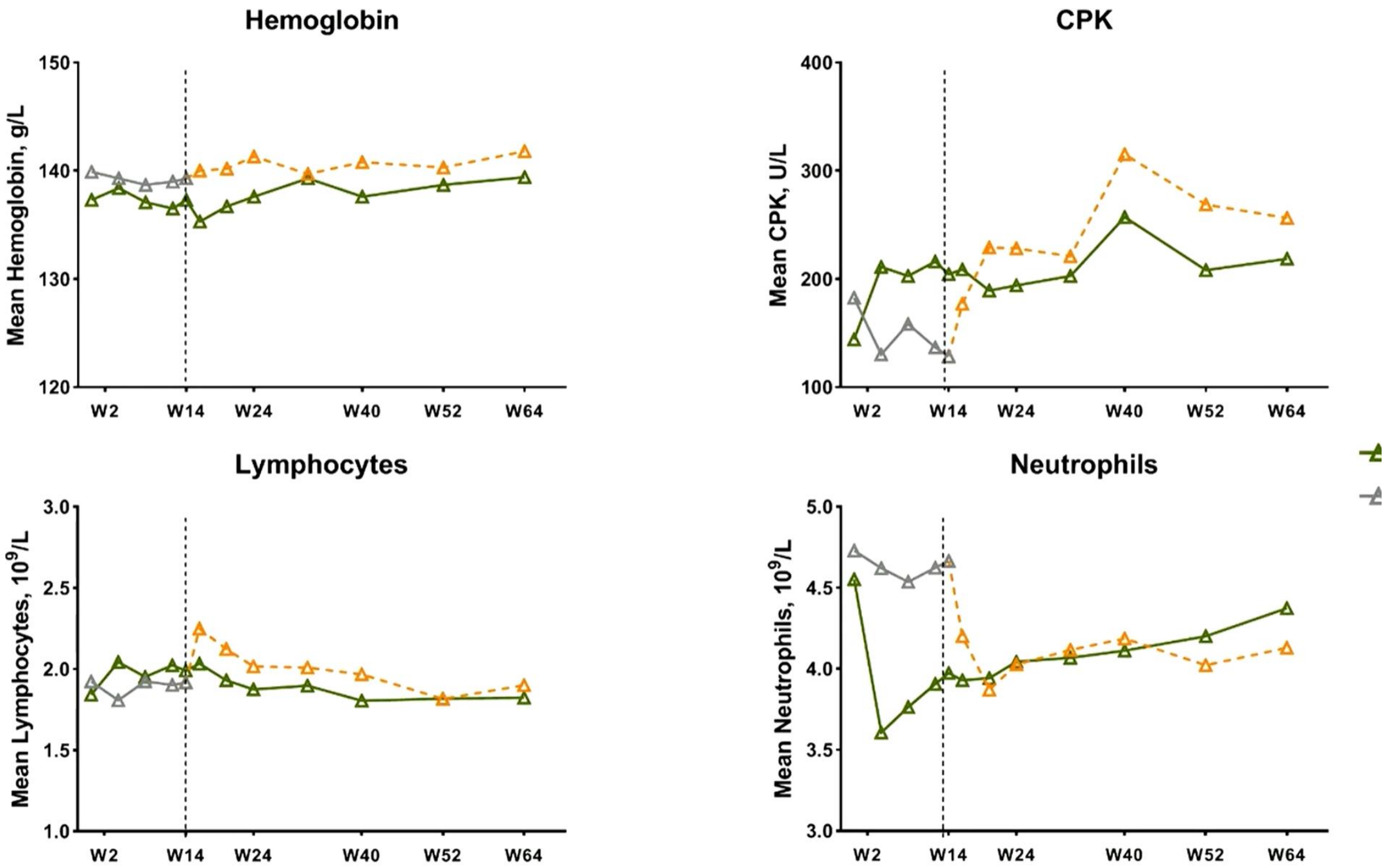
Matteo Vecellio et al. Ann Rheum Dis 2016;75:1534-1540

ARD

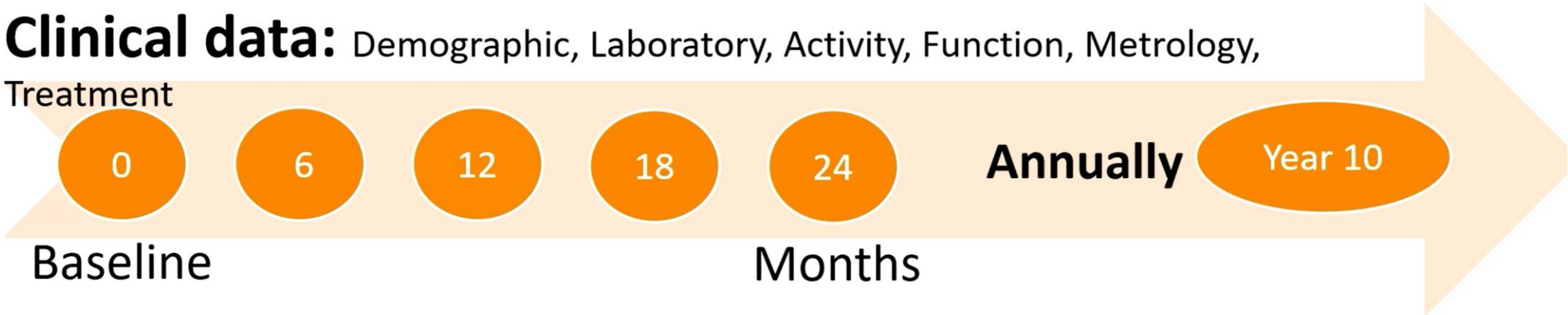

Hemoglobin
Mean Hemoglobin, g/L
150
140
130
120
W2
W14
W24
W40
W52
W64
CPK
Mean CPK, U/L
400
300
200
100
W2
W14
W24
W40
W52
W64
Lymphocytes
Mean Lymphocytes, 10^9/L
3.0
2.5
2.0
1.5
1.0
W2
W14
W24
W40
W52
W64
Neutrophils
Mean Neutrophils, 10^9/L
5.0
4.5
4.0
3.5
3.0
W2
W14
W24
W40
W52
W64

OP0137

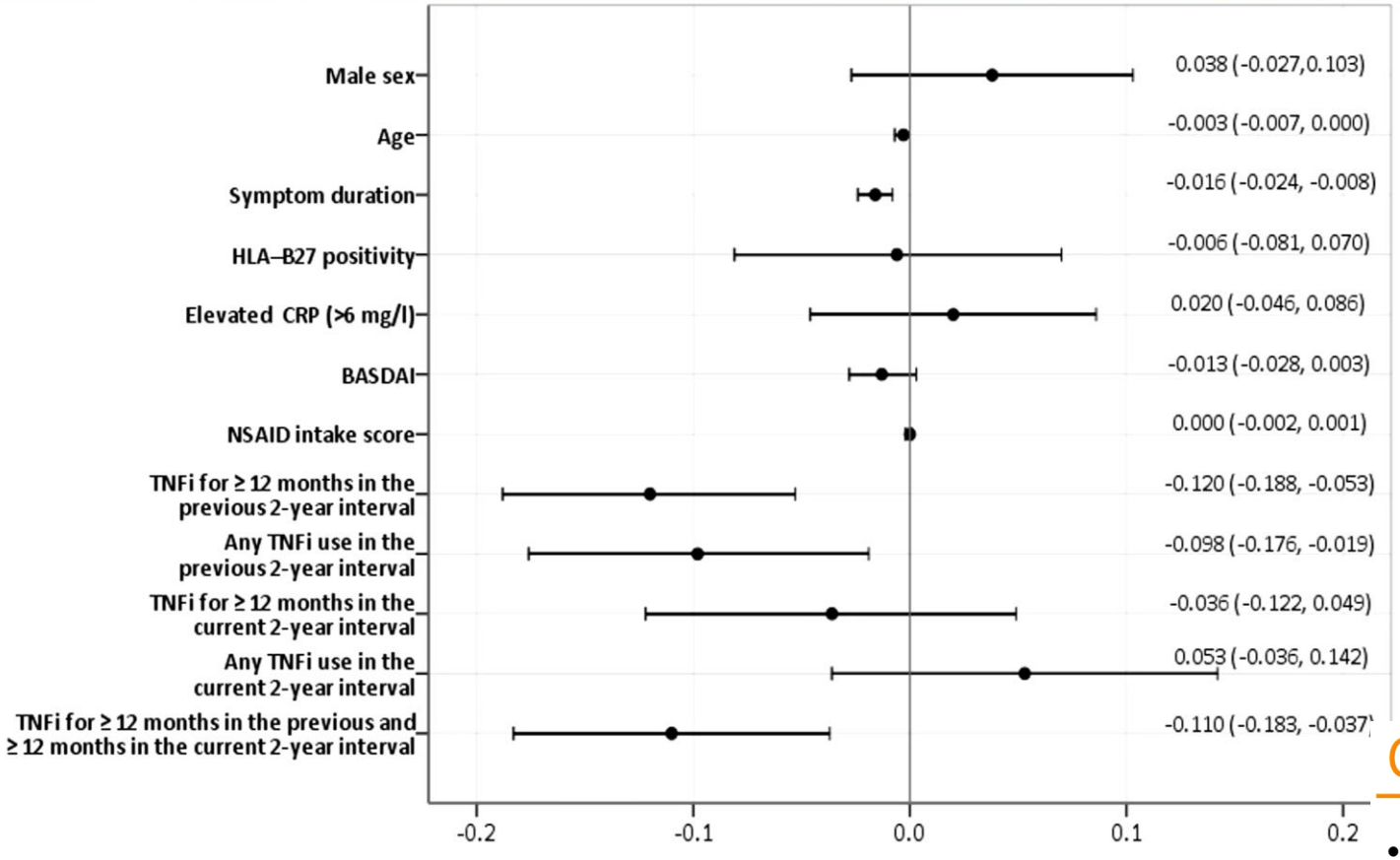
Tumor Necrosis Factor Inhibitors Show a Delayed Effect on Radiographic Sacroiliitis Progression in Patients with Axial Spondyloarthritis:

10-year Results from the German Spondyloarthritis Inception Cohort

Murat Torgutalp, Valeria Rios Rodriguez, Maryna Verba, Mikhail Protopopov, Fabian Proft, Judith Rademacher, Hildrun Haibel, Martin Rudwaleit, Joachim Sieper, Denis Poddubnyy*



Univariable GEE-Sacroiliitis sum score



Conclusion

- TNFi use was associated with retardation of radiographic sacroiliitis progression in patients with axSpA.
- This effect becomes evident between 2 and 4 years after treatment initiation.

Conclusions

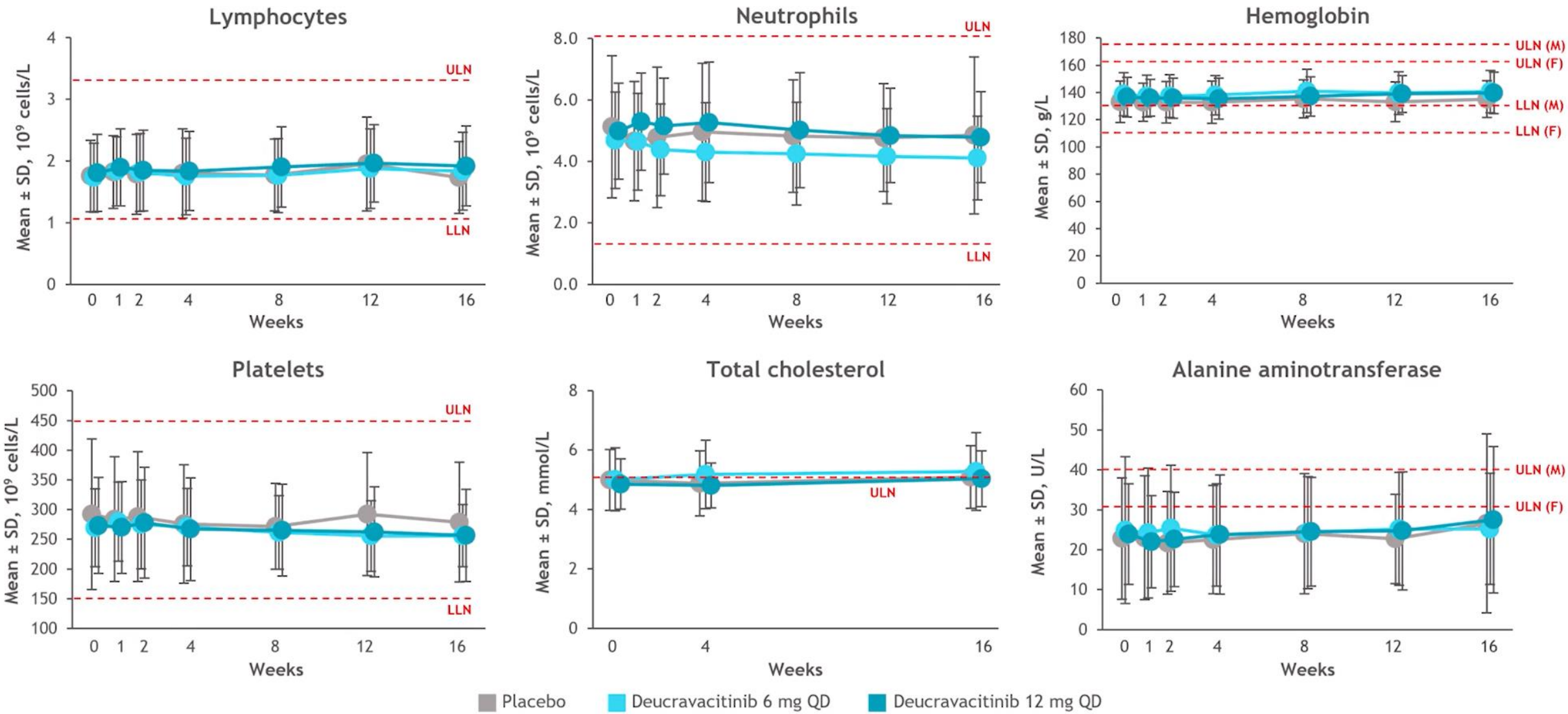
What is confirmed?

- VCI and VCFD are, both independently and combined, associated with syndesmophyte development
- Absence of VCI and VCFD protects against syndesmophyte development
- Nonetheless, syndesmophyte development occurs even in absence of VCI and VCFD

What is new?

- The results are observed when studying the thoracic spine
- The results are observed when using low dose CT for syndesmophyte detection
- VCFD more often overlapped with VCI than only occurring after VCI had resolved.

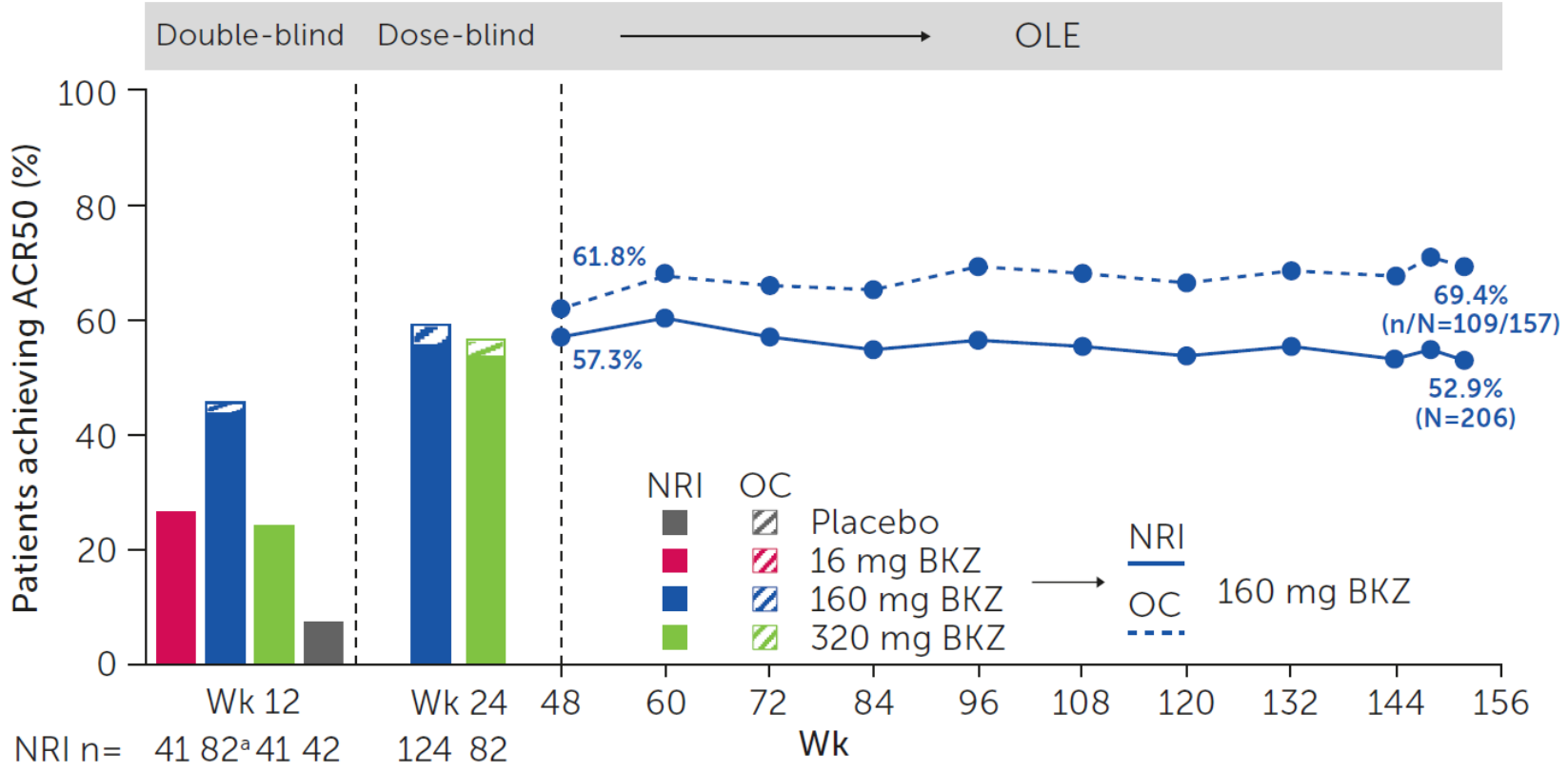
Laboratory parameters over 16 weeks



F, female; LLN, lower limit of normal; M, male; QD, once daily; ULN, upper limit of normal.

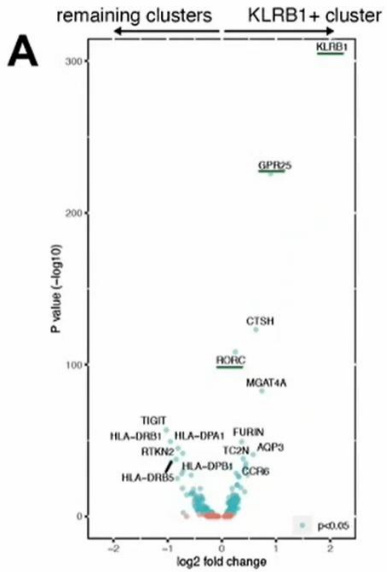
Bimekizumab Safety and Efficacy in Patients with Psoriatic Arthritis: 3-Year Results from a Phase 2b Open-Label Extension Study[1]

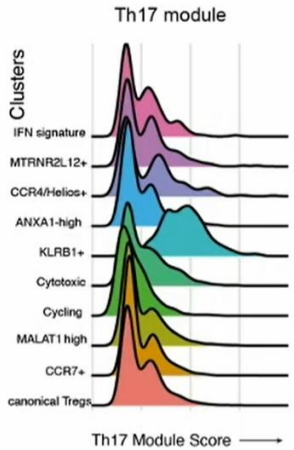
Laura C. Coates, Richard B. Warren, Christopher T. Ritchlin, Laure Gossec, Joseph F. Merola, Deepak Assudani, Jason Coarse, Jason Eells, Barbara Ink, Iain Mcinnes

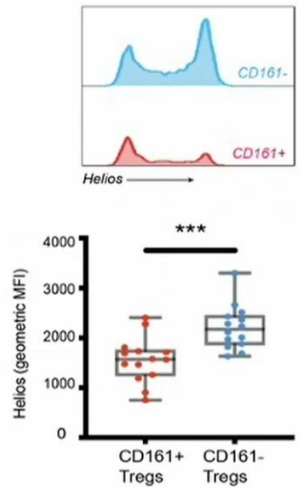


- **T**he safety profile of BKZ in patients with PsA reflects previous observations[2,3] for up to 3 years. High threshold disease control was achieved by >50% of BKZ-treated patients up to 3 years, reflected in long-term improvements in joint and skin outcomes.[1]

CD161+ ROR-γt+ subset







in mice, induced by microbiota to suppress pathogenic Th17 responses (Ohnmacht, *Science* 2015)

also found in human colon (James, *Nat Immunol* 2019)

Tregs with cytotoxic markers (a subset is CD8+)