Spondyloarthropathies:
– Thinking Beyond the current state of the art?

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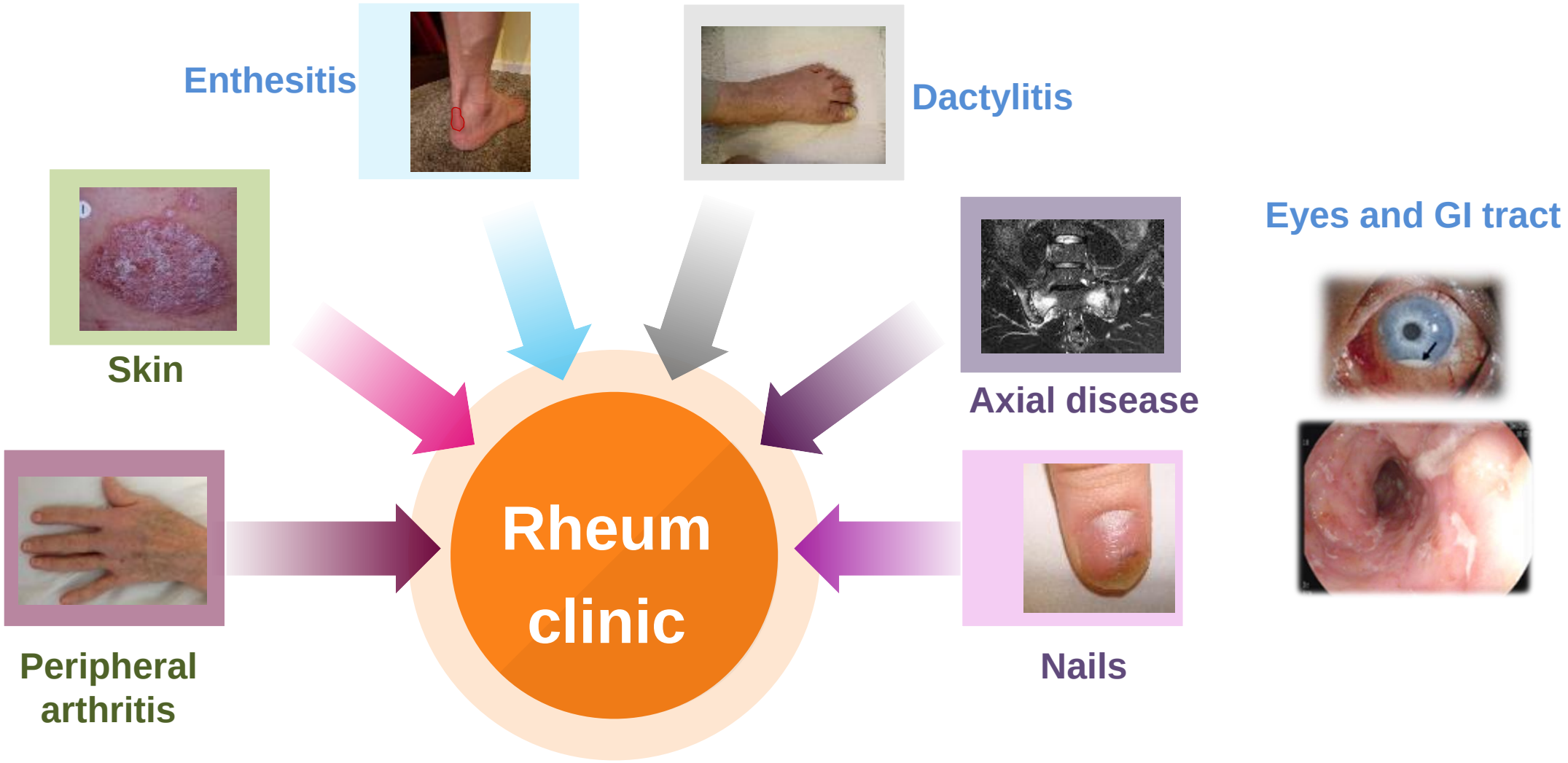
Disclosure

- I have received research funding and honoraria from Abbvie, AZ, BMS, Boerhinger, Compugen, Cabaletta, Causeway, Eli-Lilly, EveloBio, Celgene, Moonlake, Pfizer, Novartis, Janssen, Roche, UCB
- I have research support from Versus Arthritis, MRC & Wellcome Trust

Learning Objectives

- Review the latest evidence in the assessment, treatment, and management of SPA

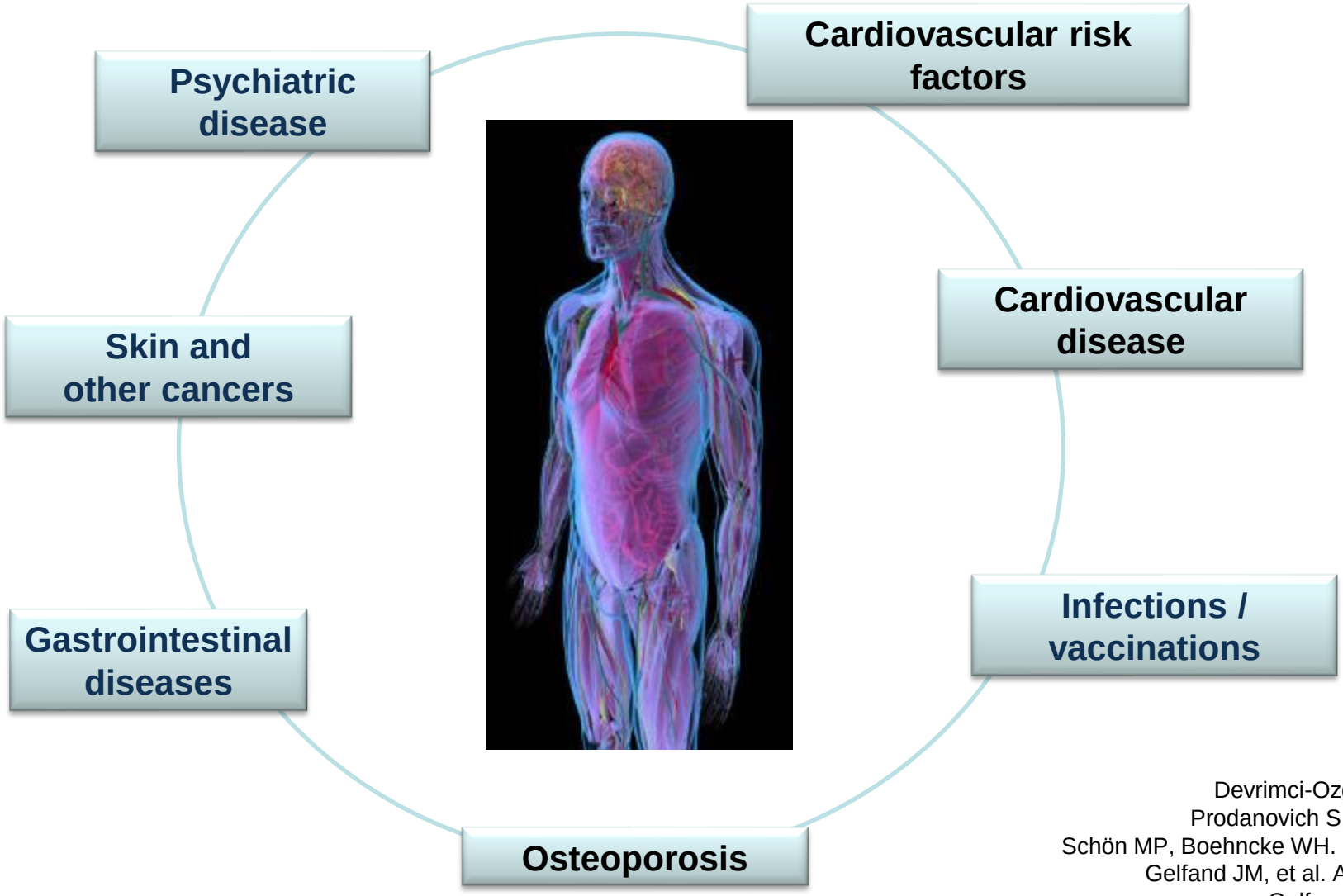
SpA – characterised by clinical heterogeneity



PsA, psoriatic arthritis

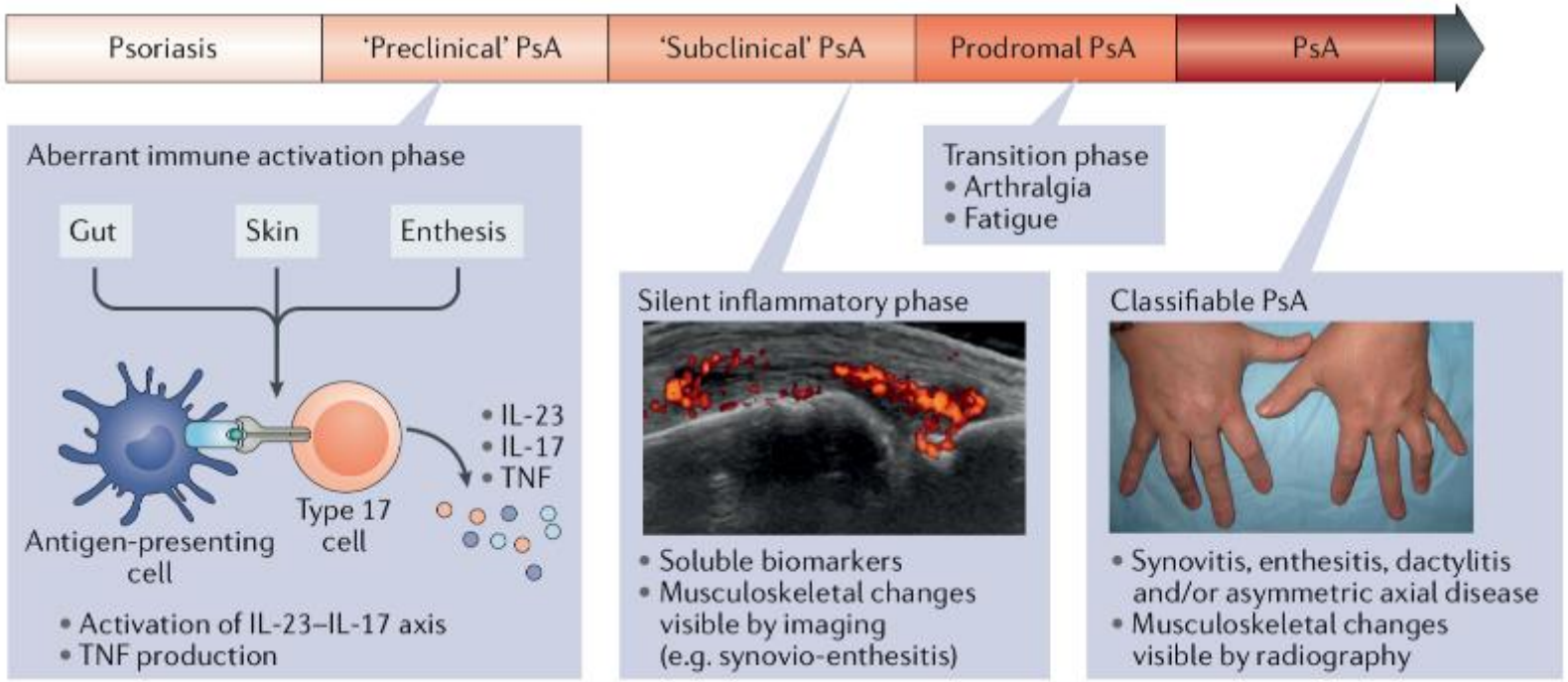
1. Coates LC, et al. Arthritis Rheumatol. 2016;68:1060–71.

The range of multi(co)morbidities in SpA is critical for outcomes...



Devrimci-Ozguven H, et al. JEADV 2000;14:267;
Prodanovich S, et al. Arch Dermatol 2009;145:700;
Schön MP, Boehncke WH. N Engl J Med 2005;352:1899–1912;
Gelfand JM, et al. Arch Dermatol 2007;143:1493–1499;
Gelfand JM, et al. Infect Dis 2006;126:2194

Integrating mechanisms driving the ‘enthesial & beyond’ syndrome that is SpA?

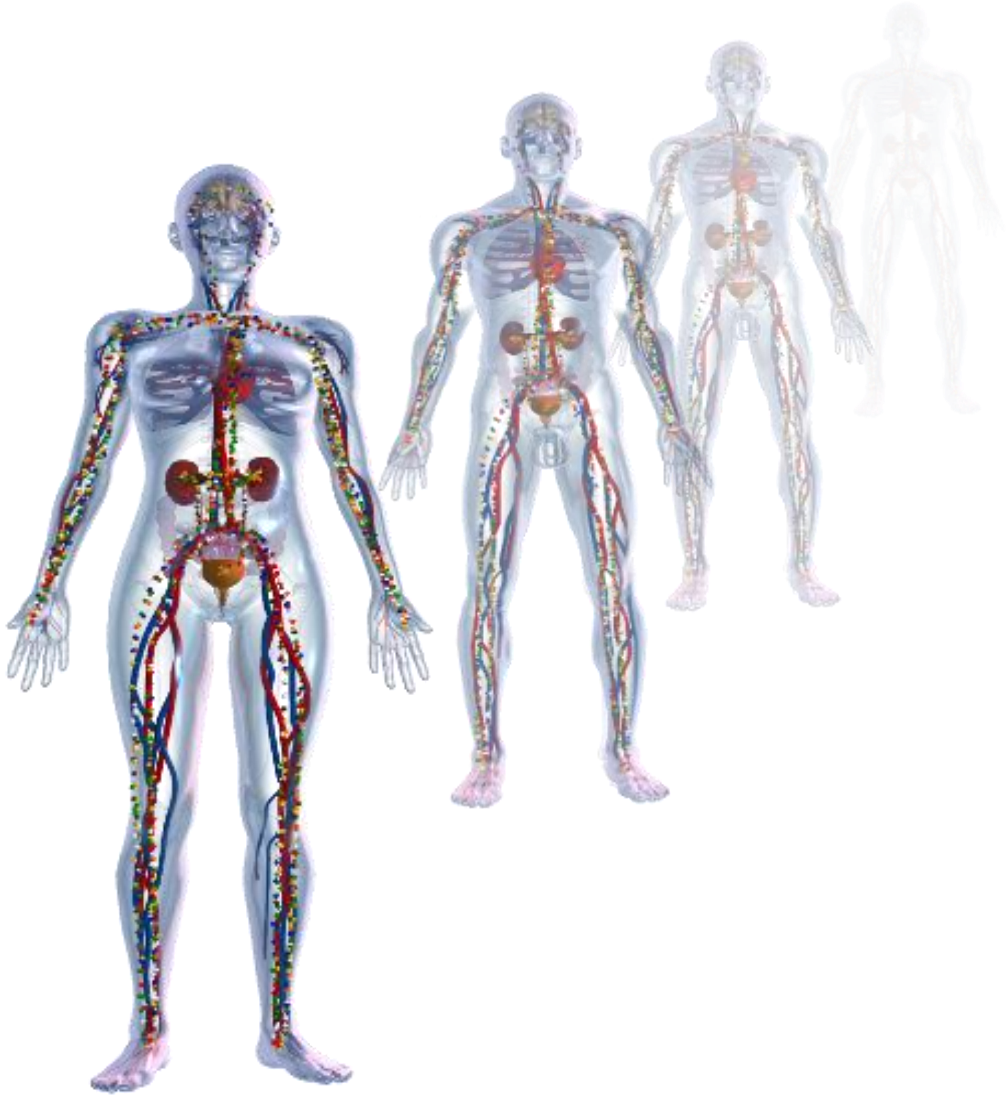


Scher J et al *Nature Reviews Rheum* 2019

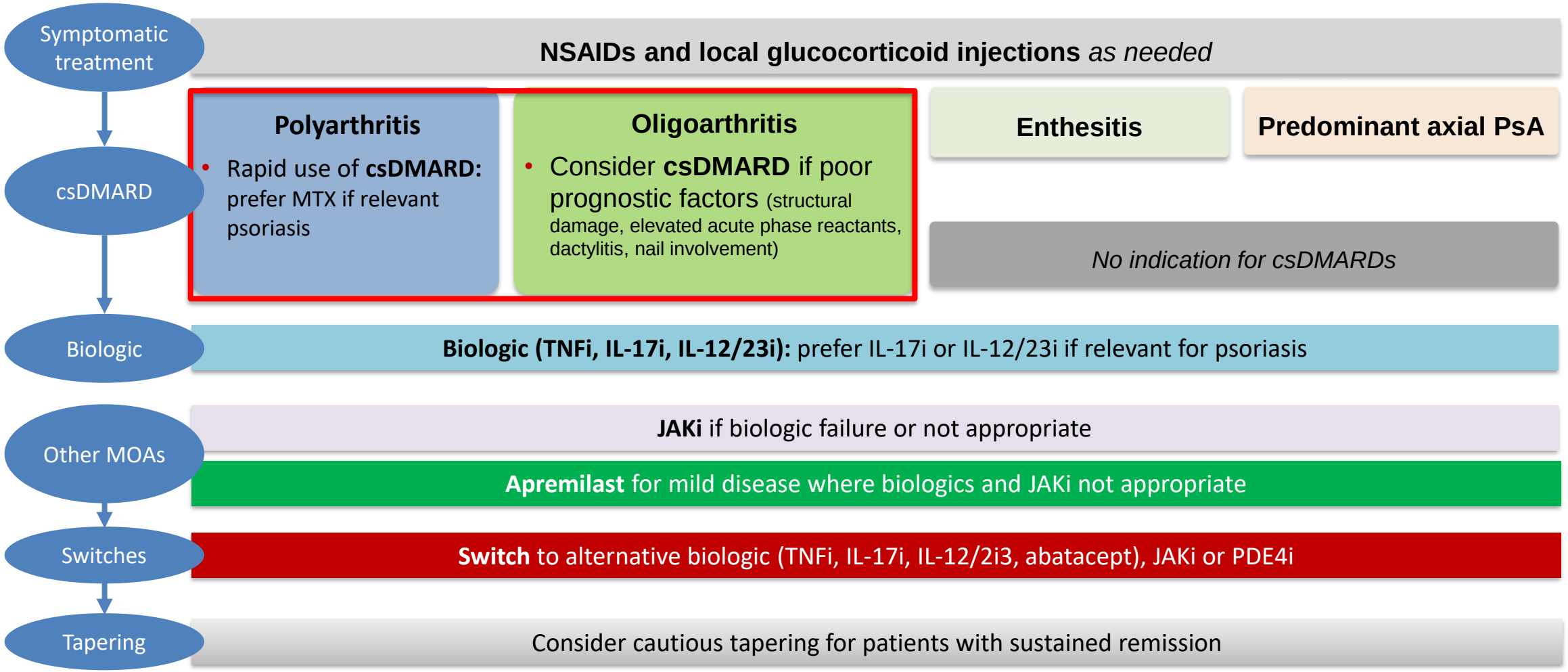
SpA – thinking beyond…(PsA as an exemplar)

1. Current state of the art therapeutics

2. Towards a new care strategy care?



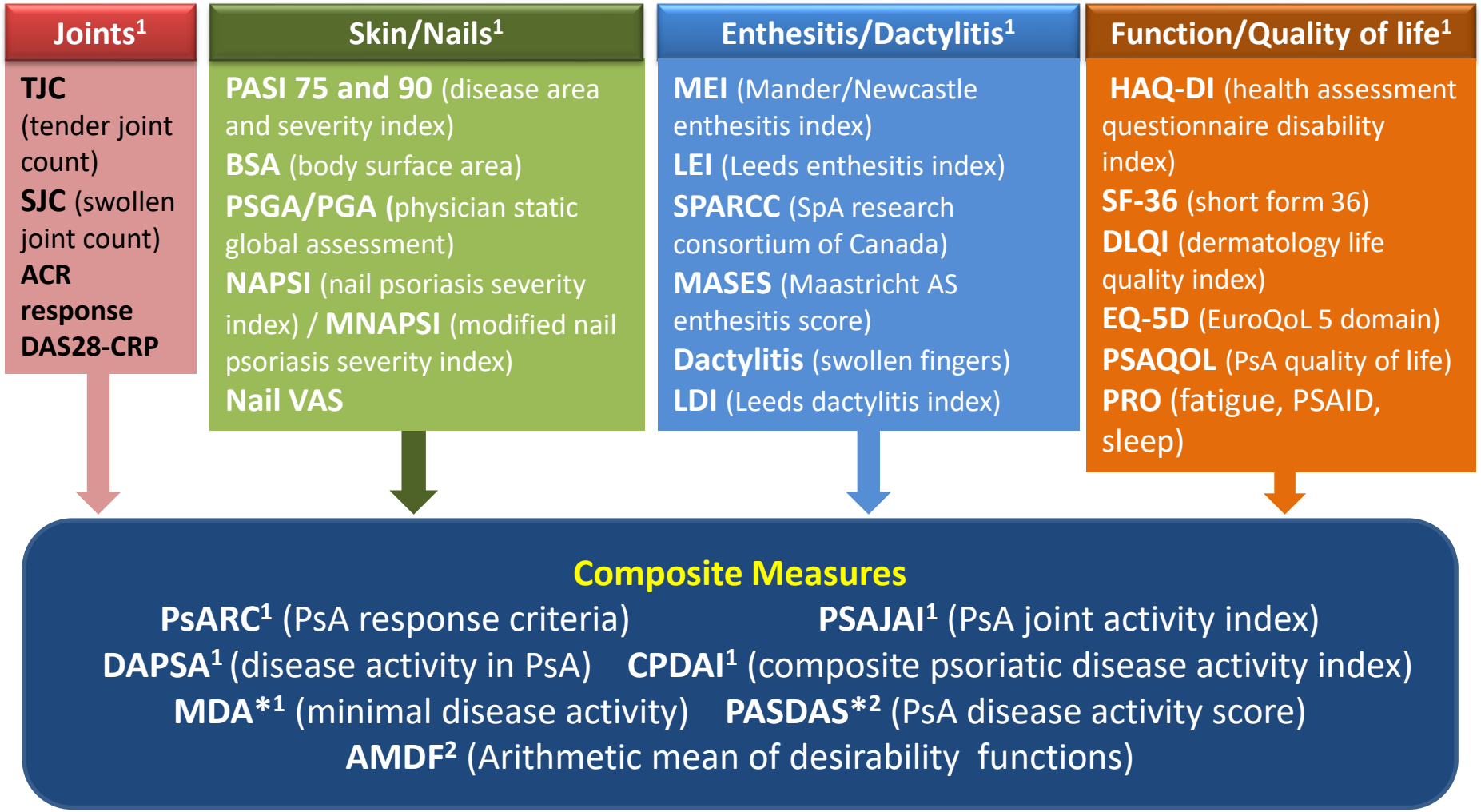
EULAR recommendations on PsA



csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; IL, interleukin; JAKi, jak kinase inhibitor; MOA, mechanism of action; PDE4i, Phosphodiesterase 4 inhibitors; PsA, psoriatic arthritis; TNFi, tumor necrosis factor inhibitors.

1. Gossec L, et al. *Ann Rheum Dis*. 2020;79:700-12.

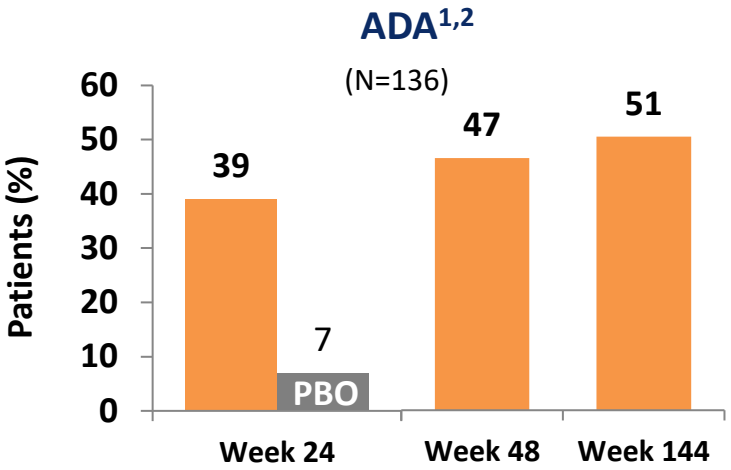
Outcome measures in PsA: a guide to understanding clinical trial data…

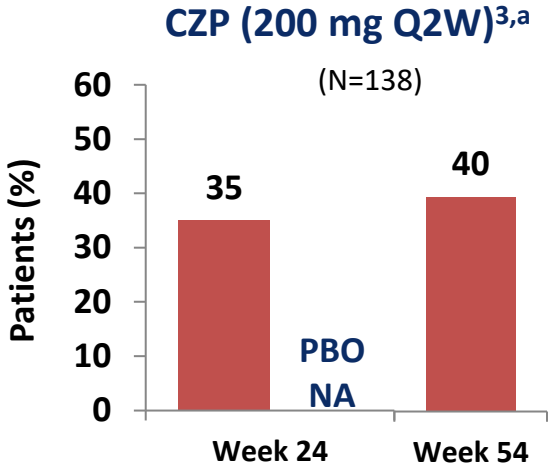


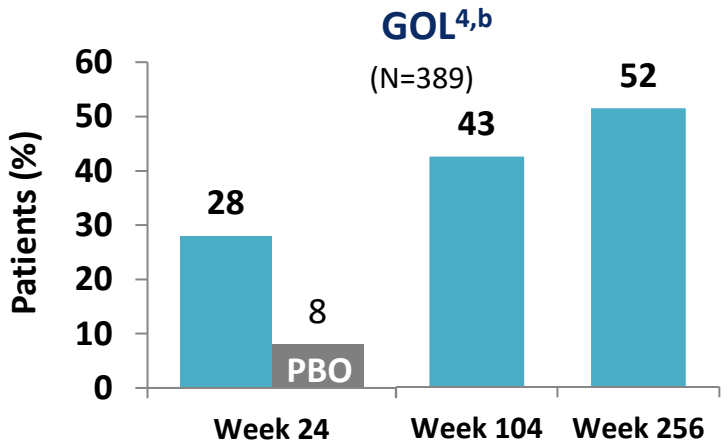
*Includes joint, enthesitis and/or dactylitis, skin and function and/or quality of life assessments

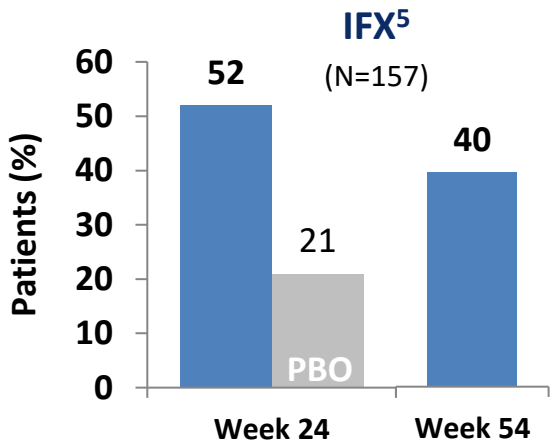
1. Mease PJ. *Arthritis Care Res* 2011;63(suppl 11):S64-85; 2. Helliwell PS et al. *Ann Rheum Dis* 2013;72:986-991.

Patients with PsA treated with TNFi therapy achieving minimal disease activity (MDA)*









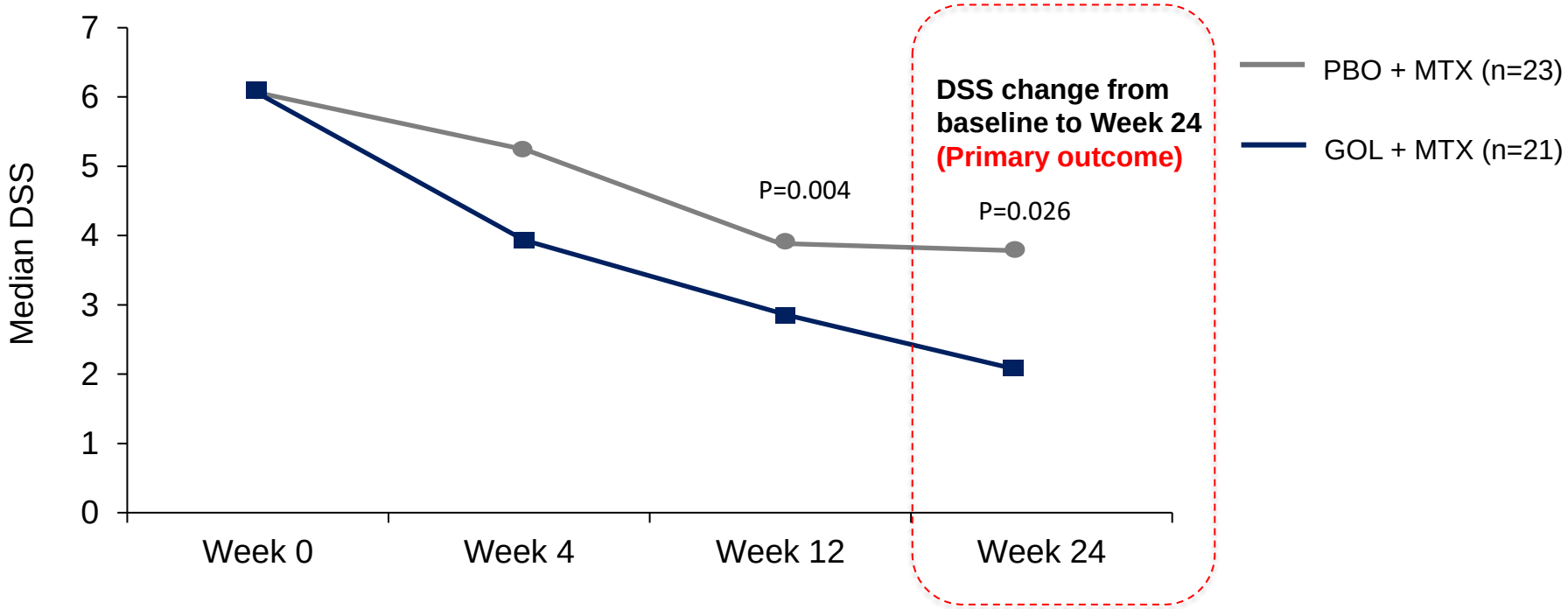
***Different studies: Not head-to-head comparison. Results of individual studies cannot be directly compared**

[a]The CZP population included treatment-naïve and treatment-experienced patients
[b]Combined data from 50 and 100 mg dose groups; data for individual doses were not presented

[1]Mease P, et al. J Rheumatol 2013;40:647–652; [2]Abbvie Data on file; [3]Mease P, et al. ACR 2013: Abstract 312; [4]Kavanagh A, et al. ACR 2013: Abstract 341; [5]Coates L and Helliwell PS. Arthritis Care Res 2010;62:965–969

Dactylitis Golimumab study – Go-DACT

- Randomized to GOL + MTX (n=21) or PBO + MTX (n=23)
- Clinical (dactylitis severity score, dactylometer) and MRI outcomes



Each digit with dactylitis was evaluated in a scale of 0–3 (0=no dactylitis, 1=mild dactylitis, 2=moderate dactylitis, 3=severe dactylitis), where scores greater than 0 indicate the presence of dactylitis and the total DSS was calculated as the sum of scores for all 20 digits (0–60).

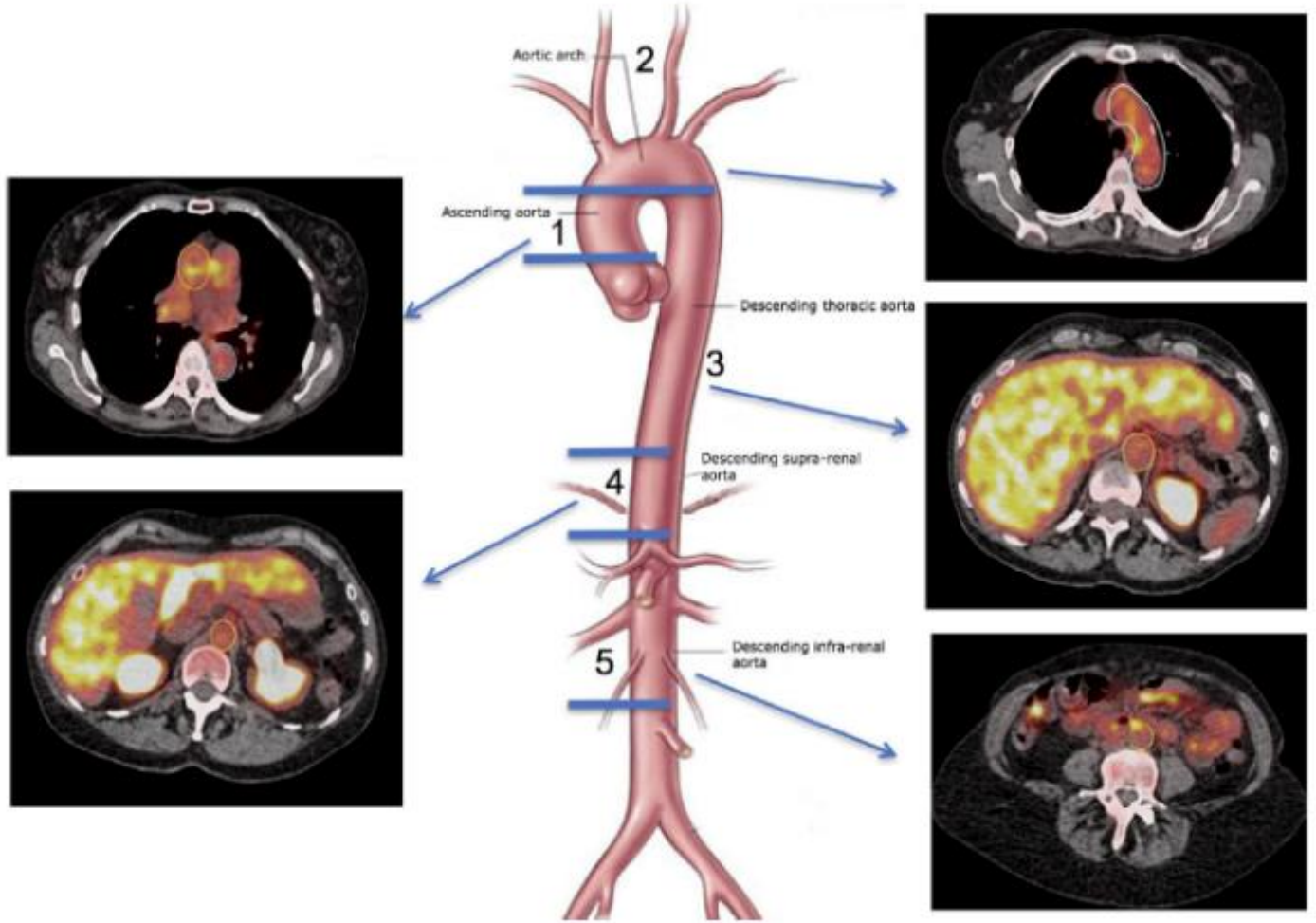
Vieira-Sousa et al, Ann Rheum Dis. 2020; 79(4): 490–498. Intention-to-treat analysis was performed for the primary endpoint, applying the last observation carried forward method and including all randomly assigned patients who received at least one dose of study medication

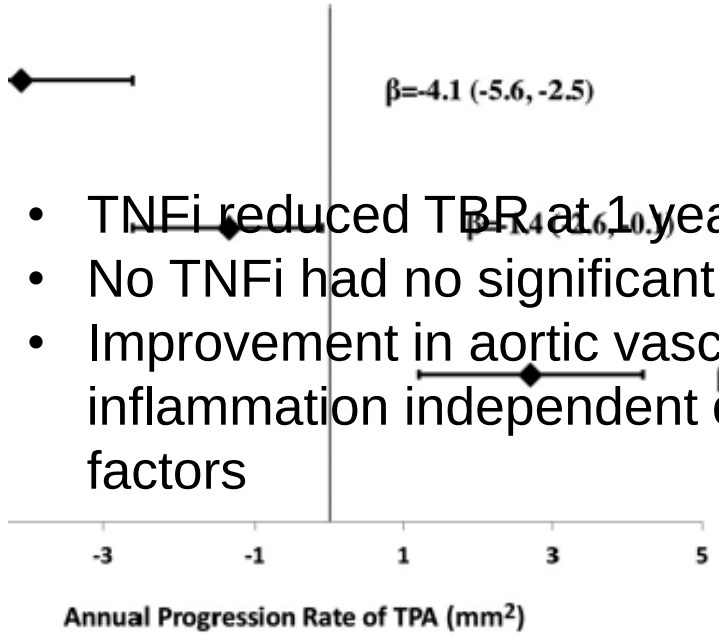
DSS, Dactylitis Severity Score; GOL, g**olimumab; MTX, methotrexate; PBO, placebo**

Polling Question

- What is the proportion of TNF-i treated PSA patients maintain ACR50 at 12 weeks of treatment?
  A. 20%
  B. 30%
  C. 40%
  D. 50%

TNF inhibition and CV risk in PsA - using imaging to investigate?

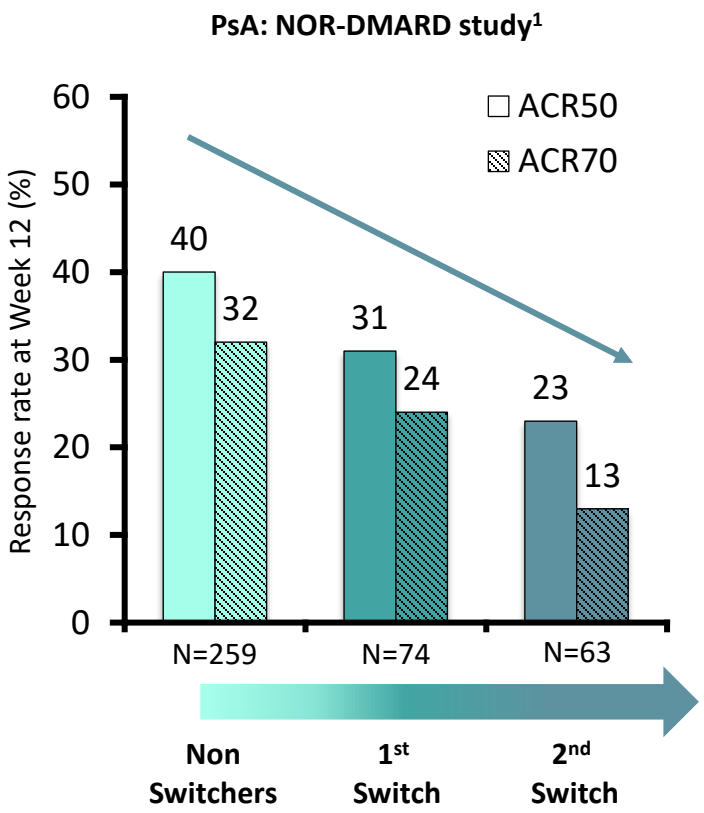


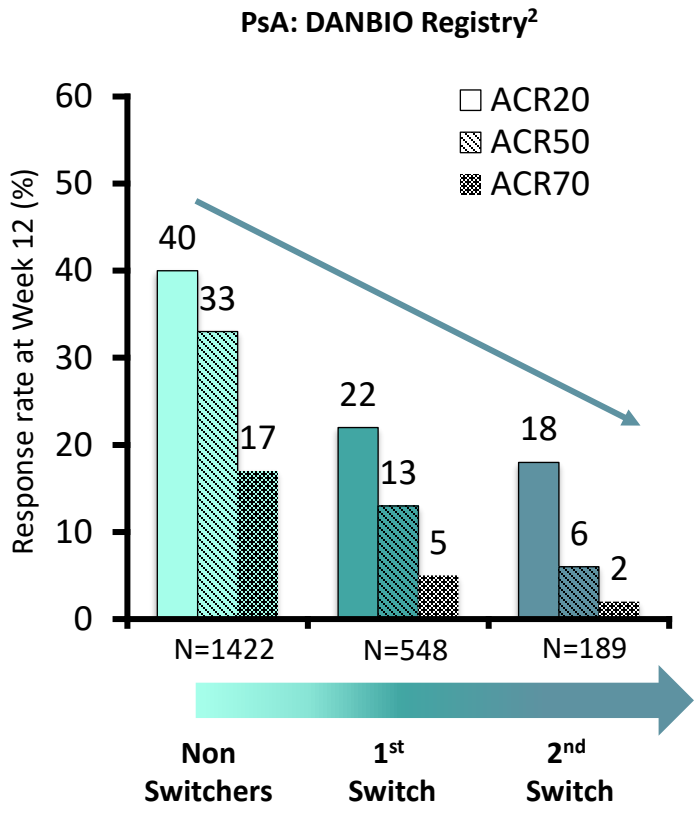


- TNFi reduced TBR at 1 year
- No TNFi had no significant change
- Improvement in aortic vascular inflammation independent of CV risk factors

Elder L et al *Arth & Rheum* 70, 408-416 (2018)

All good things come to an end…response to TNFi diminishes over time





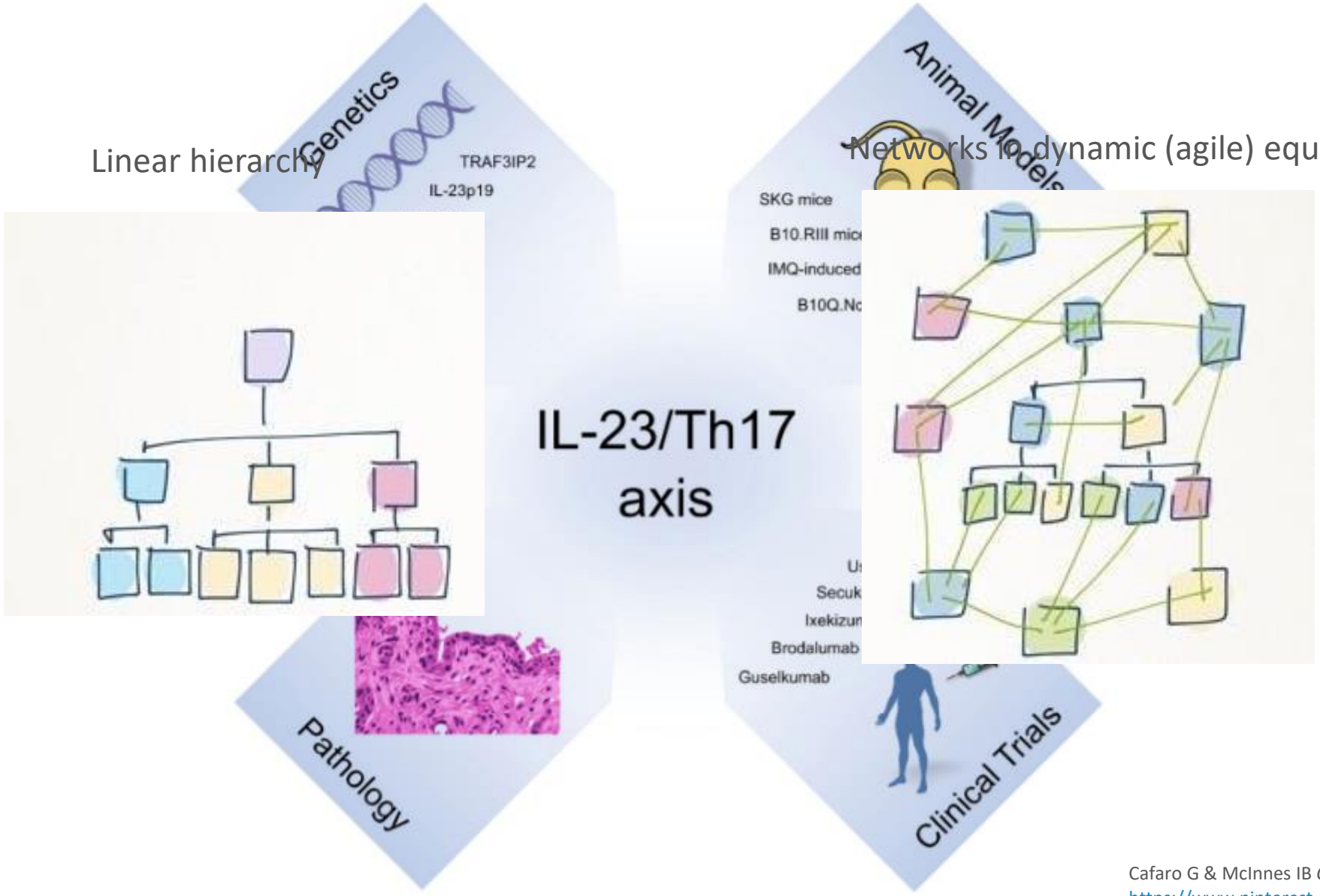
NOR-DMARD is a longitudinal observational study including patients with inflammatory arthropathies from five Norwegian centres starting a new regimen with DMARDs. Patients with a clinical diagnosis of PsA starting their first TNF inhibitor (February 2001– October 2011) were included; DANBIO is a nationwide Danish rheumatologic registry that covers 90% of patients treated with a biologic drug in routine clinical care. Patients with PsA or AS who were biologic-naïve and had been registered in DANBIO from the time of initiation of the first TNF inhibitor were included.

1. Fagerli KM, et al. *Ann Rheum Dis*. 2013;72:1840–4;
2. Glintborg B et al. *Arthritis Rheum*. 2013;65:1213–23;
3. Lie E, et al. *Ann Rheum Dis.* 2011;70:157–63

PsA - the IL-17A/IL-23 axis and therapeutic rationale?

Linear hierarchy

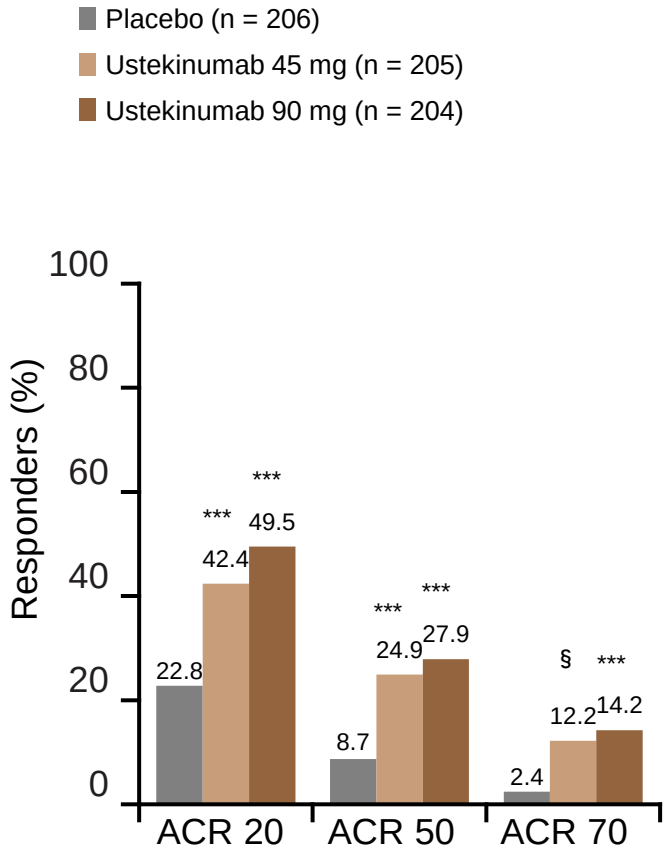
Networks in dynamic (agile) equipoise



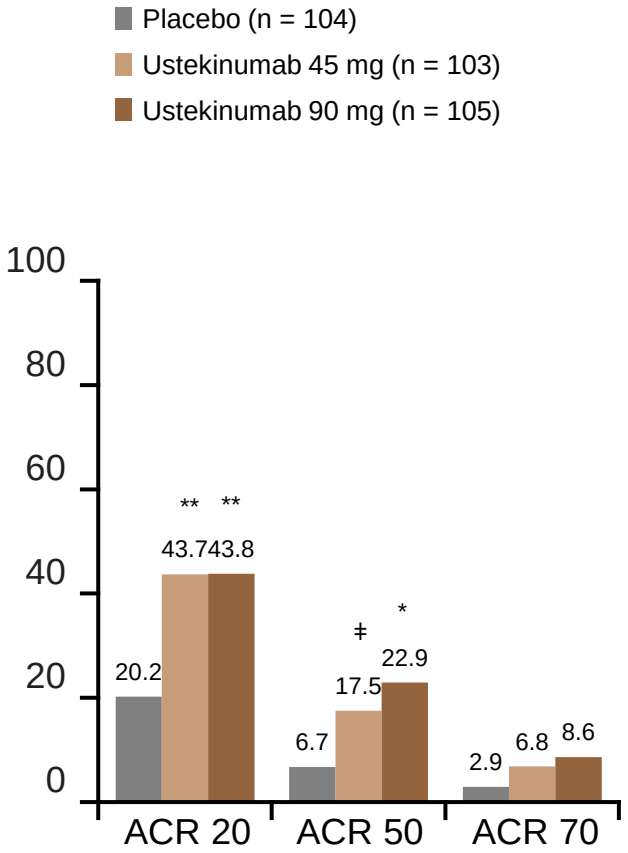
Cafaro G & McInnes IB *Clin Rheum* 2018 37(4), 859-868
https://www.pinterest.co.uk/pin/506514289333955015/
McInnes IB et al Nature Rev Rheumatol 2016;12(1):63-8

Ustekinumab (IL-12/23i) in PsA: ACR responses at Week 24

PSUMMIT 1[a1]



PSUMMIT 2[b2]



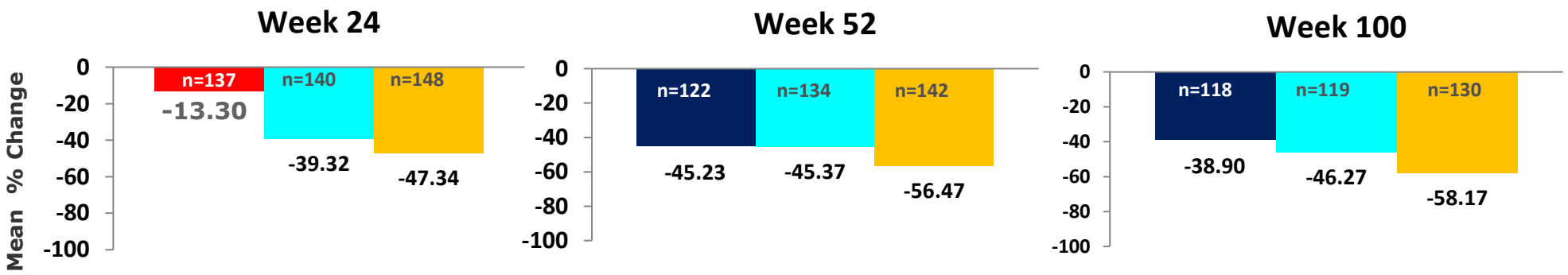
[a]Patients were biologic-naïve; [b]PSUMMIT 2 patients could have had previous anti-TNF experience

‡$P < 0.05$, *$P < 0.01$, **$P < 0.001$, §$P = 0.0001$, ***$P < 0.0001$ vs. placebo

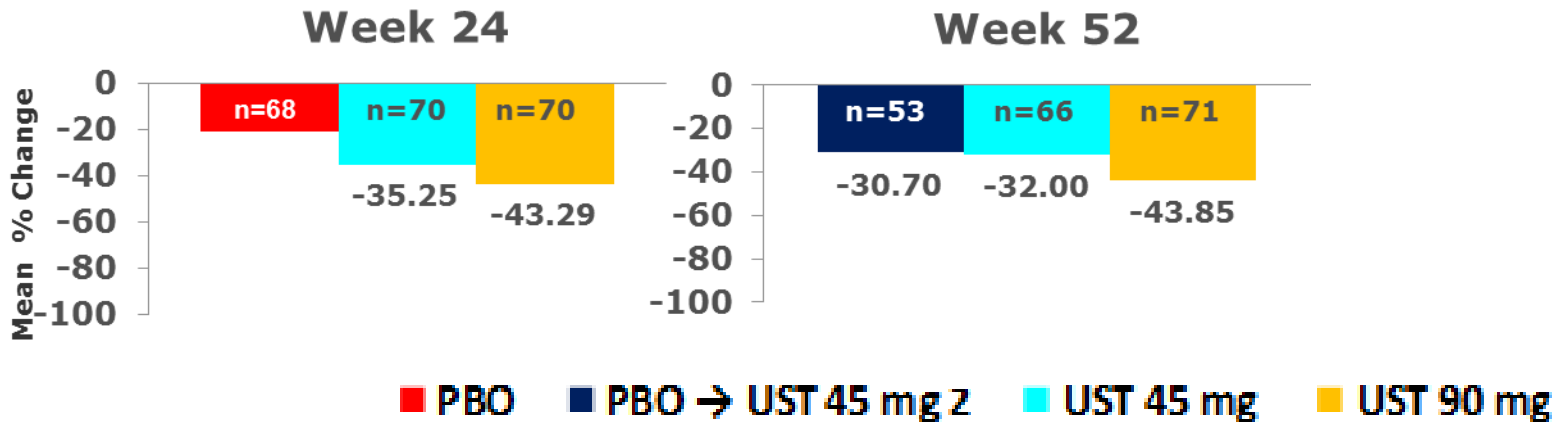
McInnes IB, et al. *Lancet.* 2013;382:780–9;
Ritchlin C, et al. *Ann Rheum Dis.* 2014;73:990–9

Ustekinumab in PsA: Mean Percent Change from Baseline in Enthesitis

PSUMMIT I



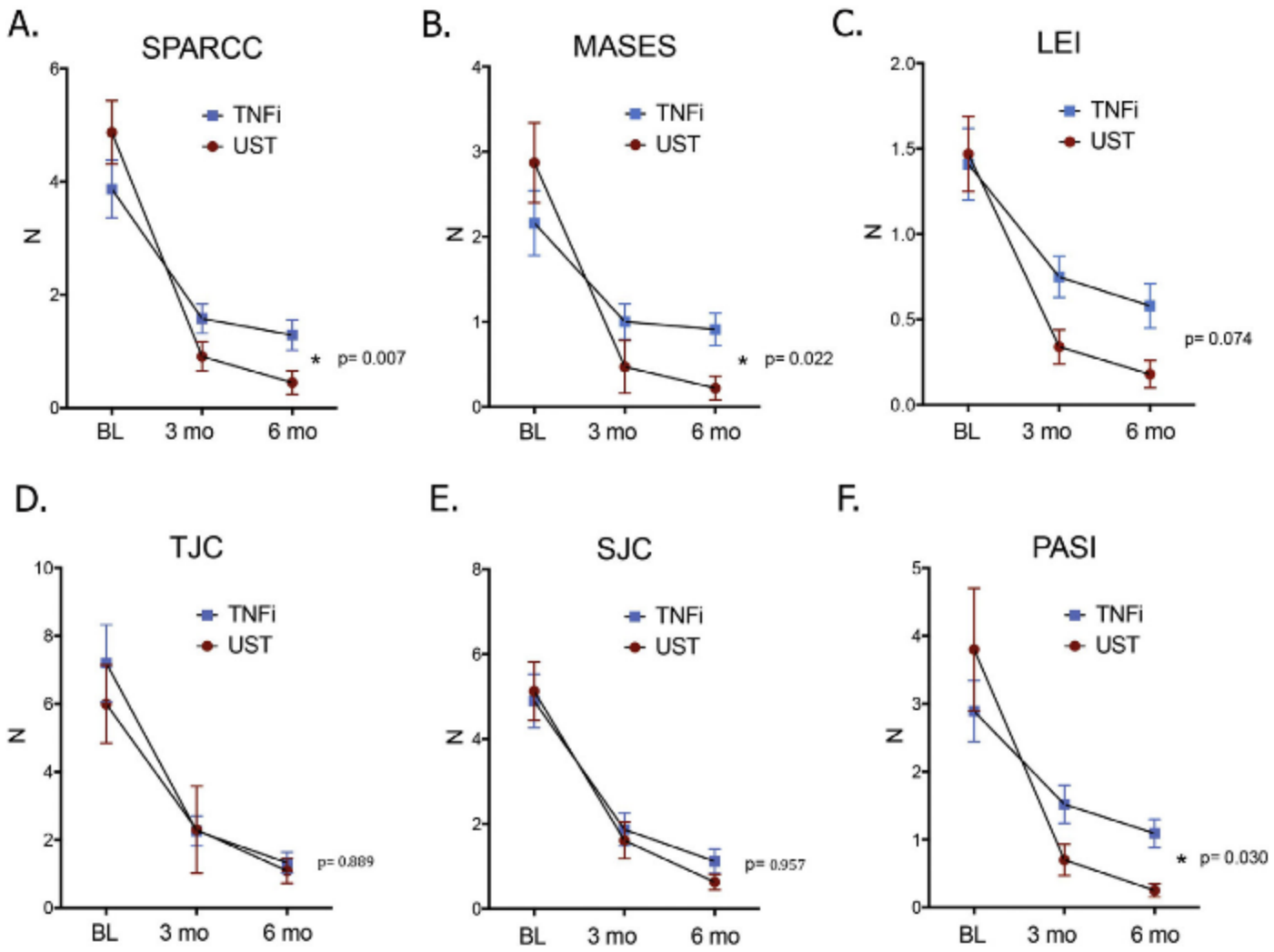
PSUMMIT 2



Enthesitis scoring based on Modified MASES Index. Includes only randomised patients with enthesitis at baseline.

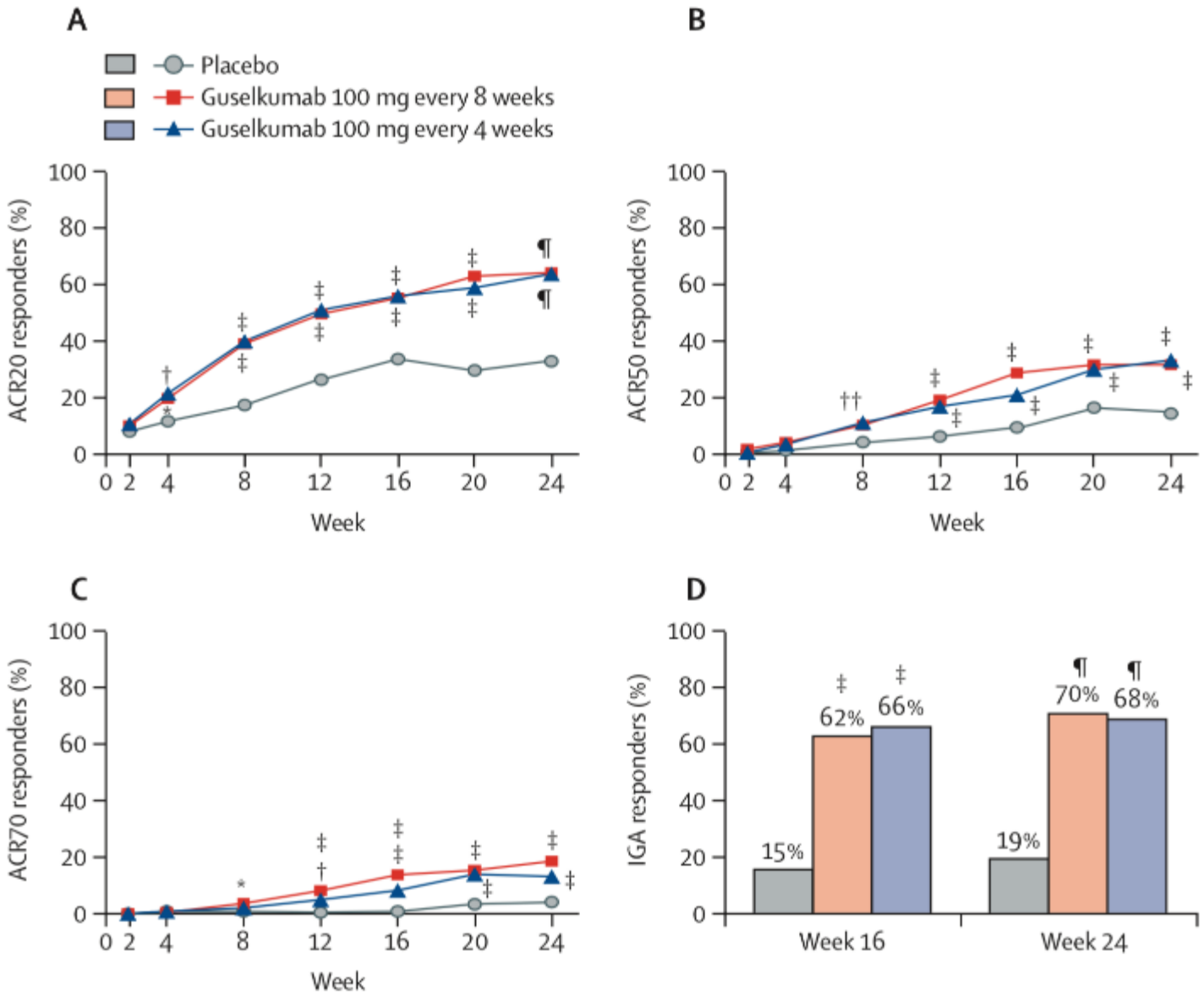
1. Kavanaugh A et al. Poster presented at EULAR 2014; SAT0396. 2. Ritchlin et al. Ann Rheum Dis 2014;73(6):990-9 Supplementary data.

Targeting enthesitis with TNFi or ustekinumab - ECLIPSA study?



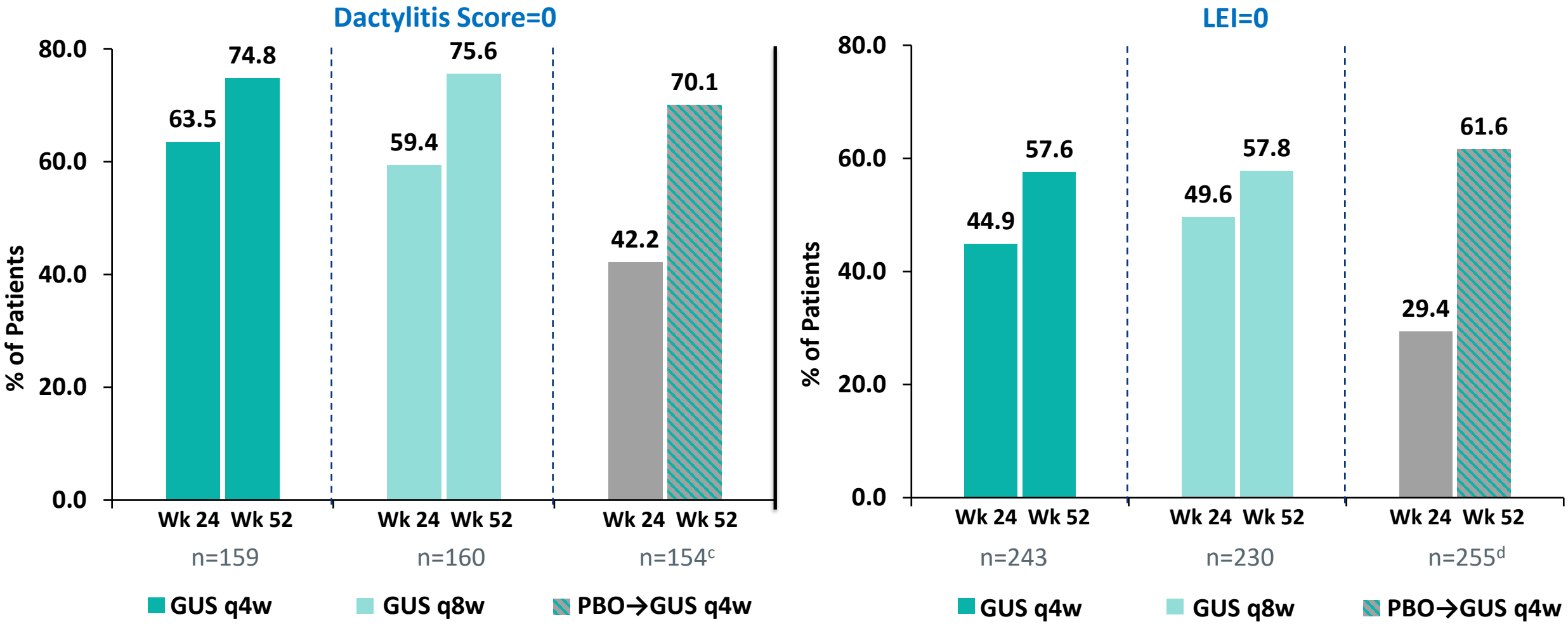
E.G. Araujo et al. *Seminars in Arthritis and Rheumatism.* 2019;48:632-637.

IL-23p19 inhibition in PsA – Guselkumab phase 3 (DISCOVER2)



Mease P et al McInnes IB *Lancet* 2020

Resolution[a] of Dactylitis and Enthesitis (LEI) Were Maintained Through Week 52: Pooled Results DISCOVER-1&2 (NRI)[b]

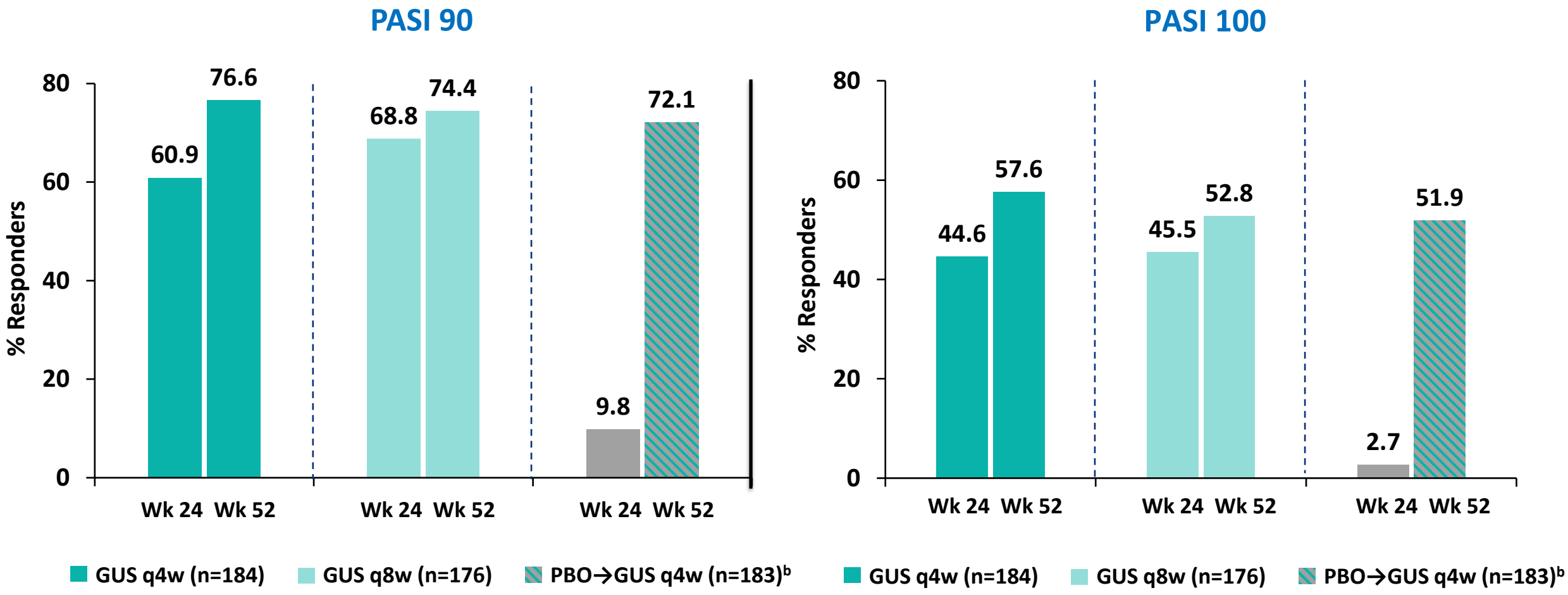


NRI - See Methods. LEI=Leeds enthesitis index. [a]Resolution of dactylitis (range 0-60) or LEI (range 0-6) determined among pts with dactylitis or enthesitis at baseline; [b]Resolution of dactylitis or enthesitis were prespecified to be pooled across studies as a controlled endpoint at Wk 24; pooled results are also reported at Wk 52; [c]142 crossed over from PBO to GUS q4w at Wk 24 and 12 received PBO only before study agent d/c; [d]243 crossed over to GUS q4w at Wk 24 and 12 received PBO only before study agent d/c.

McInnes IB, et al. ACR 2020. OP0506.

McInnes IB, et al. ACR 2020. OP0506.

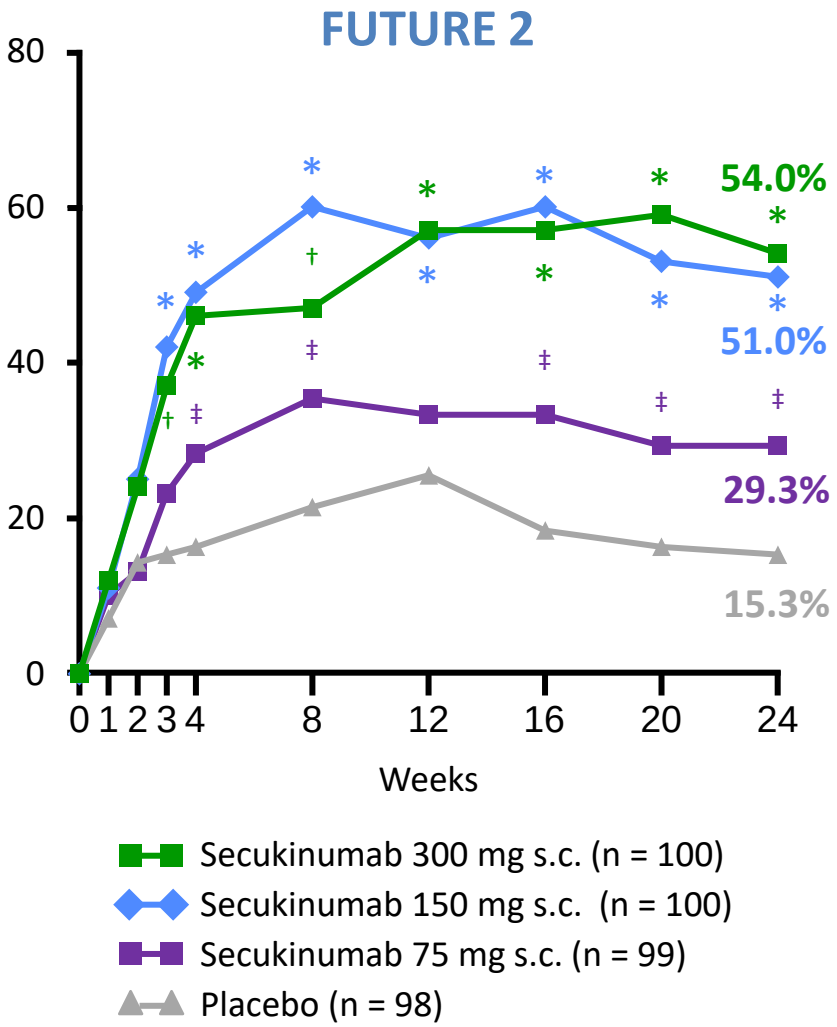
DISCOVER-2: PASI 90/100 Responses[a] Improved and Were Maintained Through Week 52 (NRI)

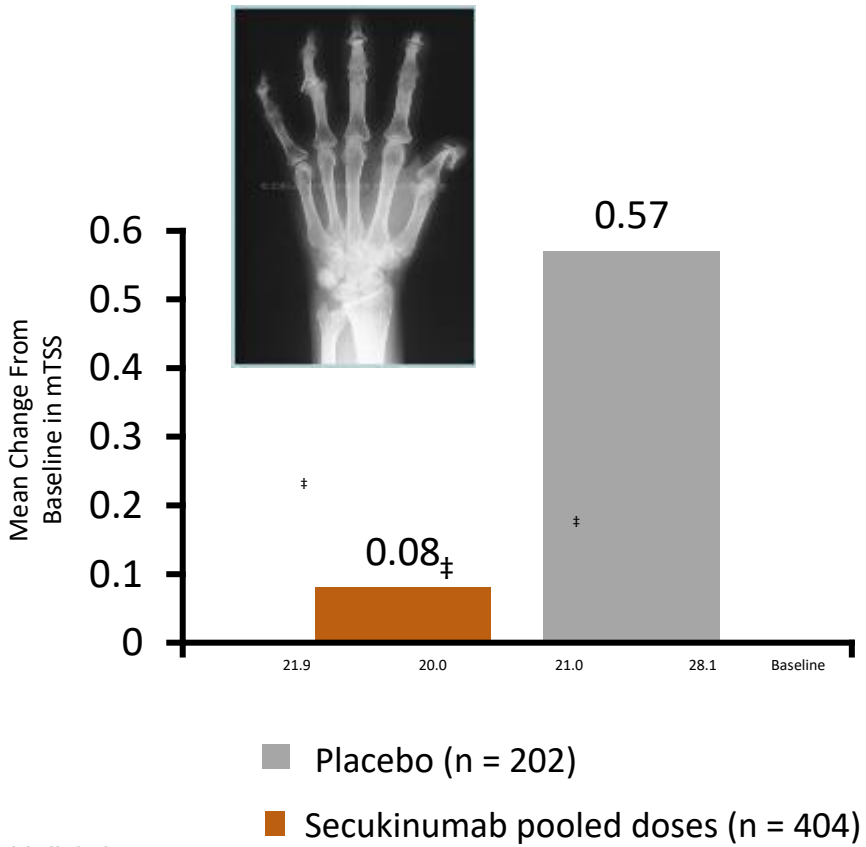


NRI - See Methods. PASI=Psoriasis Area and Severity Index. [a]Pts achieving at least 90% or 100% improvement in PASI at Wks 24 and 52 among pts with BSA ≥3% and IGA ≥2 at baseline; [b]176 crossed over to GUS q4w at Wk 24; 7 received PBO only before study agent d/c.

McInnes IB, et al. ACR 2020. OP0506.

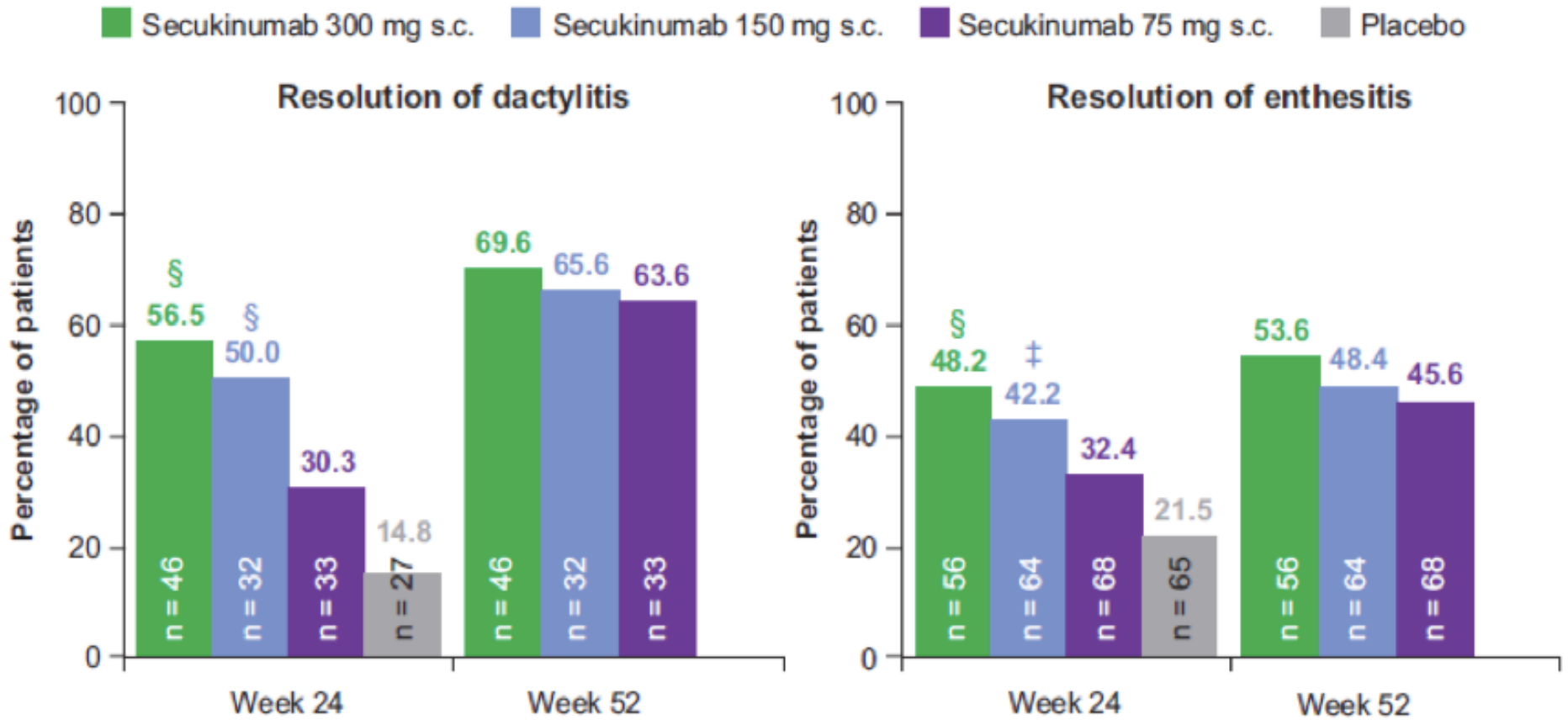
Secukinumab (IL-17Ai) in PsA: Clinical and radiographic responses





*P < 0.0001; †P < 0.001; §P < 0.01; ‡P < 0.05 vs. placebo (P-values at Week 24 adjusted for multiplicity).
Missing values imputed as nonresponse (nonresponder imputation).
Mease P, McInnes IB et al ***NEJM*** (2018); McInnes IB et al ***Lancet*** (2015)

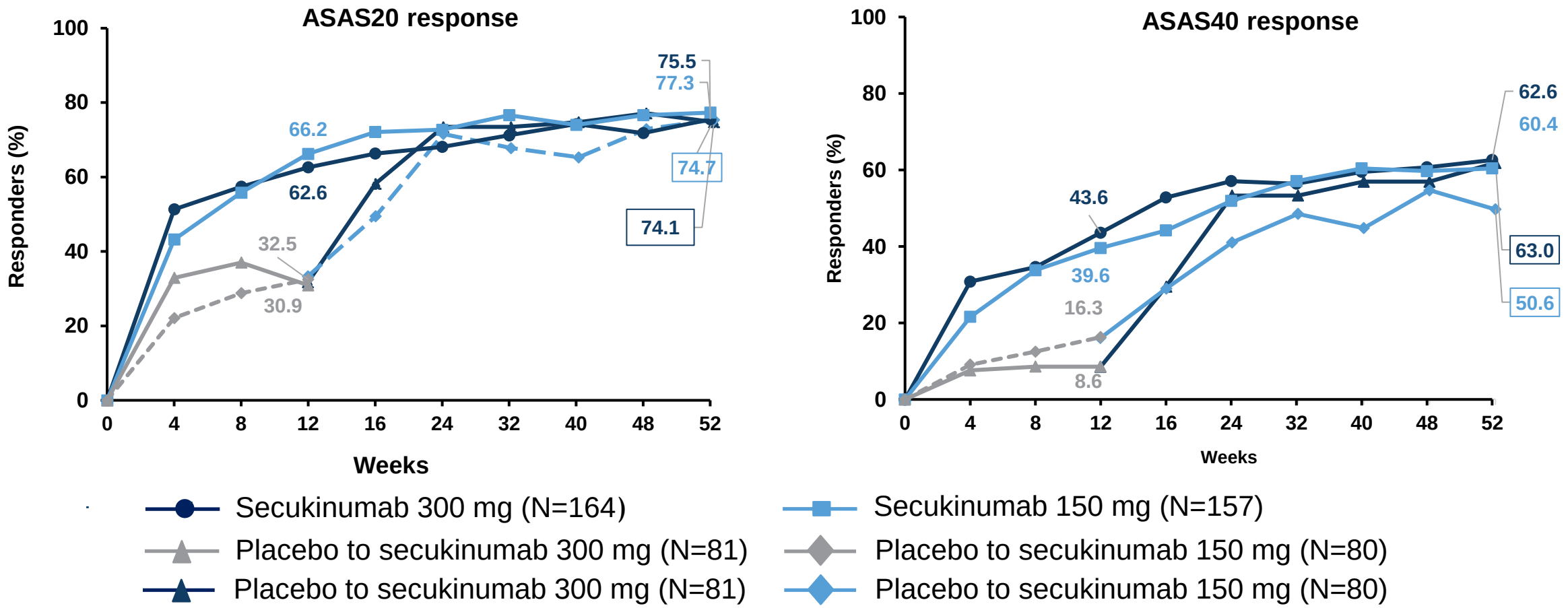
Responses to secukinumab for enthesial resolution



§P<0.01; ‡P <0.05 vs placebo; Resolution of dactylitis and enthesitis amongst those patients with these symptoms respectively at baseline. Missing values were imputed as non-response (NRI) at Weeks 24 and 52. n: number of evaluable patients

Nash et al *Arthritis Rheum* ACR (2016) suppl

MAXIMISE Study: Secukinumab improvise spinal disease in PsA

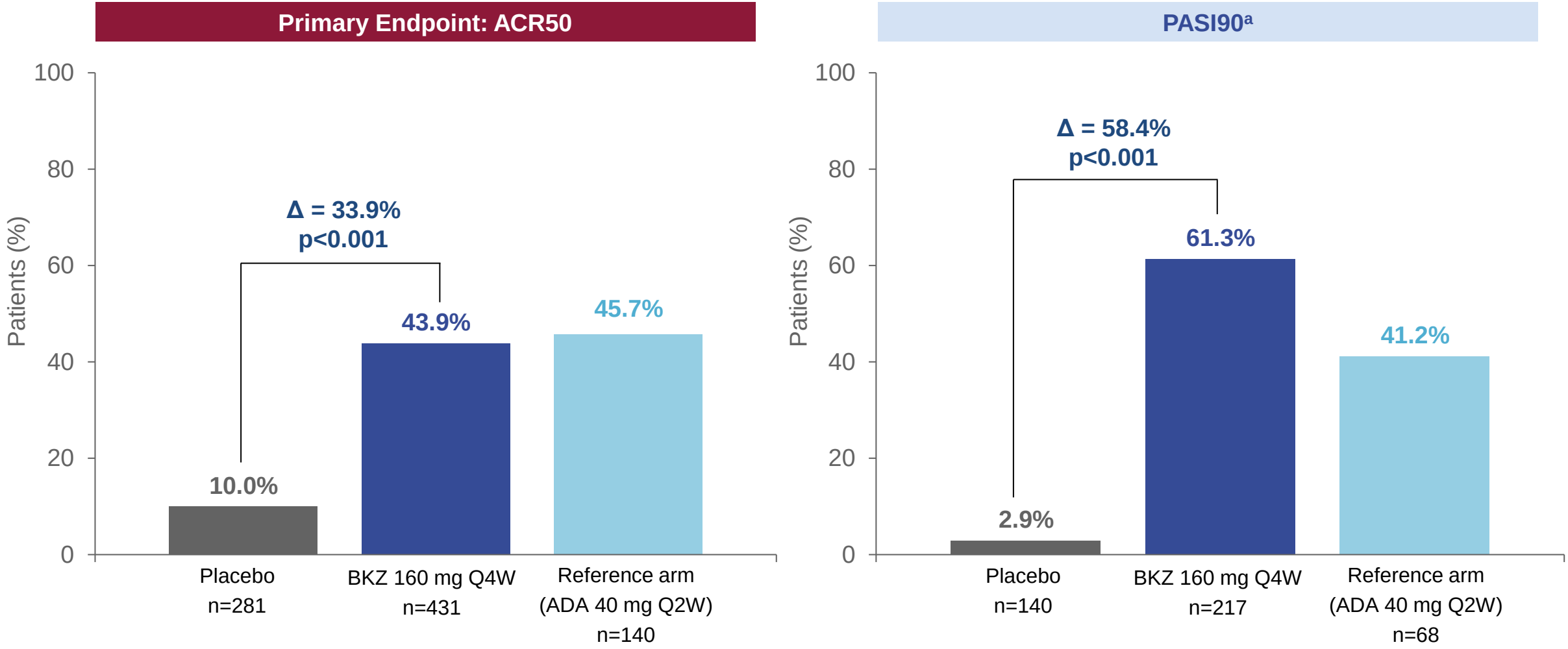


LOCF was used to account for missing data for analysis

ASAS, Assessment of Spondyloarthritis international Society; LOCF, Last observation carried forward; N, total number of patients in full analysis set

Baraliakos X, Gossec L, Pournara E, *et al*. *Ann Rheum Dis* Epub ahead of print: doi:10.1136/ annrheumdis-2020-218808

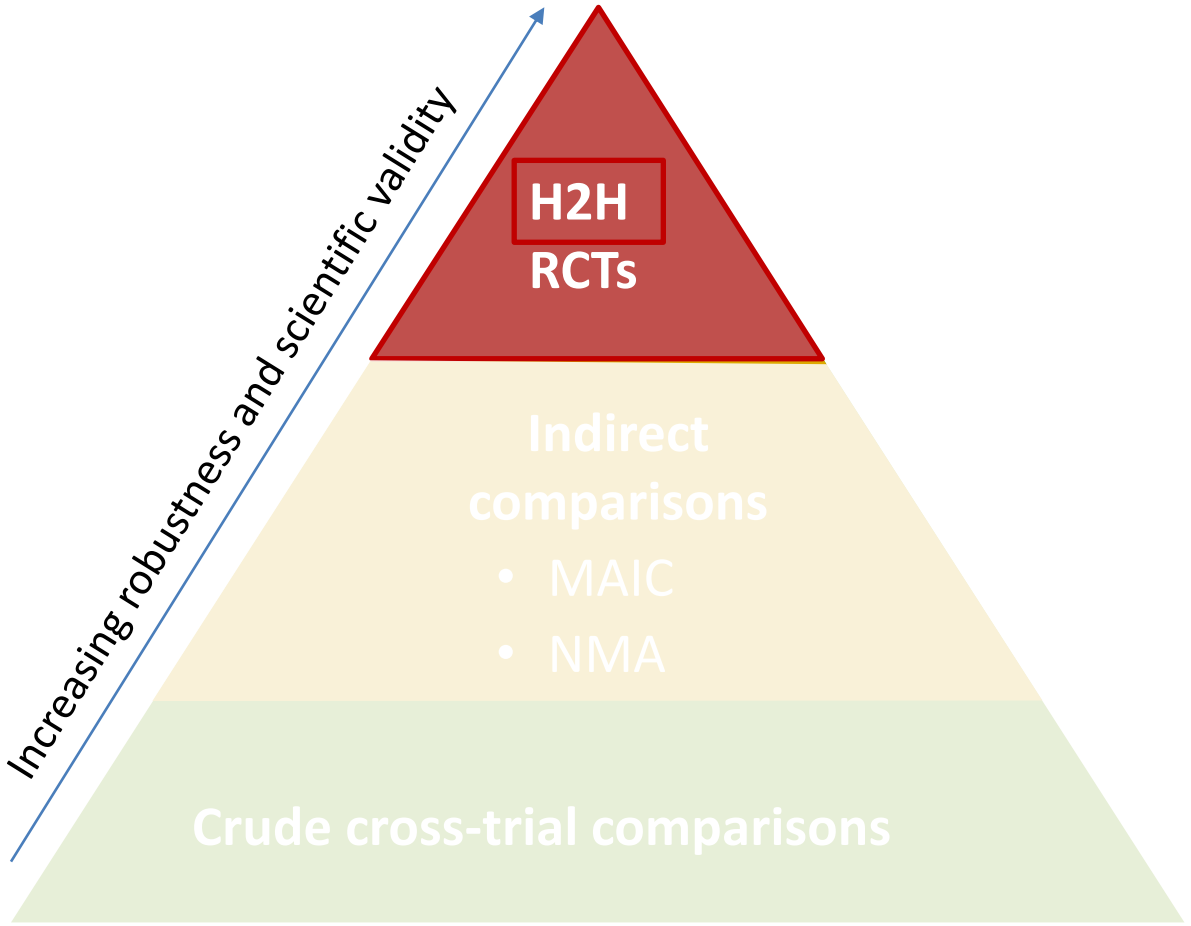
Bimekizumab - IL-17A/F dual inhibition in psoriatic arthritis (BE-OPTIMAL phase 3)



Week 16 data shown. Randomised set. p values BKZ vs placebo were obtained from logistic regression with treatment, bone erosion at baseline and region as factors. The study was not powered for statistical comparisons of adalimumab to bimekizumab or adalimumab to placebo. [a] Patients with PSO involving ≥3% of BSA at baseline. ACR50: American College of Rheumatology criteria ≥50% response; ADA: adalimumab; BKZ: bimekizumab; BSA: body surface area; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; PASI90: ≥90% improvement in PASI; PSO: psoriasis; Q2W: every 2 weeks; Q4W: every 4 weeks.

McInnes IB et al EULAR Late Breaker Oral Presentation Copenhagen June 2022

To compare effectiveness of two (or more) therapies to deconstruct guidelines?

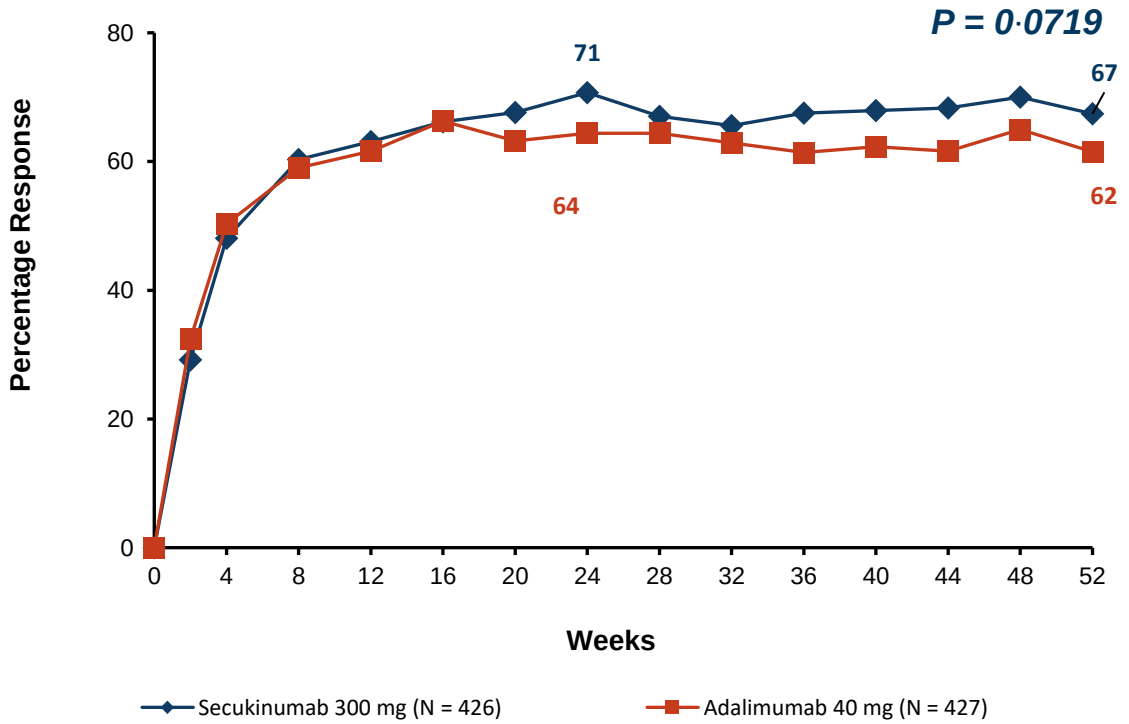


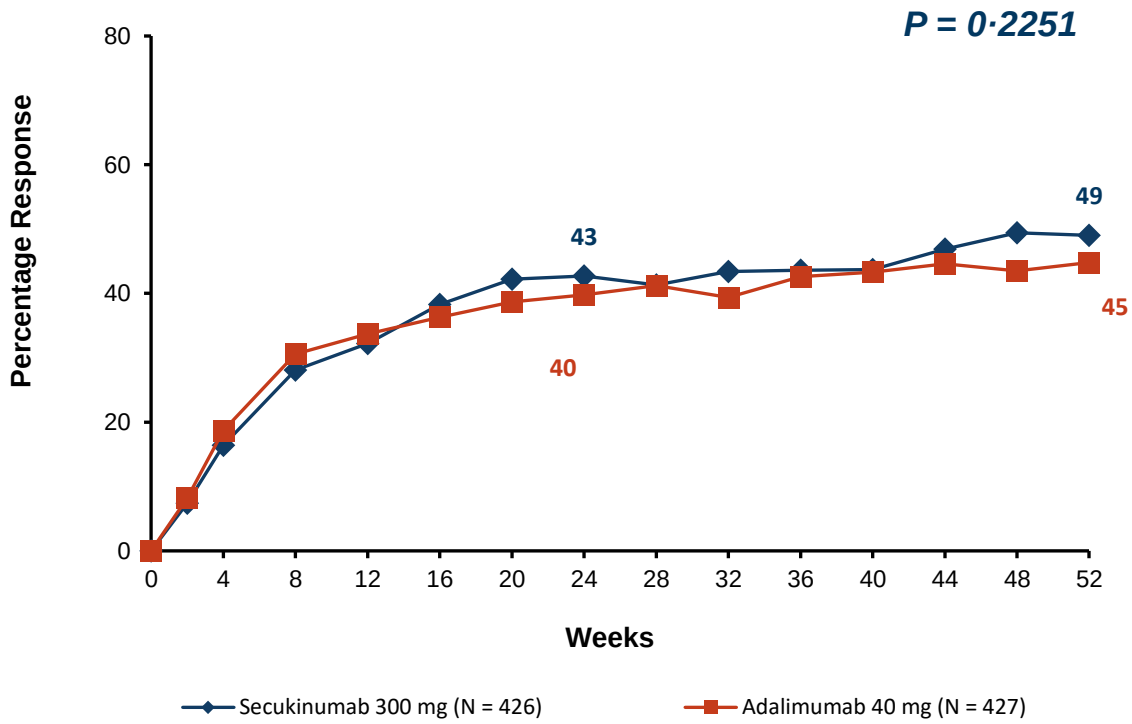
H2H, head-to-head; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; RCT, randomized controlled trial

1. Schöttker B, et al. GMS Health Technol Assess. 2009;5:Doc09; 2. Signorovitch JE, et al. Value Health. 2012;15:940–7.

EXCEED – IL-17A inhibition versus TNF inhibition?

Primary Endpoint (ACR20 response) at Week 52 not met

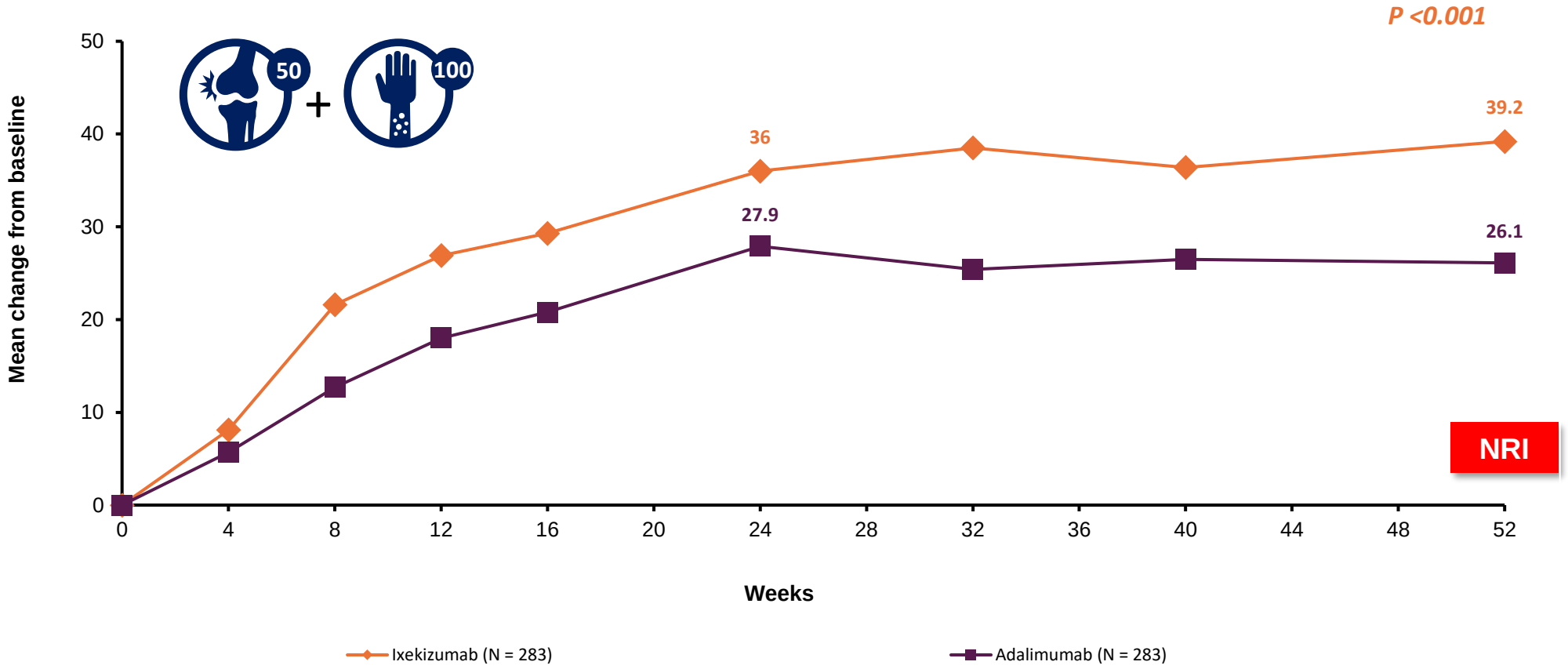




P versus adalimumab; Unadjusted p-value is reported at Week 52; Patients who discontinued study treatment before or at Week 50 or took csDMARDs after Week 36 are considered non-responders for the visits after discontinuation or taking csDMARDs. Multiple imputation is used for all other missing data. ACR, American college of rheumatology; N, Number of randomized patients

1. McInnes IB, et al. Lancet. 2020;395:1496–505.

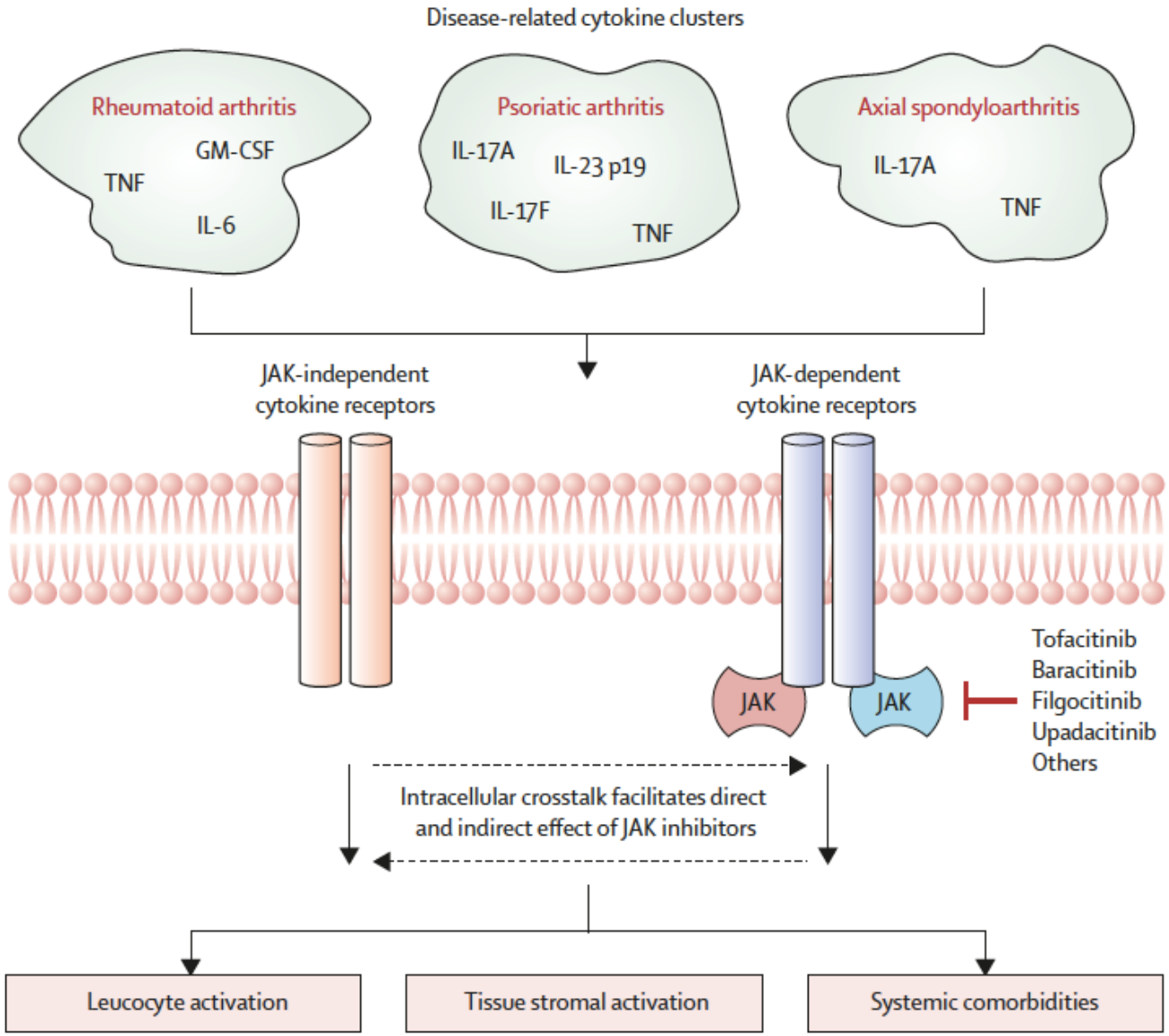
Ixekizumab v adalimumab in active psoriatic arthritis in bDMARD naïve patients: randomised, double-blind, placebo-controlled SPIRIT-H2H trial



P versus adalimumab; NRI was used for imputation of all missing data, including drop-outs as non-responder. ACR, American college of rheumatology; H2H, head to head; N, Number of available patients; PASI, psoriasis area severity index

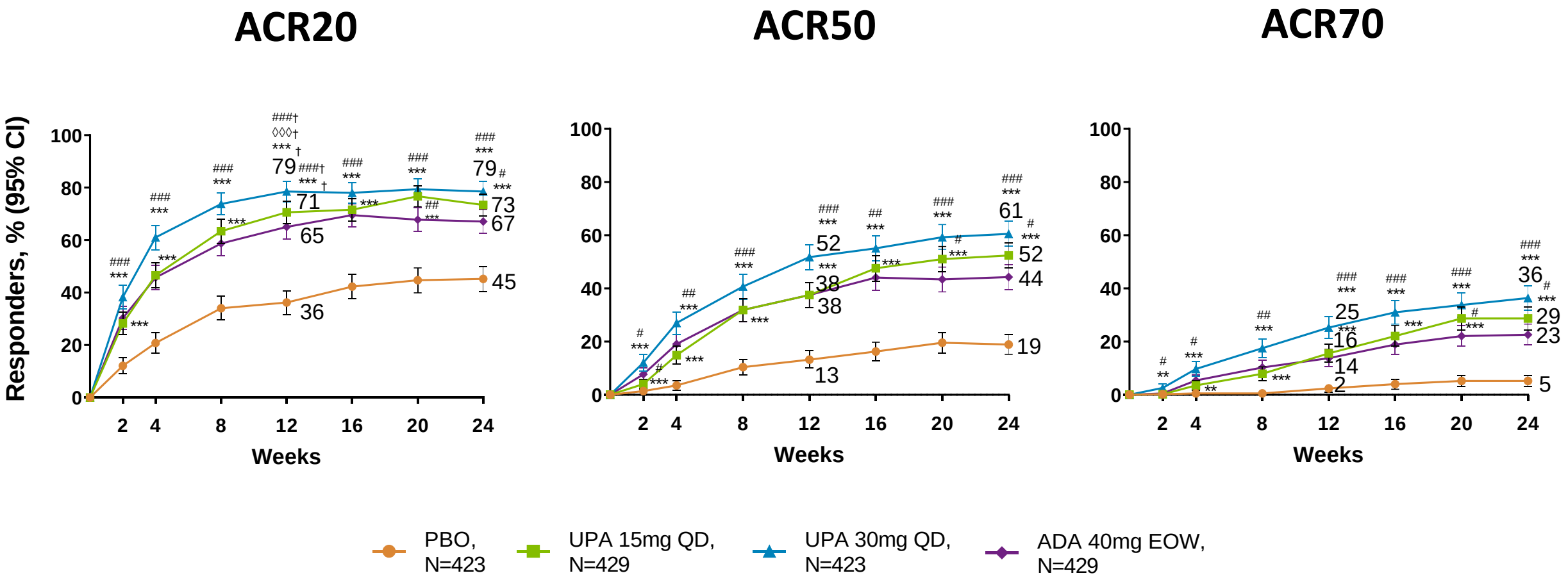
1. Smolen J, et al. American College of Rheumatology (ACR), Atlanta, USA; November 8th–13th, 2019; 2. Mease PJ et al. Ann Rheum Dis. 2020;79:123-131; 3. Smolen J, et al. Rheumatol Ther 2020;7:1021–1035.

JAK inhibitors in psoriatic arthritis?



McInnes IB & Siebert S *Lancet* 2018

SELECT PsA-1: Upadacitinib v adalimumab Through Week 24 (NRI)

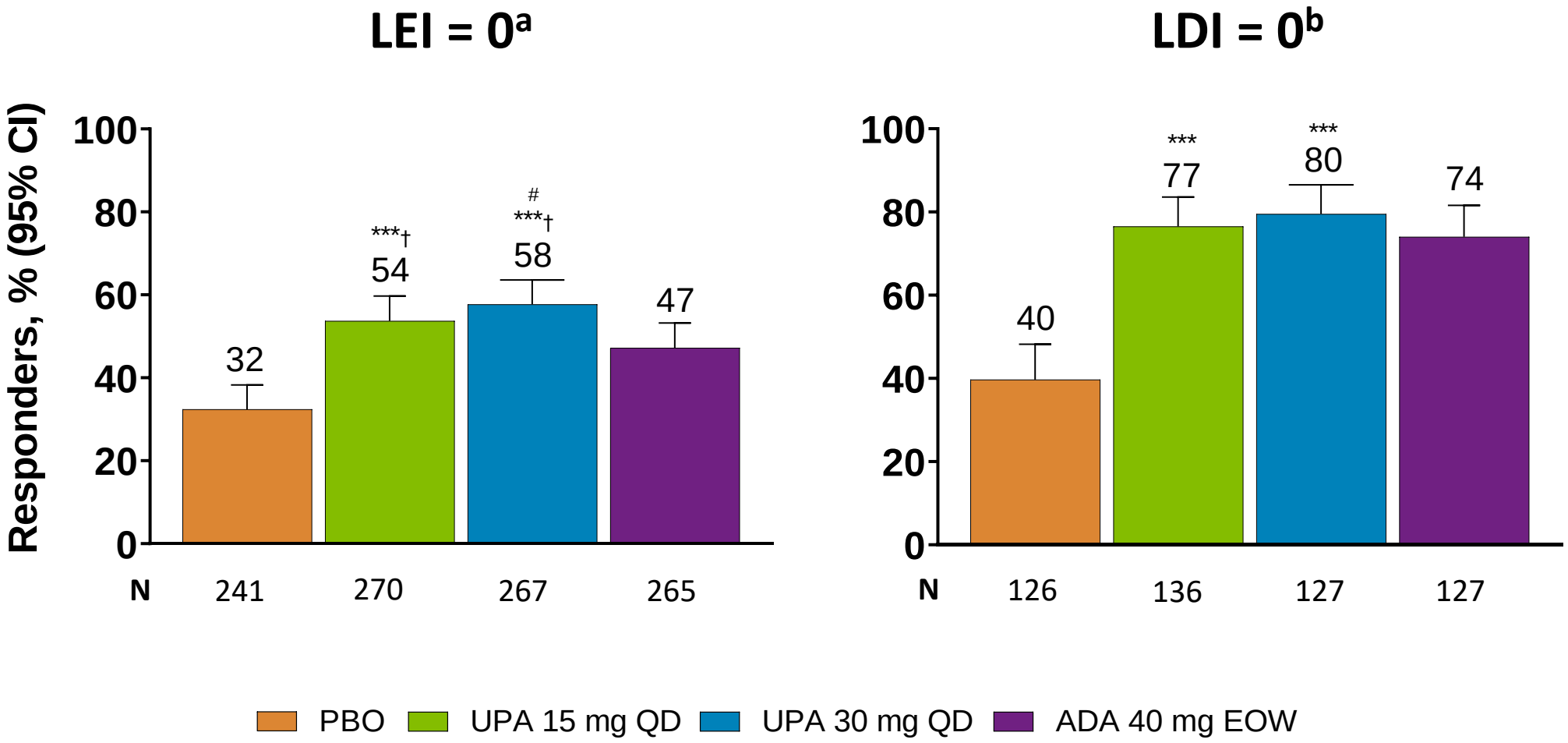


***, P<0.001 for UPA vs PBO; **, P<0.01 for UPA vs PBO; ◊◊◊, P<0.001 for noninferiority UPA vs ADA; ###, P<0.001 for UPA vs ADA; ##, P<0.01 for UPA vs ADA; #, P<0.05 for UPA vs ADA. †, Statistically significant in the multiplicity-controlled analysis.

ACR, American College of Rheumatology; ADA, adalimumab; CI, confidence interval; EOW, every other week; NRI, non-responder imputation; PBO, placebo; QD, once daily; UPA, upadacitinib.

McInnes IB, et al. *N Engl J Med* 2021; 384(13):1227-1239.

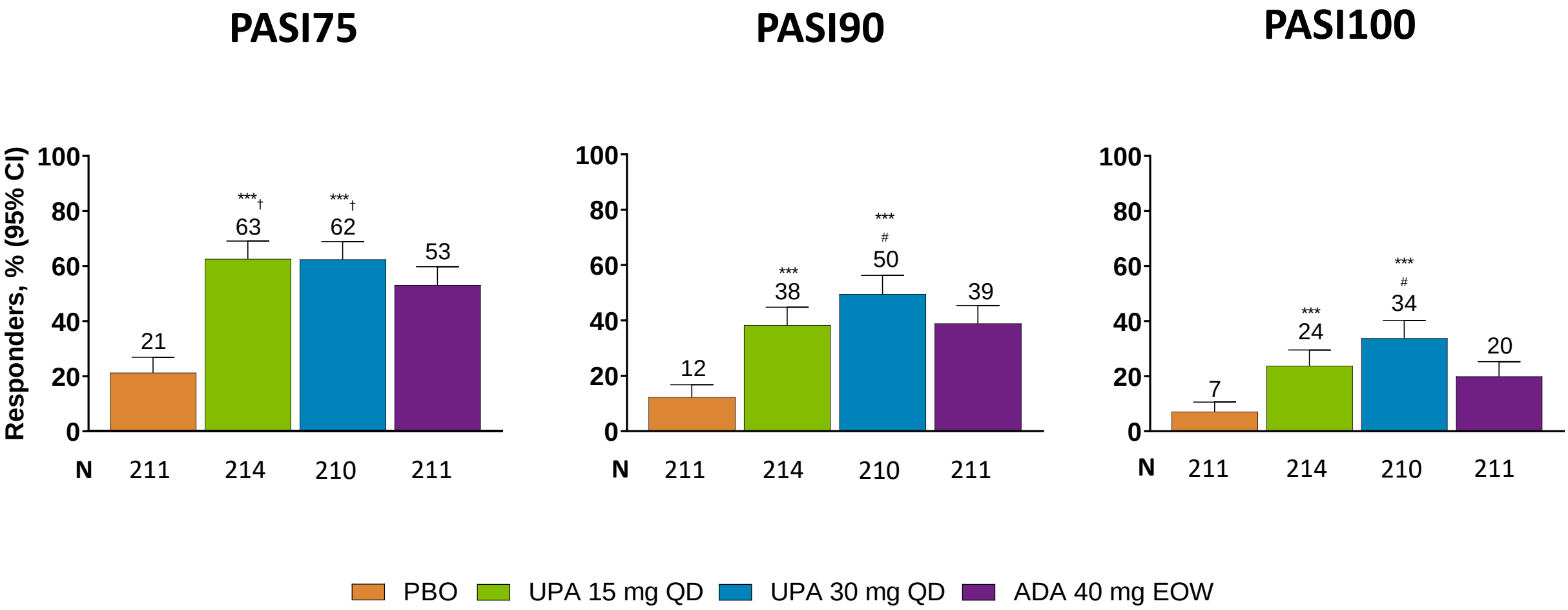
SELECT PsA-1: Upadacitinib v adalimumab Through Week 24 (NRI)



***, P<0.001 for UPA vs PBO; #, P<0.05 for UPA vs ADA. †, Statistically significant in the multiplicity-controlled analysis. [a]for patients with baseline LEI >0; [b]for patients with baseline LDI >0. ADA, adalimumab; CI, confidence interval; EOW, every other week; LDI, Leeds Dactylitis Index; LEI, Leeds Enthesitis Index ; QD, once daily; NRI, non-responder imputation; PBO, placebo; UPA, upadacitinib.

McInnes IB, et al. *N Engl J Med* 2021; 384(13):1227-1239.

SELECT PsA-1: Upadacitinib v adalimumab Through Week 24 (NRI) – skin responses



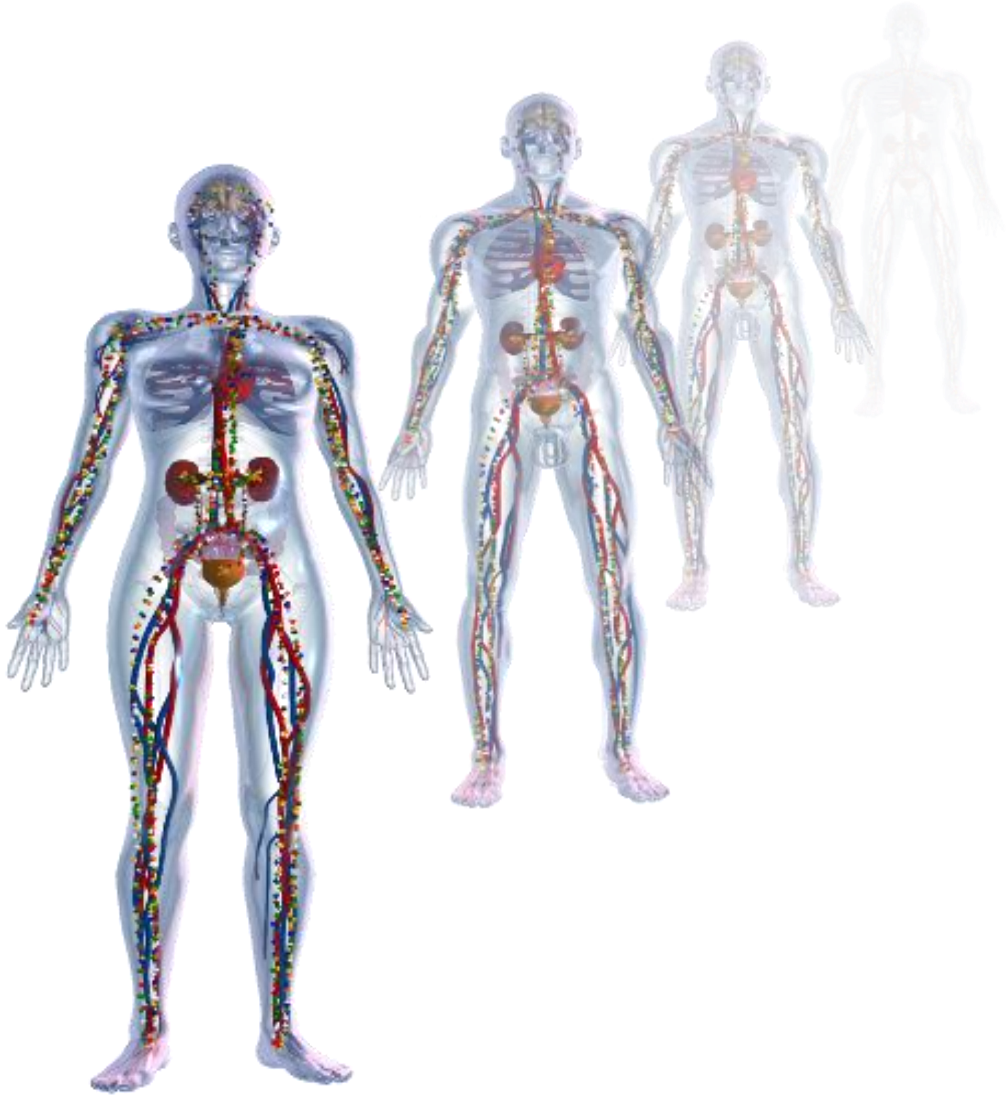
***, P<0.001 for UPA vs PBO; #, P<0.05 for UPA vs ADA. †, Statistically significant in the multiplicity-controlled analysis. ADA, adalimumab; CI, confidence interval; EOW, every other week; PBO, placebo; PASI, Psoriasis Area Severity Index; QD, once daily; NRI, non-responder imputation; UPA, upadacitinib. PASI was assessed for patients with ≥ 3% body surface area psoriasis at baseline.

McInnes IB, et al. *N Engl J Med* 2021; 384(13):1227-1239.

SpA – thinking beyond…PsA as an exemplar

1. Current therapeutics

2. Towards a new care strategy care?



In the absence of biomarkers, decisions should at the least be tissue domain driven…

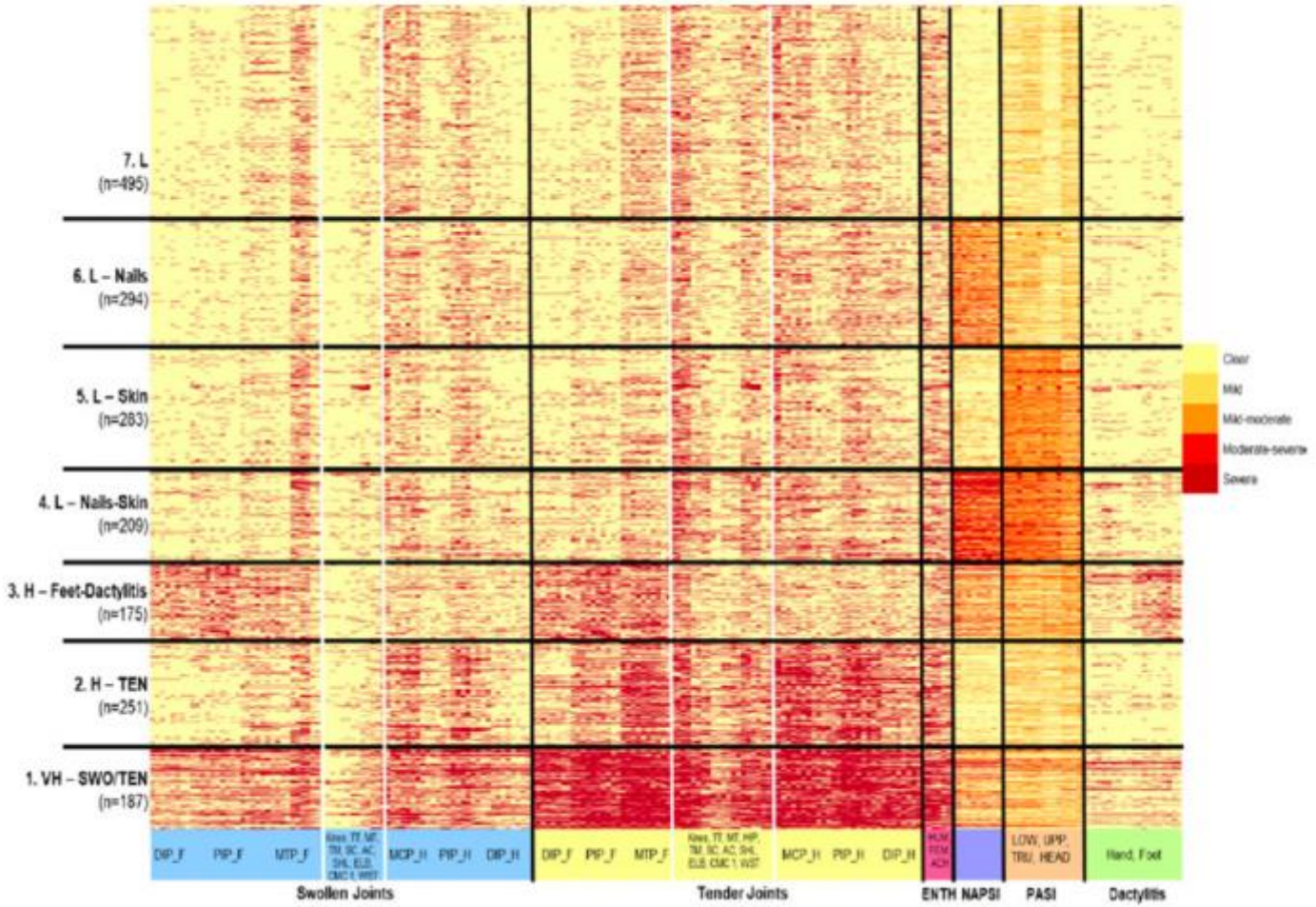
Target	Disease domain											
	Peripheral arthritis						Skin (PASI 75)[1]	Nails[2–7,a]	Enthesitis[1,b]		Dactylitis[1,b]		Axial disease (ASAS40)	
	Arthritis (ACR70)[1]		Physical function (HAQ)[1]		X-ray damage (PsA-mSvdHS)[1]									
TNF													Axial PsA[8,c]+ axSpA[2]	
IL-17A													Axial PsA[9] + axSpA[3]	
TNF/IL-17A														
CD80/86													AS[10,d]	
IL-6													AS[11]	
IL-23-p19	GUS	RIS	GUS	RIS			GUS	RIS	GUS	RIS	GUS	RIS	GUS	RIS
													GUS – Axial PsA[12,e]	RIS – AS[13]
JAK													AS[14]	
PDE-4													AS[15,f]	

[a]Efficacy demonstrated in nail psoriasis or patients with PsA with nail psoriasis; [b]Different instruments used in studies; [c]As judged on evidence in axial SpA; [d]Open-label study – no major clinical response observed; [e]Assessed with BASDAI in patients with active PsA with imaging-confirmed sacroiliitis from DISCOVER-1&2; [f]No significant difference vs placebo (ASAS20)

1. Adapted from: Kerschbaumer A, et al. *Ann Rheum Dis*. 2020;E-pub ahead of print; 2. Adalimumab SmPC. Available at: https://www.medicines.org.uk/emc/product/2150/smpc. Accessed May 2020; 3. Secukinumab SmPC. Available at: https://www.medicines.org.uk/emc/product/3669/smpc. Accessed May 2020; 4. Guselkumab SmPC. Available at: https://www.medicines.org.uk/emc/product/8662/smpc. Accessed May 2020; 5. Risankizumab SmPC Available at: https://www.medicines.org.uk/emc/product/10199/smpc. Accessed May 2020; 6. Merola J, et al. *J Am Acad Dermatol.* 2017;77:79–87; 7. Apremilast SmPC. Available at: https://www.medicines.org.uk/emc/product/3648/smpc. Accessed May 2020; 8. Gossec L, et al. *Ann Rheum Dis* 2020;79:700–12; 9. Baraliakos X, et al. EULAR 2020. Oral OP0053; 10. Song H, et al. *Ann Rheum Dis.* 2011;70:1108–10; 11. Sieper J, et al. *Ann Rheum Dis*. 2015;74:1051–7; 12. Helliwell P, et al. EULAR 2020. Oral OP0054; 13. Baeten D, et al. *Ann Rheum Dis*. 2018;77:1295–302; 14. van der Heijde D, et al. *Ann Rheum Dis*. 2017;76:1340-47; 15. Pathan E, et al. *Ann Rheum Dis*. 2013;72:1475–80.

A new approach to clinical heterogeneity (in PsA) – application of machine learning?

N= 1894 patients

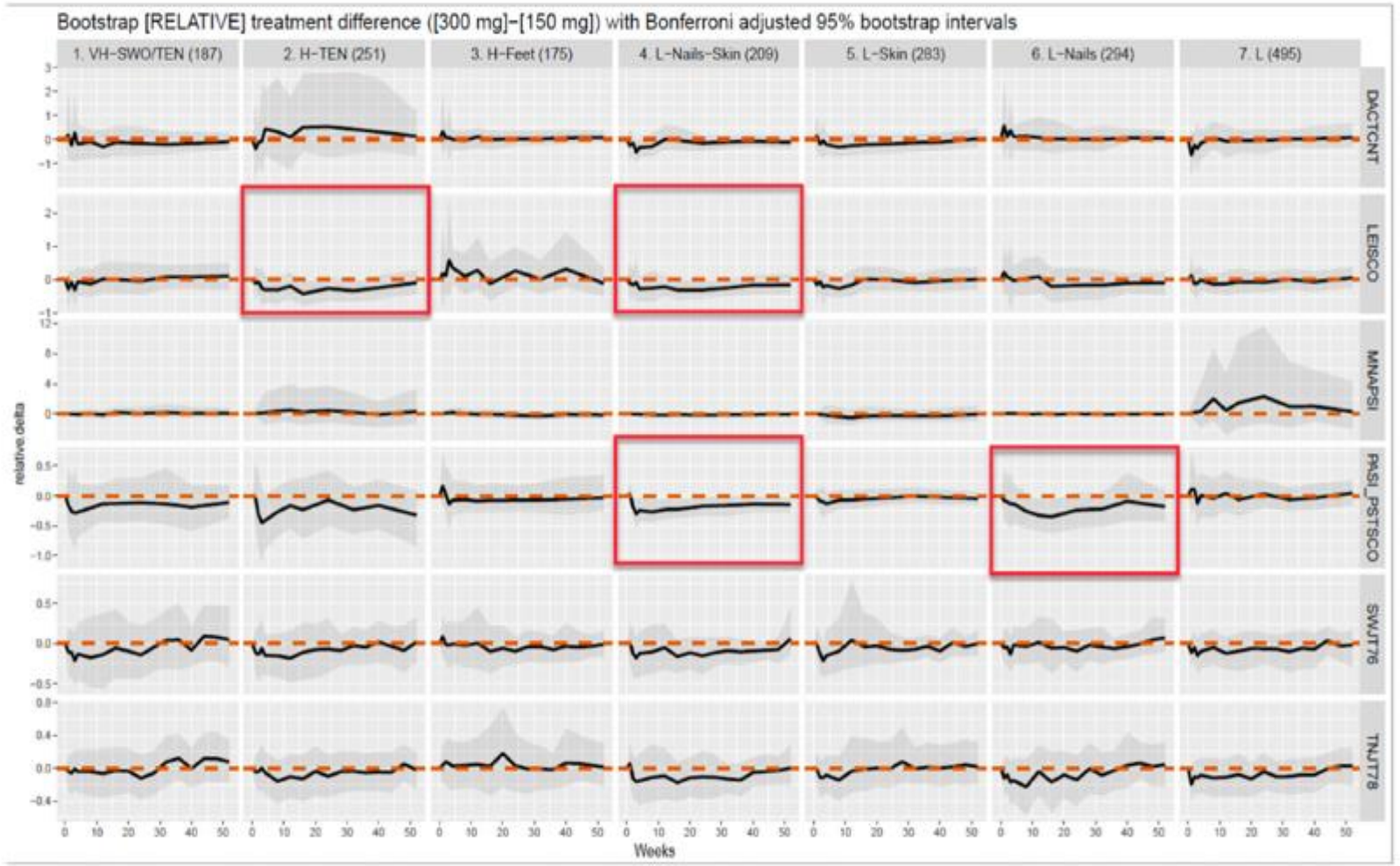


N= 206 clinical variables

Pournara E, et al. RMD Open 2021;**7**:e001845

How should we characterise clinical heterogeneity in PsA

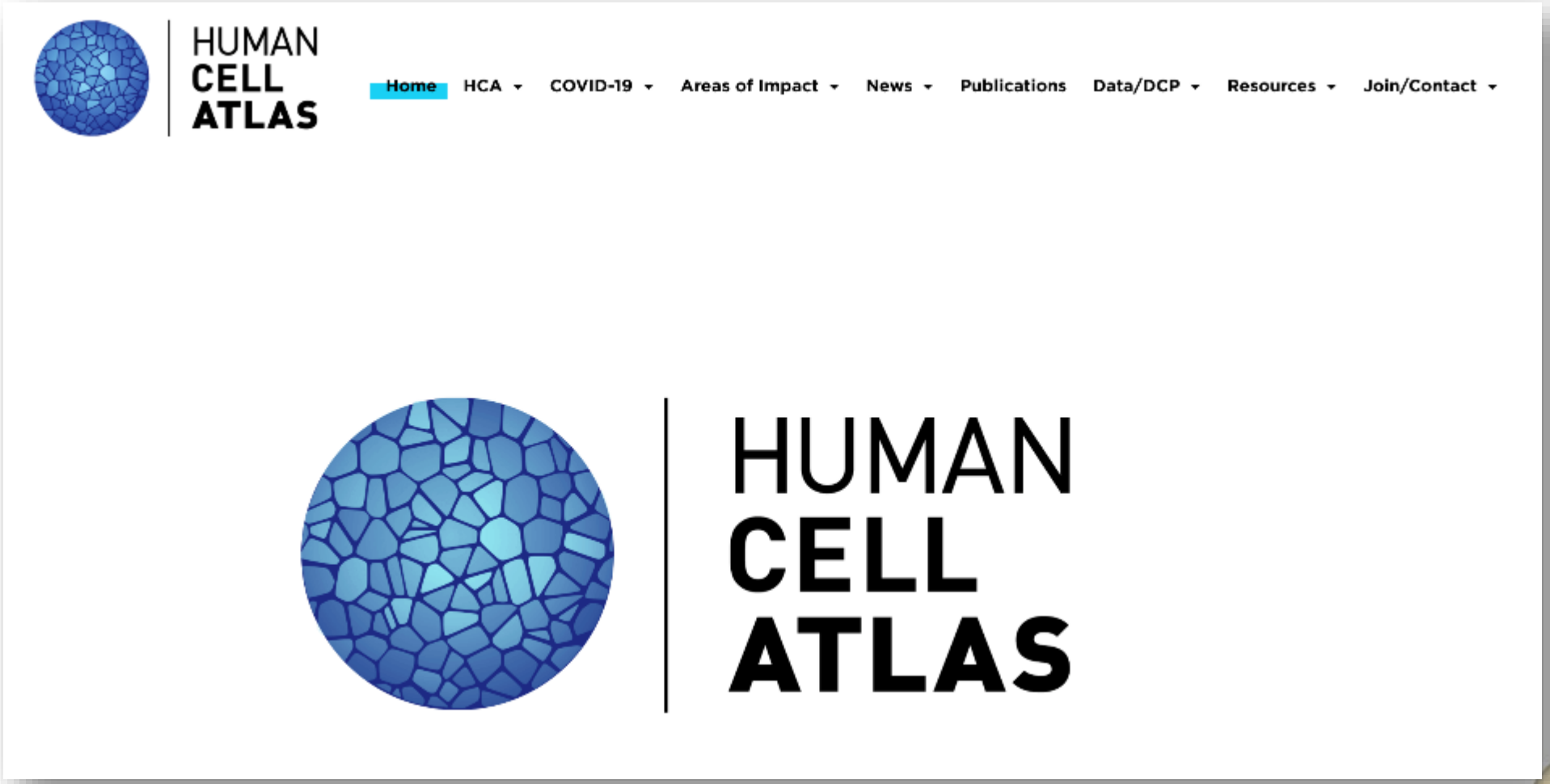
– Discrete clusters exhibit differential dose responses to an IL-17i



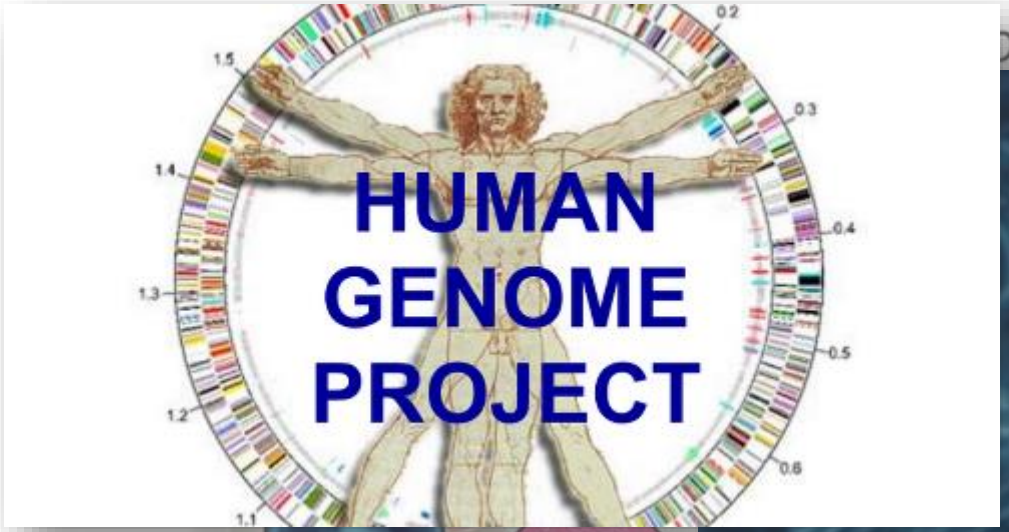
- Longitudinal responses > improvements in PASI scores and enthesitis resolution for secukinumab 300 mg compared with 150 mg in some clusters.
- Validates the approach and permits rational biomarker interrogation

Pournara E, et al. RMD Open 2021;**7**:e001845

What is/are the strategic consequence(s) of clinical heterogeneity – some obvious questions?



From (wo)man to molecule and back…the molecular revolution



DNA, deoxyribonucleic acid; RNA, ribonucleic acid

Adapted from Goldman AW, et al. Front Physiol 2015;6:225

SpA– tissues accessed with variable ease…

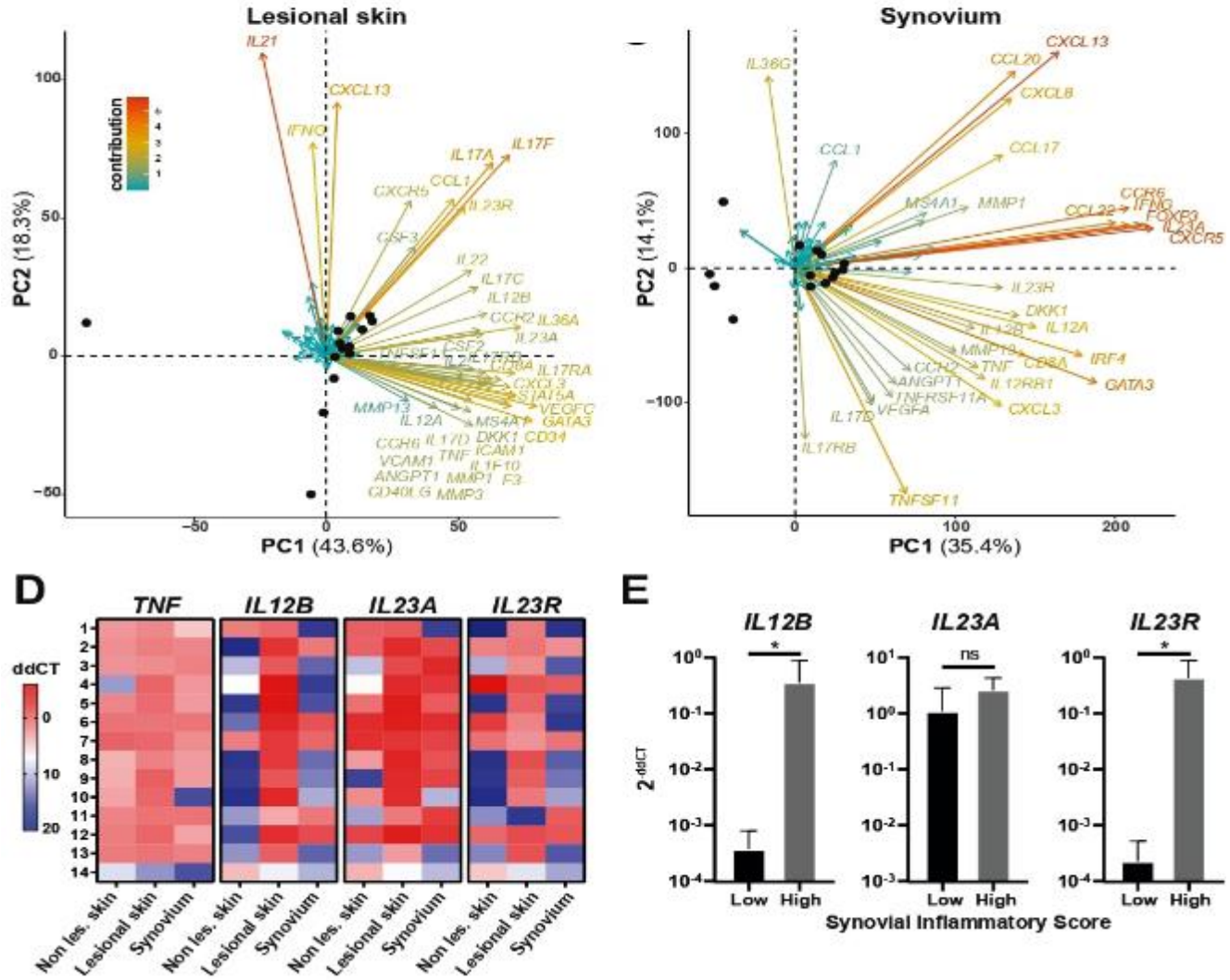
The Inaccessible Pinnacle: Britain's most notorious climb

The terrifying, sheer flanks of the Inaccessible Pinnacle on the Isle of Skye are a holy grail for mountaineers. Andrew Gilchrist ropes up for the climb of his life

▲ '150ft of climbing mayhem' ... the Inaccessible Pinnacle. Photograph: Krause, Johansen/Caters News Agency

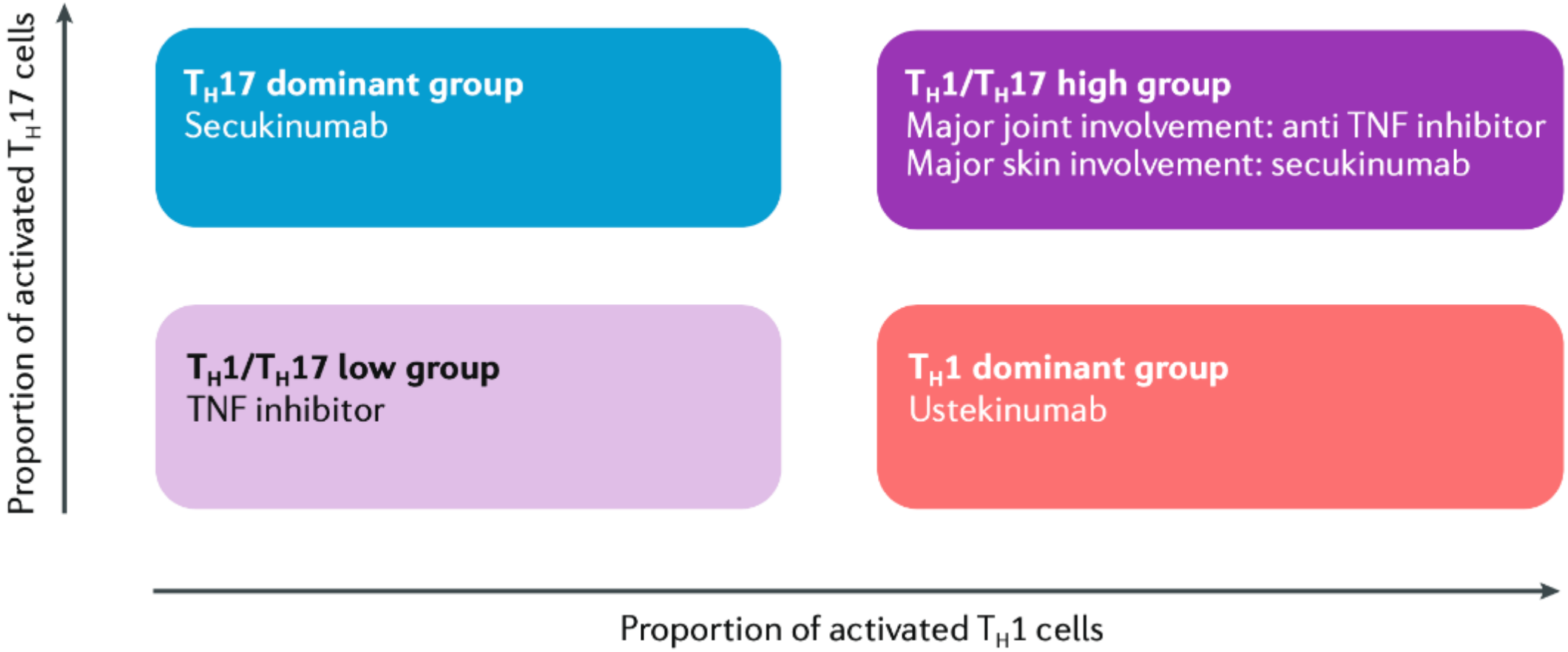
https://www.theguardian.com/travel/2016/sep/30/wild-climbing-the inaccessible-pinnacle-cuillin-isle-of-skye
https://www.economist.com/1843/2019/07/15/riding-on-the-edge

Differential immune signatures in psoriatic skin and synovium



Nerviani A, Boutet M-A, Tan WSG, *et al*. *Ann Rheum Dis* 2021;**80**:591–597

Use of blood T cell subsets to predict biologic response rates in PsA?

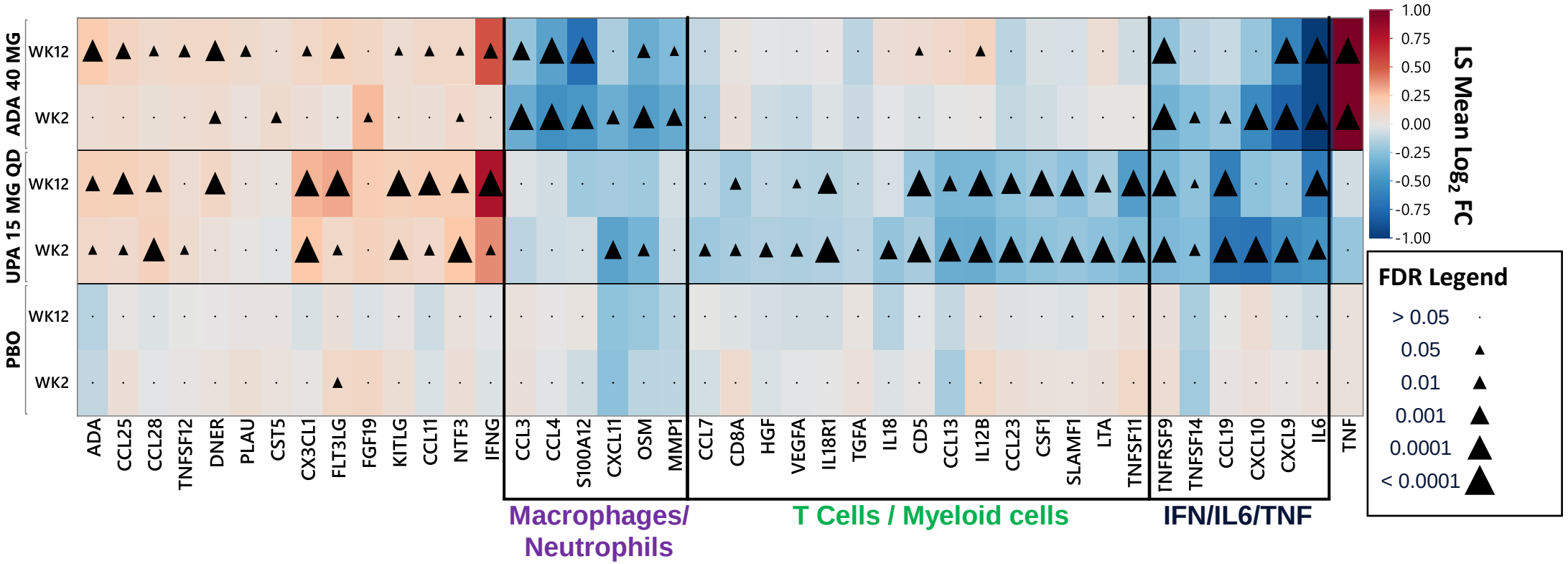


Al-Mossawi H , Coates L Nature Reviews Rheum (2018). https://doi.org/10.1038/s41584-018-0043-3
Referring to: Miyagawa I et al *Rheumatology* 2019;58:336-344

.

Treatment with UPA and ADA in non-biologic-DMARD-IR PsA patients using proteomics to separate repsonses?

- **UPA** down modulated biomarkers associated with **T cells** and **myeloid cells** - not observed with **ADA**
- **ADA** down modulated biomarkers associated with **Macrophages and neutrophils** - not observed with **UPA**



Sornasse T et al, McInnes IB EULAR, 2-5 June 2021

In the absence of biomarkers, decisions should at the least be tissue domain driven…

No axial disease
Severe skin
IBD
Infrequent injections

IL-12/23i

All six domains
No IBD
Demyelination
Severe skin

IL-17i

No axial disease
Severe skin
Long response

IL-23i

TNFi

Longest data
All six domains
Moderate/severe skin
IBD/uveitis

JAKi

Oral
Mild/mod skin
All six domains
IBD
Itch

i, inhibitor; IBD, inflammatory bowel disease; IL, interleukin; JAK, Janus kinase; TNF, tumour necrosis factor.

Towards precision medicine in SpA?

Strategic revolution?

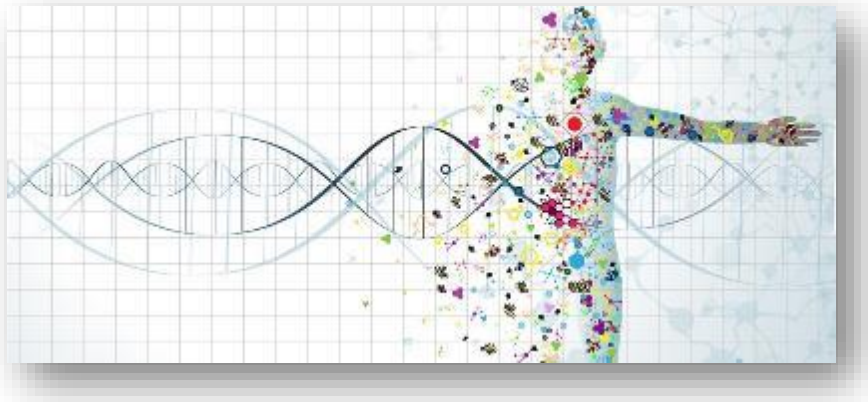
– aiming for remission and cure

Therapeutic application trialled?

– rational combination, precision selection, tissue focussed

Underlying pathogenesis sufficiently defined?

– genetics, epigenetics, blood & tissue analyses

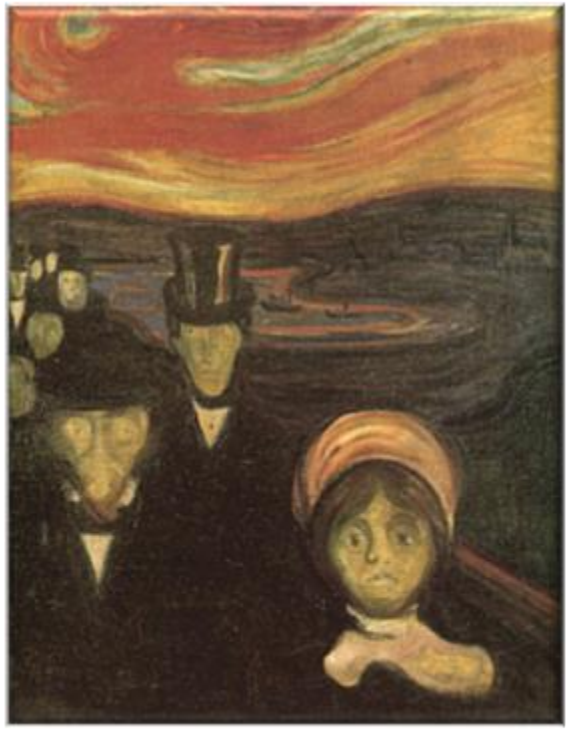


A holistic approach to PsA…

using drugs as molecular scalpels will eventually allow us to treat the whole person!

Diagnosis…
Guidelines
Patient focused

Special consideration:
Vascular
Metabolic syndrome



QoL
Participation
Psychologic *dysfunction*

Edvard Munch 1863-1944

Are we ready for ‘pathology-based’ precision in inflammatory arthritis?

I revert to the Scottish Legal System

- Guilty
- Not guilty
- Not proven

https://theconversation.com/scotlands-not-proven-verdict-helps-juries-communicate-their-belief-of-guilt-when-lack-of-evidence-fails-to-convict-108286