WORKSHOP

Πώς μπορούμε να αναπτύξουμε μια εξατομικευμένη στρατηγική αντιμετώπισης σε ασθενείς με Ψωριασική Αρθρίτιδα;

Γκ. Κατσιφής MD, PhD, RhMSUS
Διευθυντής Ρευματολογικής Κλινικής
Ναυτικού Νοσοκομείου Αθηνών

Γεώργιος Φραγκούλης
Ρευματολόγος, Επίκ Καθηγητής
Παθολογίας-Ρευματολογίας, Ιατρική Σχολή ΕΚΠΑ,
Α' Προπαιδευτική Παθολογική Κλινική, ΓΝΑ «ΛΑΪΚΟ»

Καλαμάτα, 1 Ιουνίου 2024

JAKa-GR-00268-E |May 2024

Disclosures

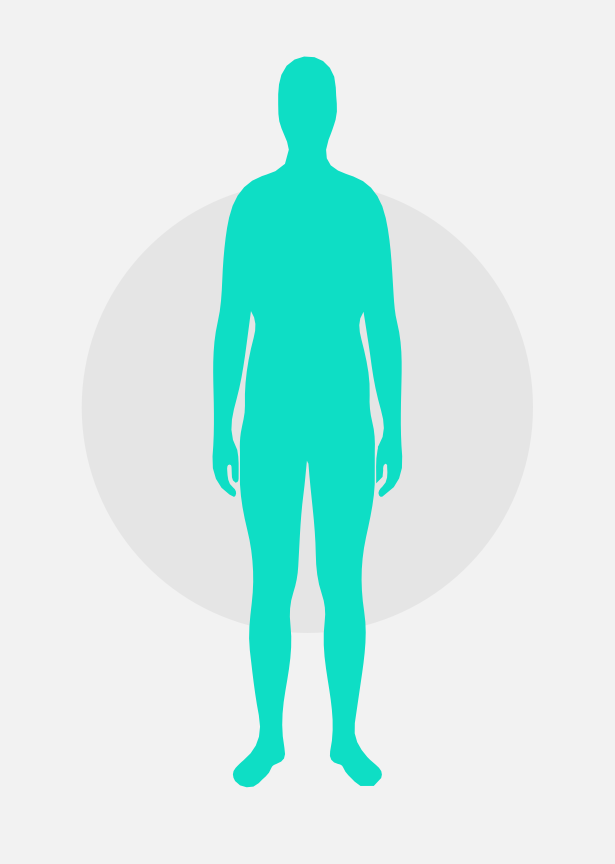
Τιμητική αμοιβή από την AbbVie για τη συμμετοχή σε αυτήν την εκδήλωση

Εκπαιδευτικές-ερευνητικές-συμβουλευτικές επιχορηγήσεις την τελευταία διετία:

Γκ. Κατσιφής: Abbvie, Aenorasis, Amgen, Celgene, Janssen, Genessis, Lilly, MSD, Novartis, Sobi, Roche, Pfizer, UCB

Γ. Φραγκούλης: Janssen, UCB, Novartis, Aenorasis, Amgen, Pfizer, Genesis

Περίπτωση #1



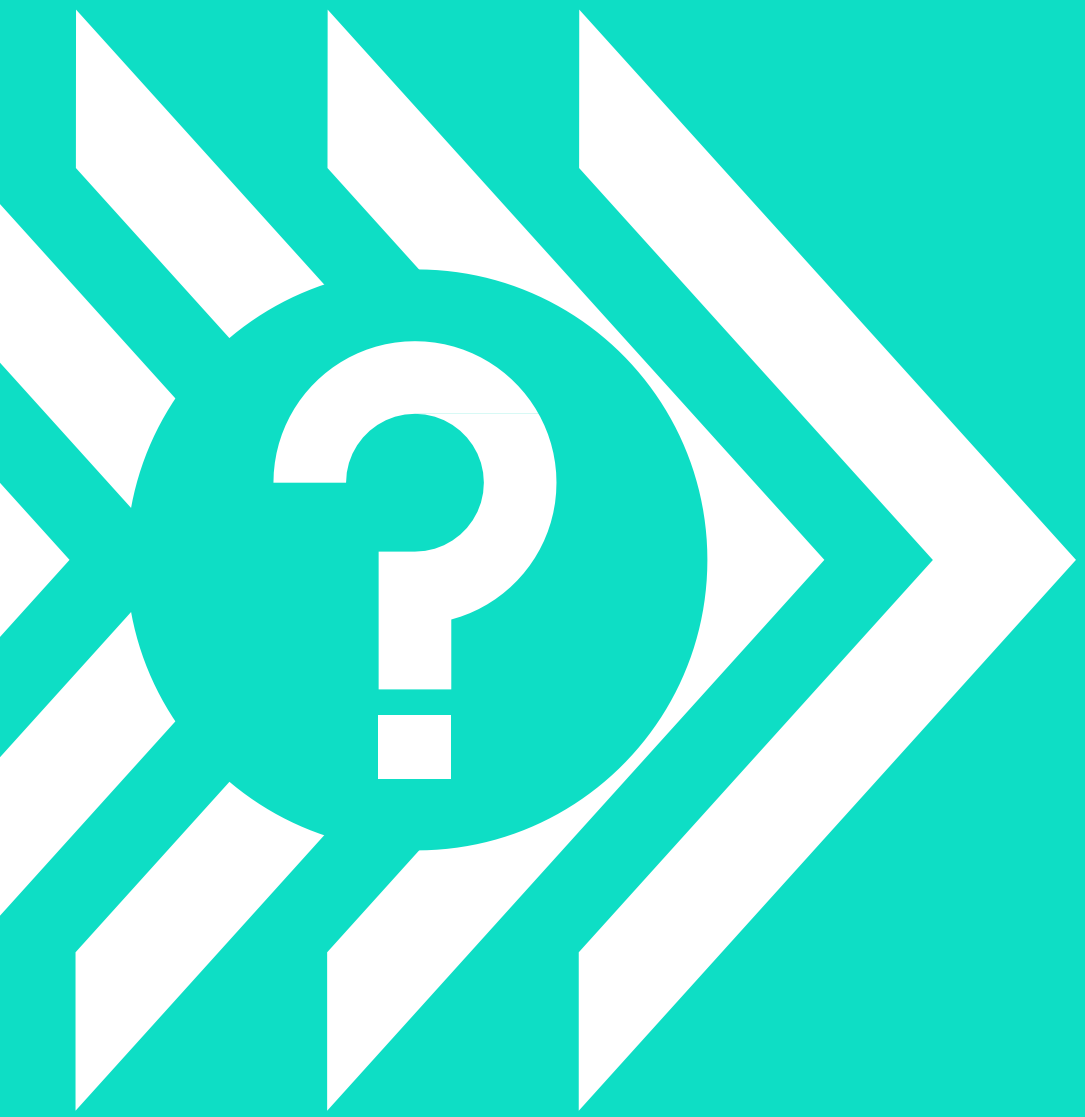
Άνδρας 52 ετών

BMI: 30.8 kg/m2

Κλινικά χαρακτηριστικά		
CRP (mg/L)		**7**
TKE		**30**
TJC/SJC (68/66)		**16/12**
PASI		**4.4**
BSA		**3**
Patient global assessment	(VAS 100 mm)	**75**
Pain VAS (100 mm)		**80**
HAQ-DI		**1.8**
DAS28-CRP		**5.9**
Μικροσκοπική κολίτιδα		

Προηγηθείσα θεραπεία: Ανεπαρκής ανταπόκριση σε MTX 17,5mg/w

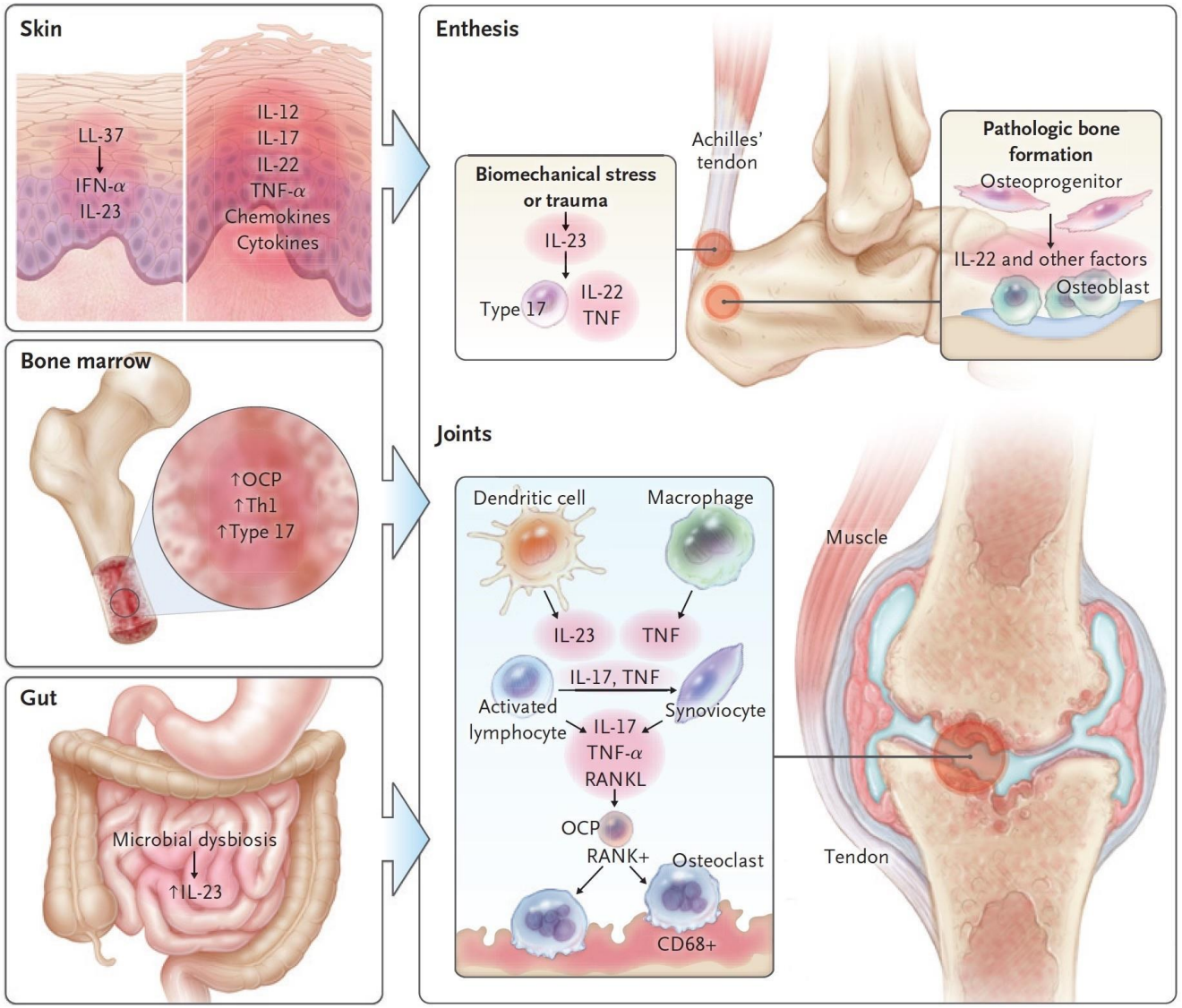
Θεραπευτική αντιμετώπιση Περιστατικού



<u>Προσθήκη</u>

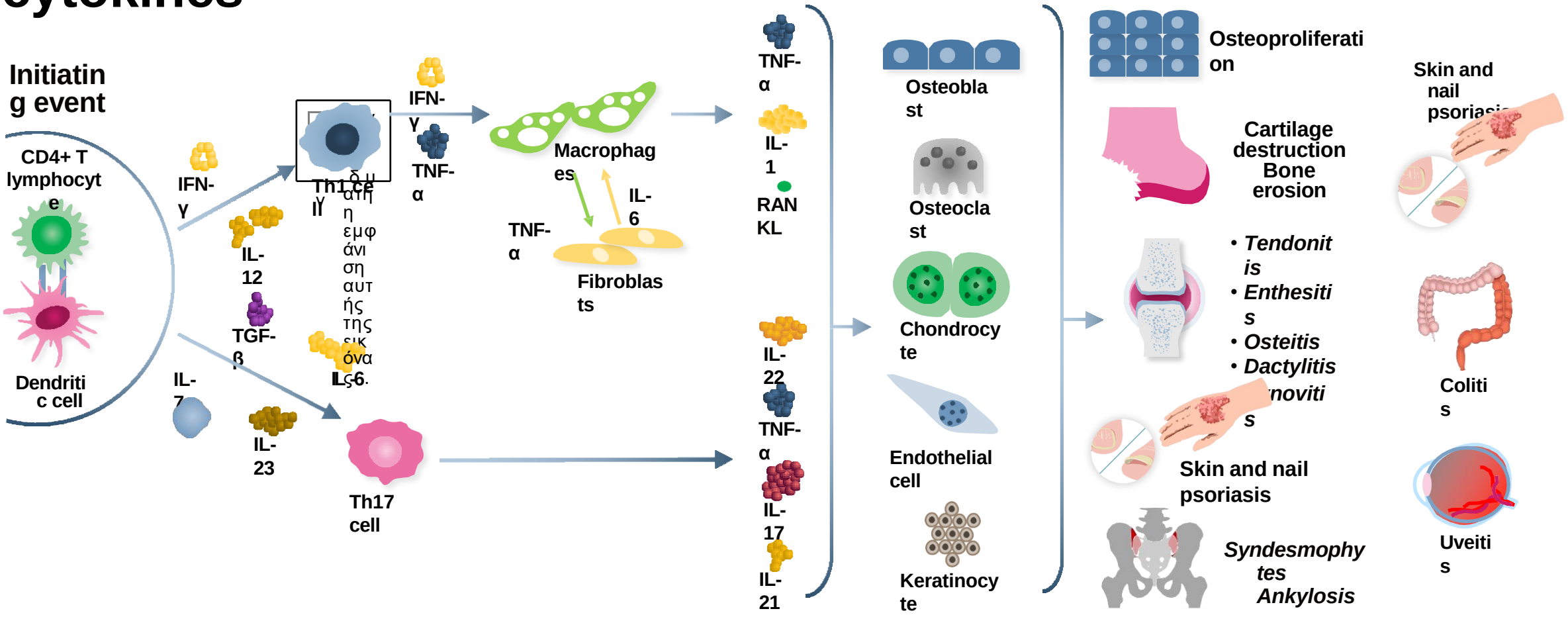
1. **Anti-IL17**
2. **Anti-IL12/23**
3. **JAK inhibitor**
4. **PDE4 inhibitor**
5. **Anti-TNFα**

Pathogenic Pathways in Psoriatic Arthritis



Ritchlin et al NJM 2017

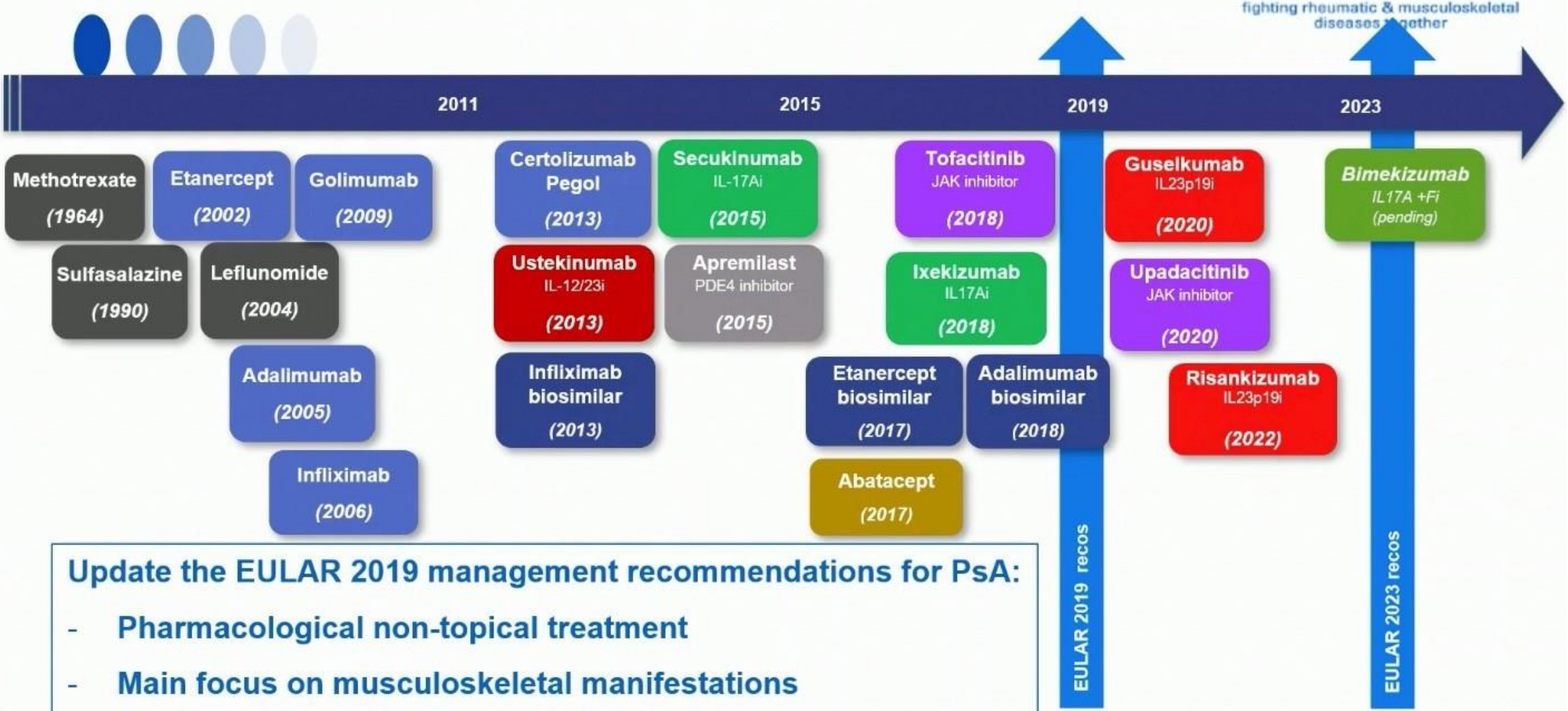
Pathogenic pathways in SpA are directly and indirectly mediated by JAK-dependent cytokines



Coates LC et al. Semin Arthritis Rheum 2016 Lories RJ. Best Pract Res Clin Rheumatol 2018 Furst DE et al. Arthritis Res Ther 2019 Gravallese EM et al. Nat Rev Rheumatol 2018 Ritchlin CT et al. N Engl J Med 2017
Veale DJ et al. Lancet 2018
van Praet L et al. Nat Rev Rheumatol 2012
Schwartz DM et al. Nat Rev Rheumatol 2016

Timeline: PsA recommendations and drugs

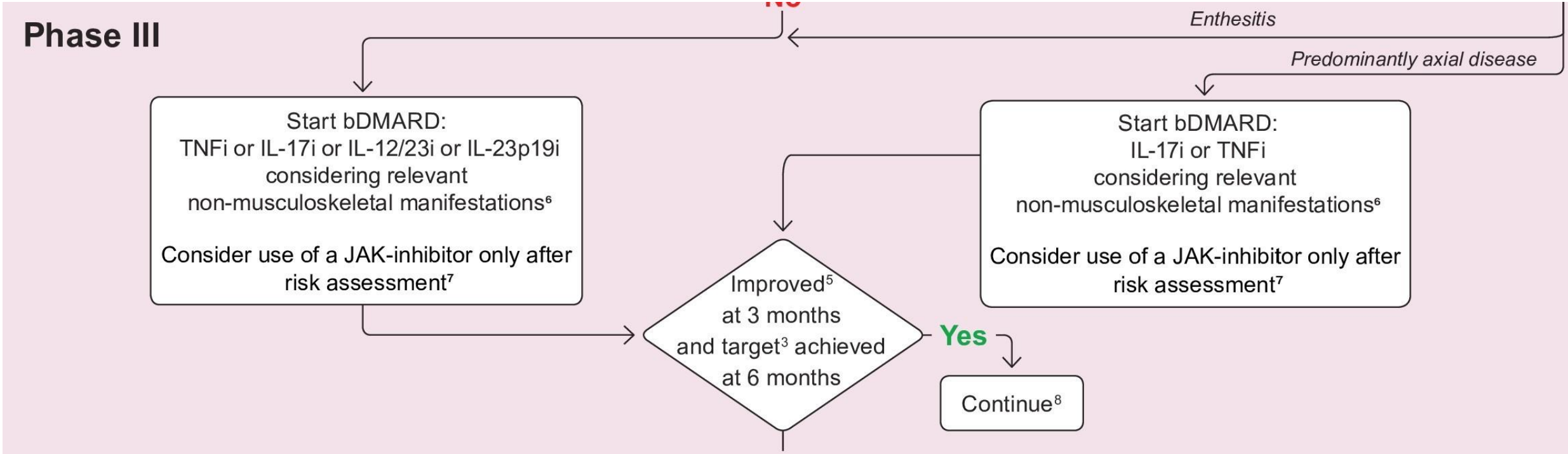
eular
fighting rheumatic & musculoskeletal diseases together



Update the EULAR 2019 management recommendations for PsA:

- Pharmacological non-topical treatment
- Main focus on musculoskeletal manifestations
- Decisions based on the data: balance efficacy/safety

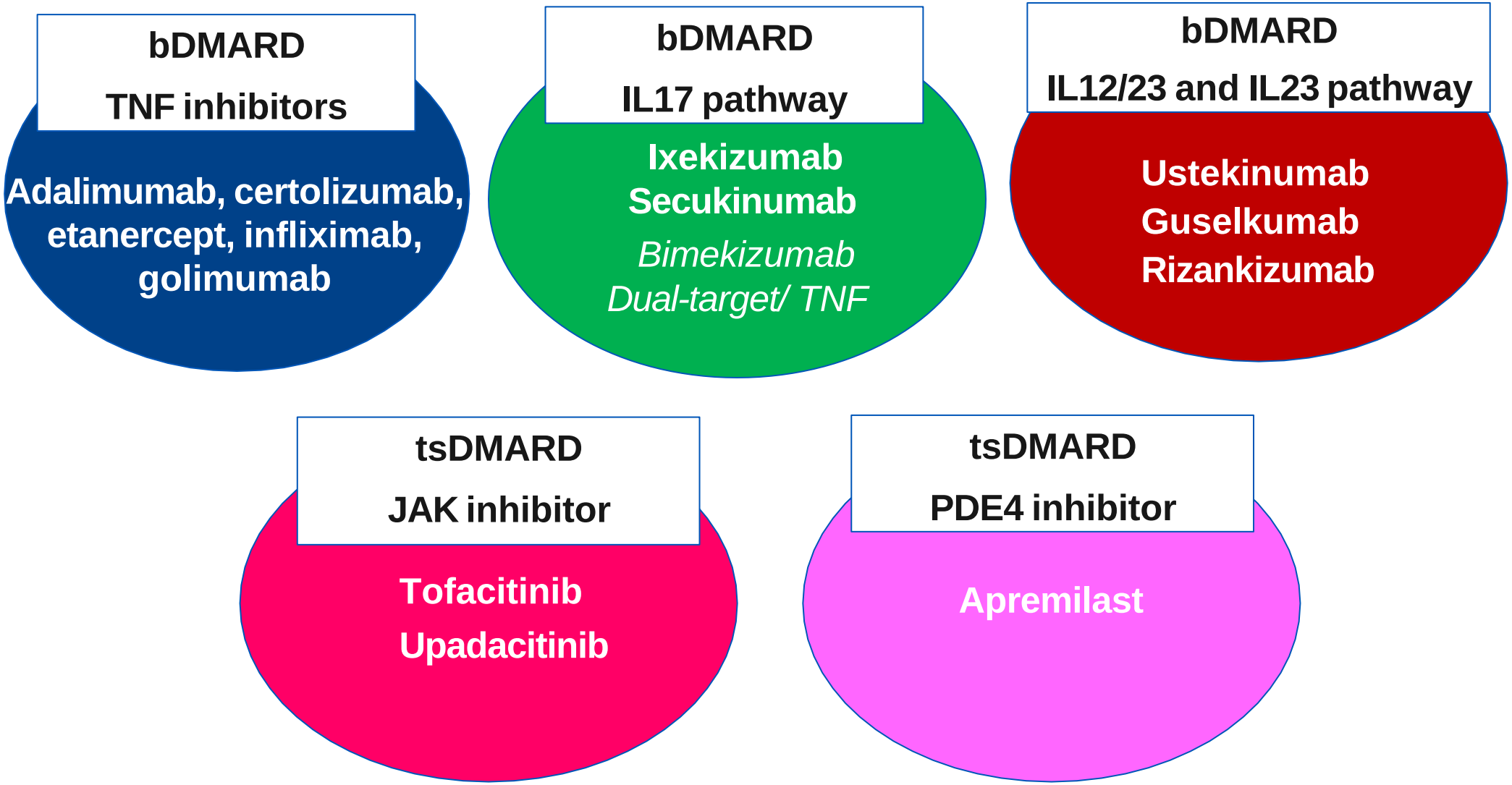
Italics: drug not approved as of June 2, 2023



*For JAKis, caution is needed for patients aged 65 years or above, those who are current or past long-time smokers, with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors or with other malignancy risk factors, and with known risk factors for venous thromboembolism.

Gossec L. et al ARD 2024

Drugs on top of conventional synthetic ones in PsA



Περιφερική αρθρίτιδα

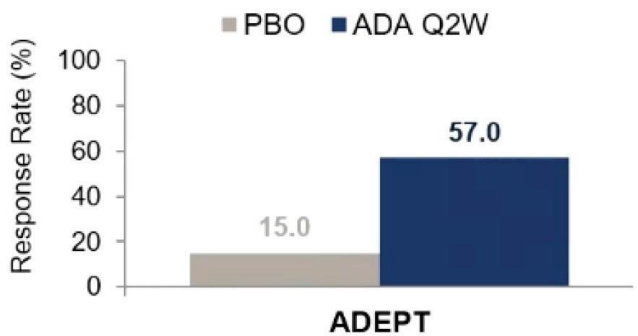
TNF Inhibitors in PsA: Summary of Key Data From Placebo-Controlled Phase 3 Trials

Agent (Route)/Dosing Regimen Evaluated	ACR 20 (week 24)	ACR 50 (week 24)	ACR 70 (week 24)	PASI 75 (week 24)	Common Side Effects[2]
Adalimumab (SC) 40 mg every 2 weeks	57%	39%	23%	59%	Injection-site reactions, infections
Certolizumab pegol (SC) 400 mg at weeks 0, 2 and 4; then 200 mg every 4 weeks*	64%	44%	28%	62%	Injection-site reactions, infections
Etanercept (SC) 25 mg twice weekly†	59%‡	NR	NR	23%	Injection-site reactions, infections
Golimumab (SC) 50 mg every 4 weeks	52%	NR	NR	56%	Injection-site reactions, infections
Infliximab (IV) 5 mg/kg at weeks 0, 2, 6; then every 8 weeks	54%	41%	27%	60%	Infusion reactions, infections

1. D'Angelo S et al. Open Access Rheumatol. 2017;9:21-28;
2. Gladman D, et al. N Engl J Med. 2017;376(10):957-970.

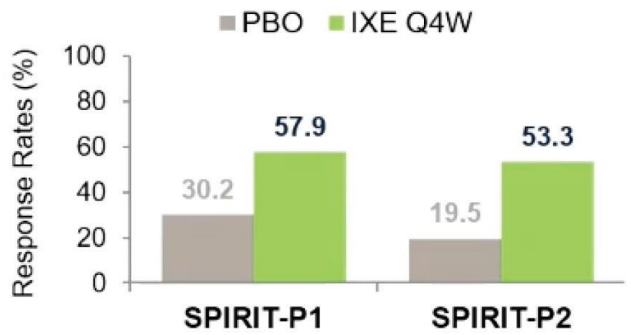
Overview of ACR20 responses with bDMARDs at week 24 in major randomized controlled trials

TNFi: Adalimumab[1]

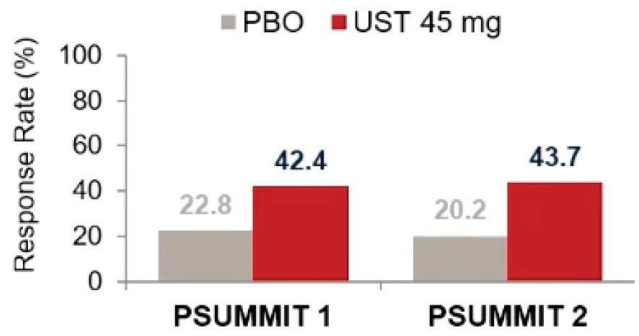


IL17i: Secukinumab[2]

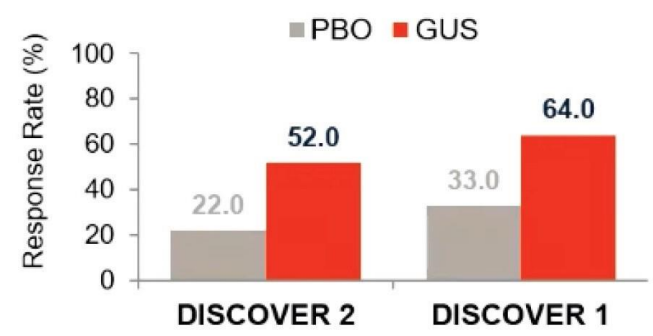
IL17i: Ixekizumab[8]



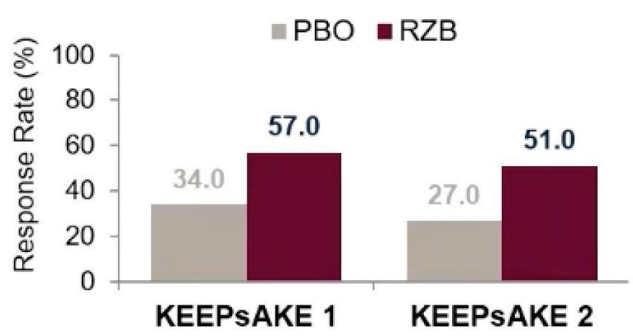
IL12/23i: Ustekinumab[3,4]



IL23p19i: Guselkumab[9,10]



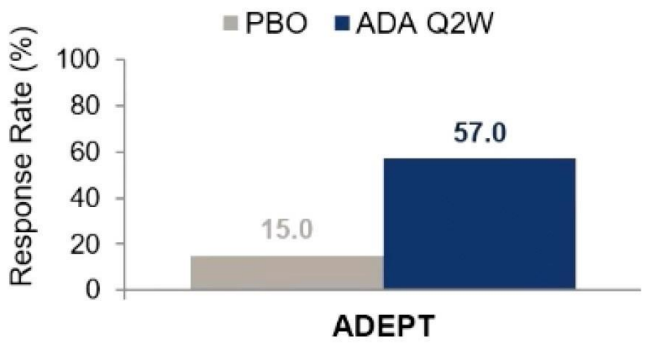
IL23p19i: Risankizumab[11–14]



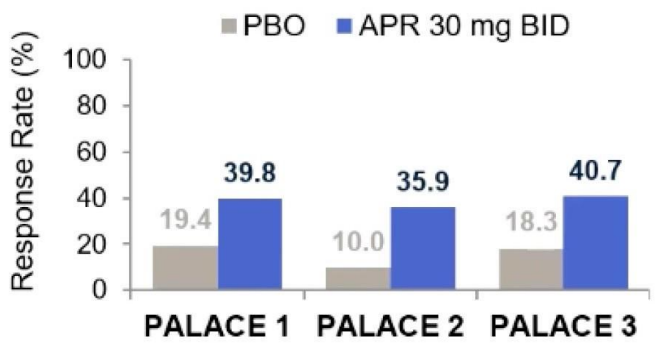
1. Mease PJ, et al. Arthritis Rheum. 2005;52(10):3279-3289. 2. Mease P, et al. Rheumatol Ther. 2016;3(1):5-29. 3. McInnes IB, et al. Lancet. 2013;382(9894):780-789. 4. Ritchlin C, et al. Ann Rheum Dis. 2014;73(6):990-999. 5. Kavanaugh A, et al. Ann Rheum Dis. 2014;73(6):1020-1026. 6. Cutolo M, et al. J Rheumatol. 2016;43(9):1724-1734. 7. Edwards CJ, et al. Ann Rheum Dis. 2016;75(6):1065-1073. 8. Kerschbaumer A, et al. Ann Rheum Dis. 2020;79(6):778-786. 9. Deodhar A Lancet 2020; 10. Mease PJ. et al. Lancet. 2020;395(10230):1126-1136; 11. Kristensen LE et al. Ann Rheum Dis. 2022. 81:225-231; 12. O stor A et al. Ann Rheum Dis. 2022. 81:351-358; 13. Kristensen LE, et al. Ann Rheum Dis 2021;80:1315–6; 14. Kristensen LE, et al. Oral presentation D1T01 4 presented at the 30th European Academy of Dermatology and Venereology Congress, 29 September–2 October2021, EADV Virtual congress

Overview of ACR20 responses with tsDMARDs at week 24 in major randomized controlled trials

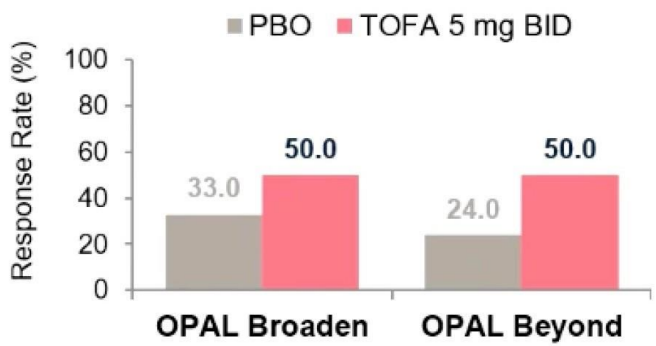
TNFi: Adalimumab[1]



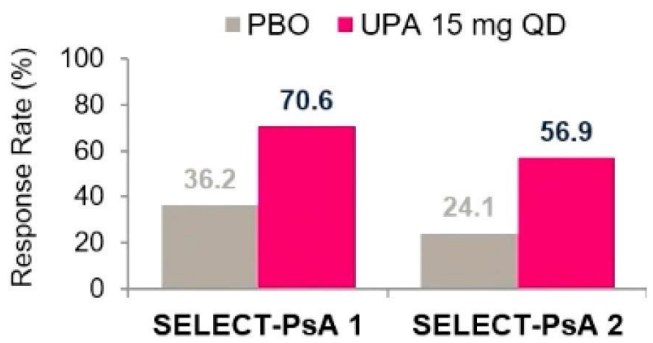
PDE4i: Apremilast at week 16[2–4]



JAKi: Tofacitinib[5, 6]



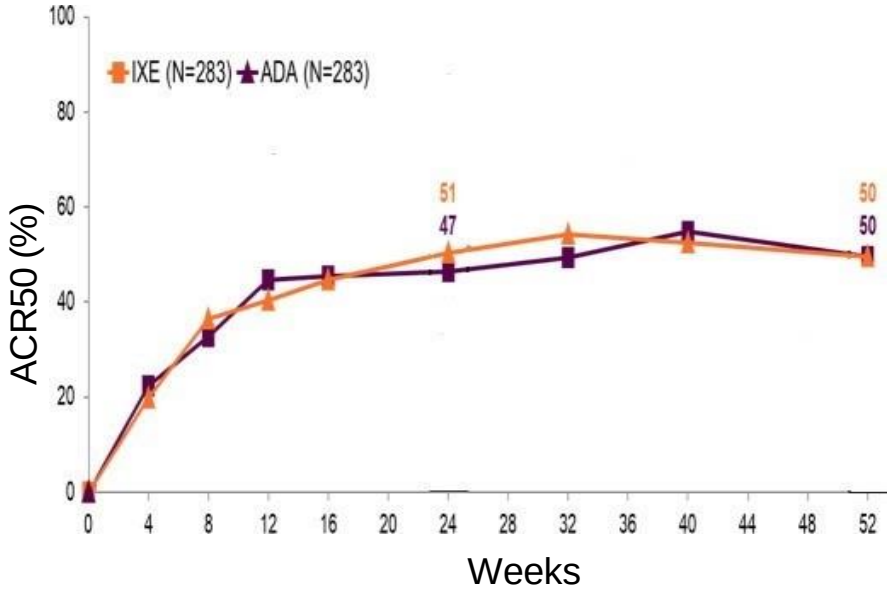
JAKi: Upadacitinib at week 12[7,8]



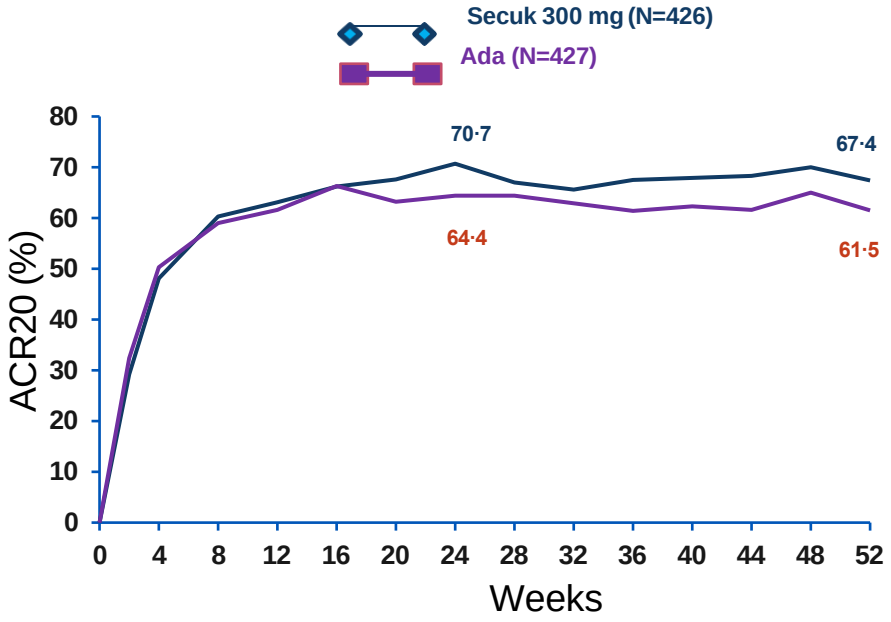
1. Mease PJ, et al. Arthritis Rheum. 2005;52(10):3279-3289. 2. Kavanaugh A, et al. Ann Rheum Dis. 2014;73(6):1020-1026; 3. Cutolo M, et al. J Rheumatol. 2016;43(9):1724-1734. 4. Edwards CJ, et al. Ann Rheum Dis. 2016;75(6):1065-1073; 5, Mease P. et al. N Engl J Med 2017; 377:1537-1550; 6. Gladman D et al. N Engl J Med 2017; 377:1525-1536; 7. McInnes IB et al. N Engl J Med 2021;384(4):1227–1239; 8. Mease PJ, et al. Ann Rheum Dis. 2021;80:312-320.

2 head-to-head trials, IL-17Ai vs adalimumab (PsA): similar efficacy on joints

SPIRIT H2H: ixekizumab vs adalimumab,
%ACR50 at 1 year

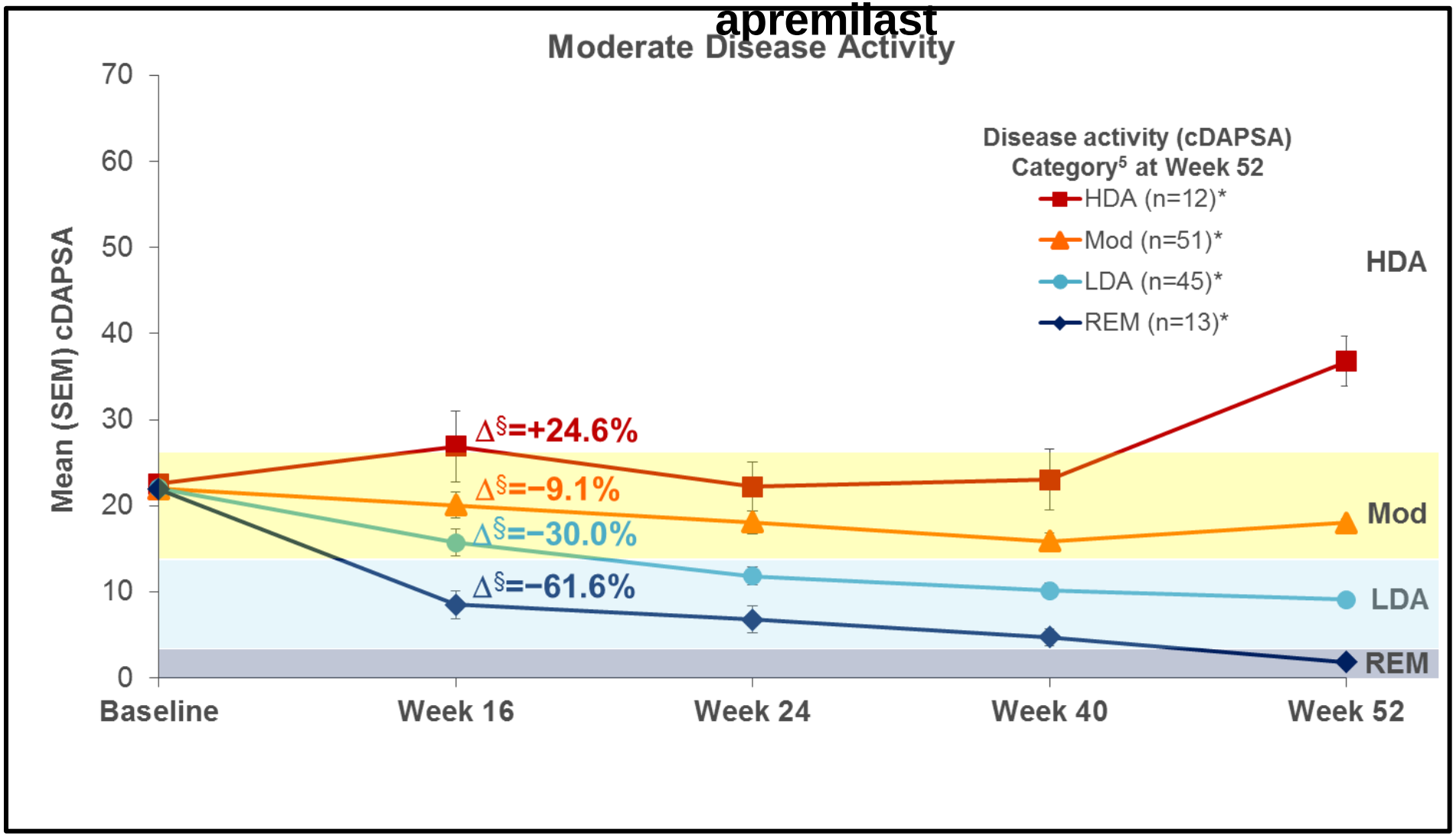


EXCEED: secukinumab vs adalimumab,
%ACR20 at 1 year



Smolen JS, et al. Ann Rheum Dis. 2020 Jan
McInnes I et al, Lancet. 2020 May

Μεταξύ ασθενών με μέτρια ενεργότητα νόσου (Mod) κατά την έναρξη, μέση βελτίωση ≥30% έως την εβδομάδα 16 συσχετίστηκε με την επίτευξη των θεραπευτικών στόχων την εβδομάδα 52 με apremilast



Mease PJ. et al., Arthritis Care & Research. 2020

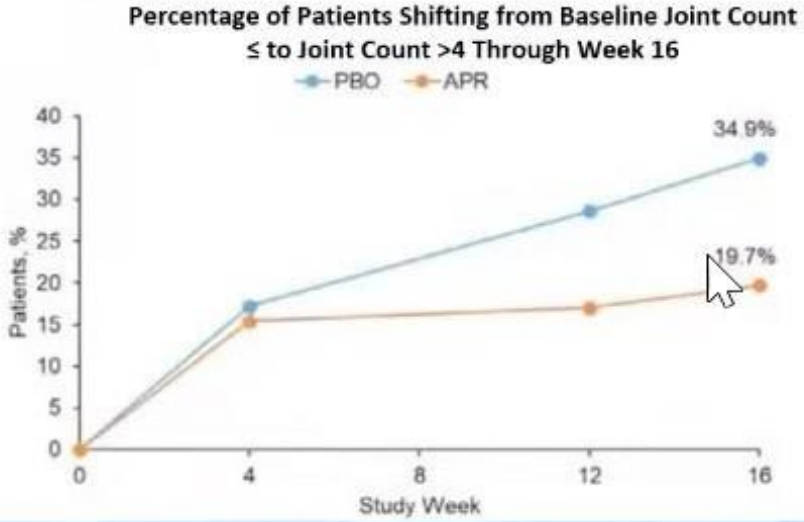
16w Results from a Placebo-Controlled Study Involving Oligoarticular Psoriatic Arthritis Treated with Apremilast

Background

- FOREMOST (NCT03747939) is a phase 4, multicenter, randomised, double-blind, placebo (PBO)-controlled, parallel-group study examining the safety and efficacy of APR in oligoarticular PsA (defined as 2–4 swollen and 2–4 tender joints [2–8 active joints]), using a modified minimal disease activity score (MDA-Joints)
- Patients were randomised 2:1 to APR or placebo (PBO) for 24 weeks, with an early escape at week 16. The primary endpoint was defined as the proportion of patients achieving MDA-Joints at week 16

Key results

- In the overall population, MDA-Joints response was achieved by significantly more patients with APR (33.9%) vs PBO (16.0%) at week 16
- cDAPSA REM/LDA was achieved in 70.2% of APR patients versus 51.8% in PBO patients at week 16
- In patients with 2–4 joints involved at baseline, there was an increase in the proportions of patients who switched to a joint count >4 through Week 16 among those receiving PBO but not among those receiving APR
- No new safety signals were identified

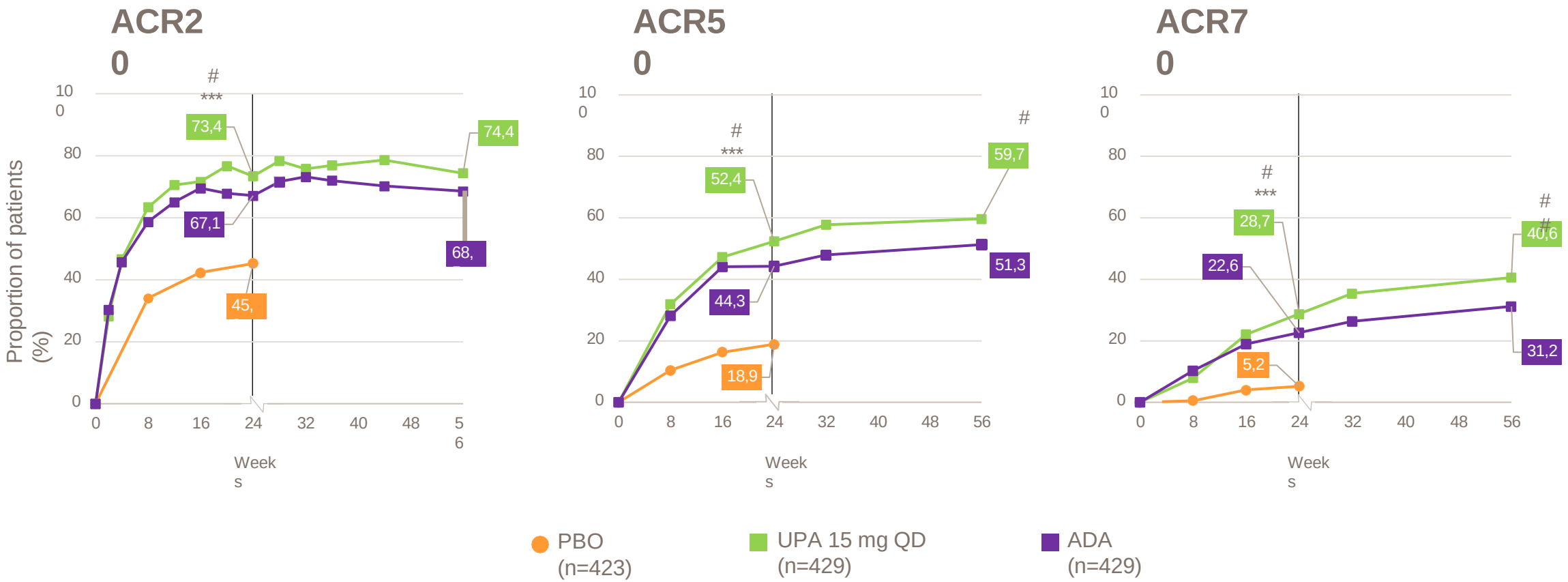


FOREMOST, the first global randomised controlled trial in oligoarticular PsA, demonstrated superior disease control with APR versus PBO at 16 weeks, measured by MDA-Joint response

APR, apremilast, cDAPSA, clinical Disease Activity Index for Psoriatic Arthritis; LDA, low disease activity, MDA, minimal disease activity PBO, placebo; PsA, psoriatic arthritis

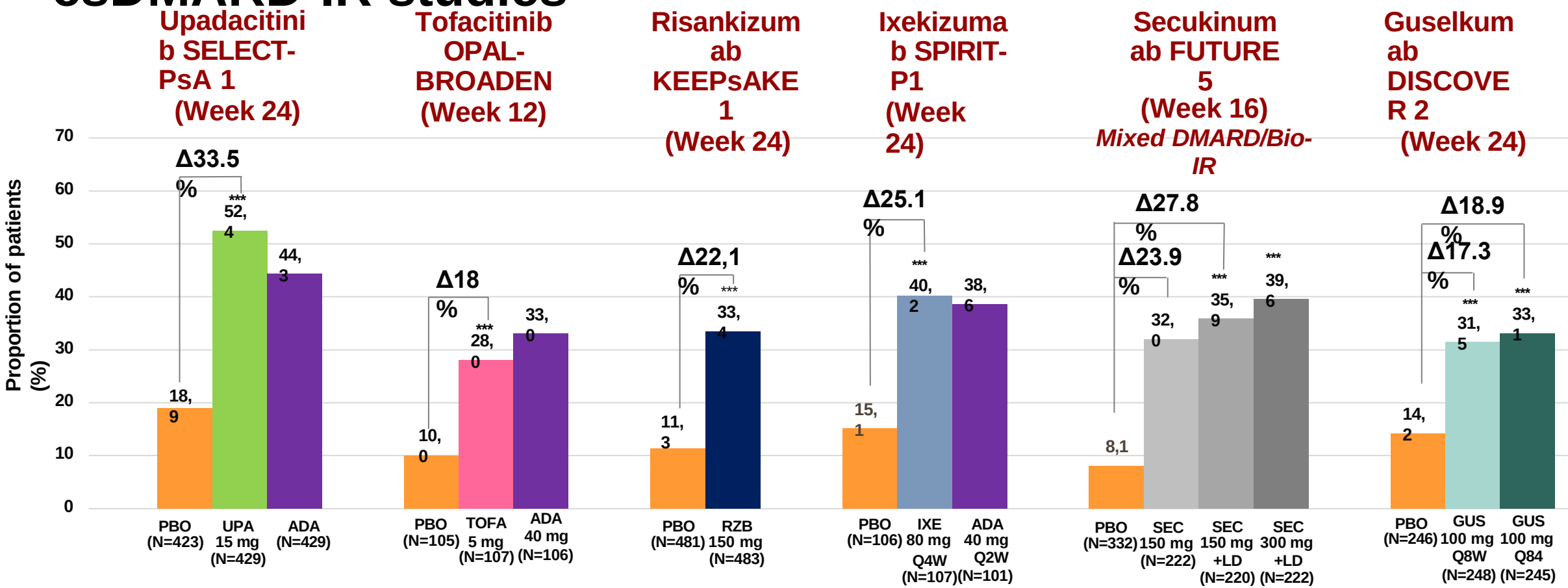
1. Kivitz, A et al. ACR 2023. Abstract 0776

ACR20/50/70 responses with upadacitinib over time through Week 56



1. McInnes IB et al. N Engl J Med 2021
2. McInnes IB et al. Ann Rheum Dis 2020

IL-17, IL-23 and JAK inhibitors in PsA: ACR50 responses in csDMARD-IR studies

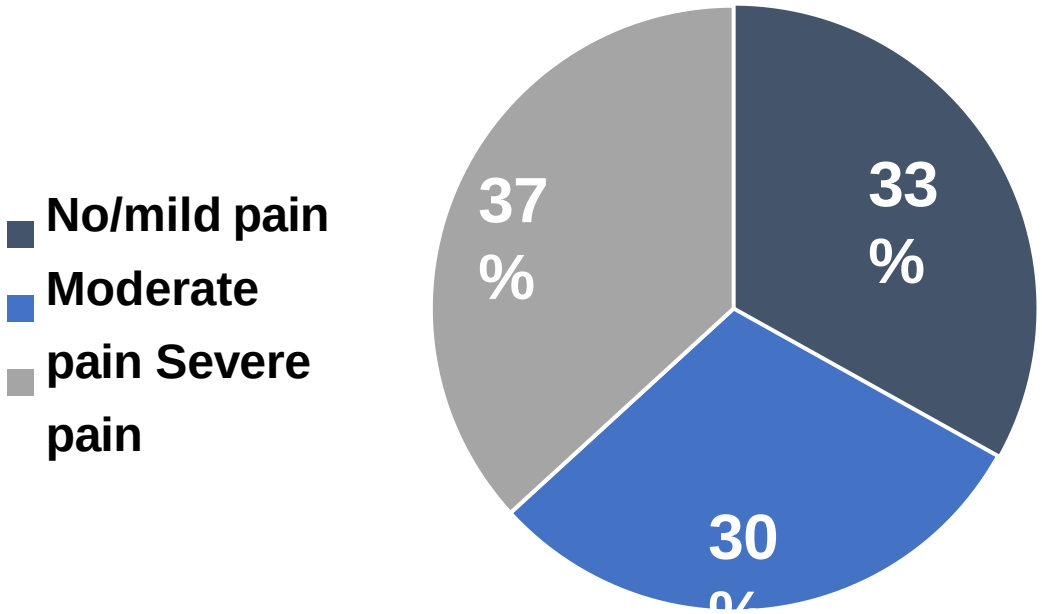


Direct comparisons are not appropriate as data are not from H2H trials.

1. McInnes IB et al. N Engl J Med 2021;384(4):1227–1239; 2. Mease P et al. N Engl J Med 2017;377:1537–1550; 3. Kristensen LE, et al. Ann Rheum Dis 2021;80:1315–1316; 4. Mease PJ et al. Ann Rheum Dis. 2017;76:79–87;
5. Mease P et al. Ann Rheum Dis. 2018;77:890–897;
6. Mease PJ, et al. Lancet 2020;395:1126–1136.

Two-thirds of PsA pts (n=782) reported experiencing moderate or severe bodily pain despite treatment with biologics

- Cross-sectional survey data from rheumatologists and dermatologists (specialists) treating PsA and their patients in 13 countries spanning the Americas, Asia Pacific, EU, Turkey, and the Middle East
- **782 patients with PsA** receiving biologic treatment (mainly anti-TNF) for ≥3 months who completed SF-36 questionnaires

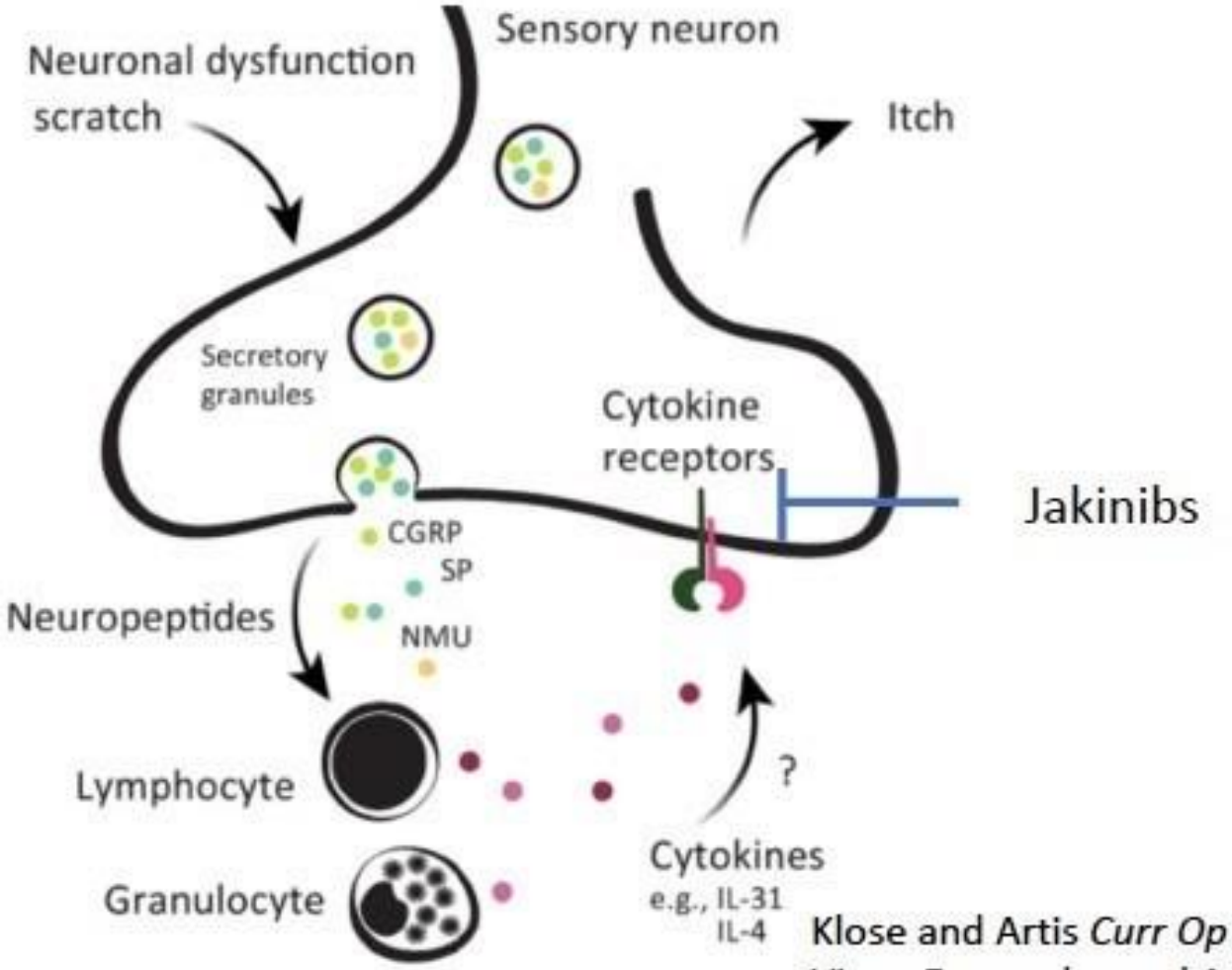


- ✓ The level of HRQoL impairment assessed by SF-36 domains among PsA patients significantly increased as pain increased (p<0.0001)
- ✓ Severe pain in patients with PsA was associated with greater disability (higher HAQ-DI scores), and greater activity impairment, overall work impairment, work time missed and impairment while working (all p<0.0001)

- Pain was evaluated as SF-36 bodily pain domain tertiles: BP >75–100 = mild/no pain; BP >52–≤75 = moderate pain; 0–≤52 severe pain
- HAQ-DI, Health Assessment Questionnaire-Disability Index; HRQoL, health-related quality of life; PsA, psoriatic arthritis; SF-36, Short Form 36 Health Survey Questionnaire; TNF, tumor necrosis factor

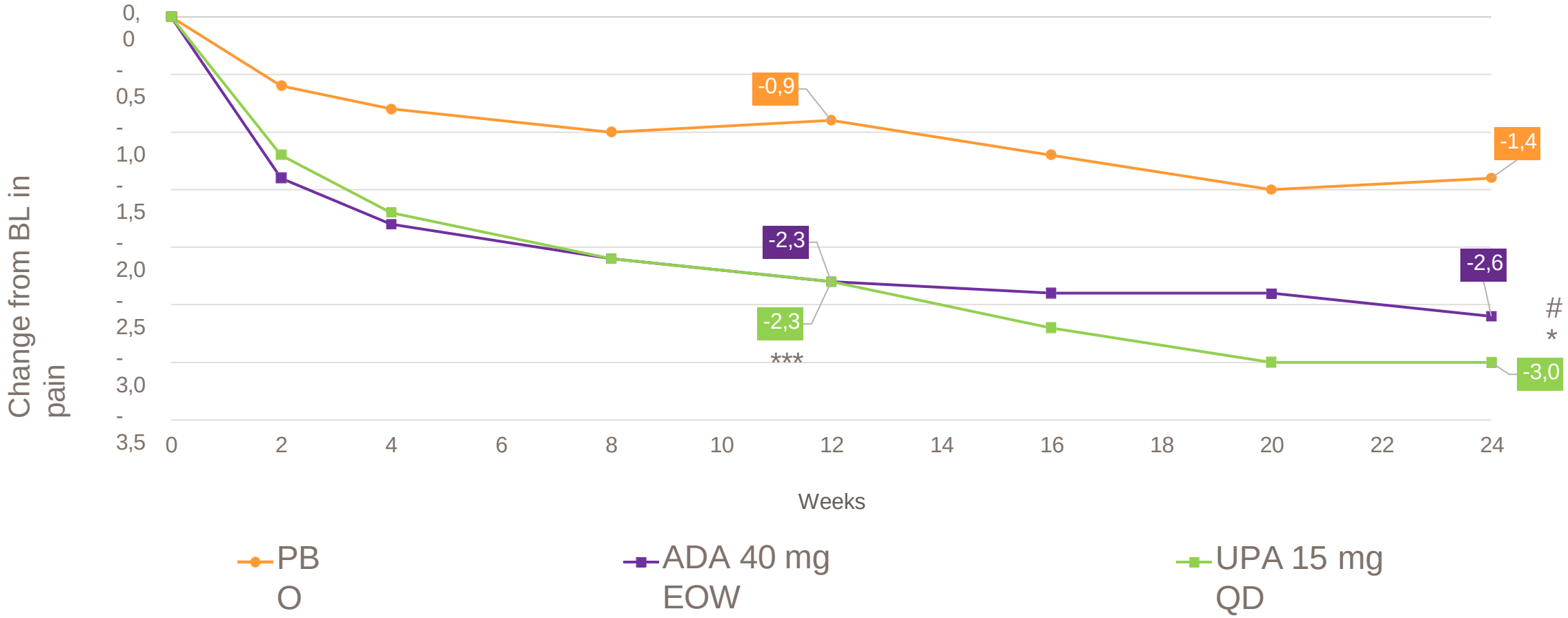
Conaghan PG et al. Ann Rheum Dis 76 (Suppl 2)

Jakinibs and Cytokines in Pain: Neural Immune Crosstalk



Klose and Artis *Curr Op Immunol* 2019
Viega-Fernandes and Artis *Science* 2018
Trier and Kim, *Curr Op Immunol* 2018
Mack and Kim *Trends Immunol* 2018
Oetjen LK et al, Cell 2017

Patient’s assessment of pain (NRS) through Week 24



1. McInnes IB et al. N Engl J Med 2021
2. McInnes IB et al. Ann Rheum Dis 2020

Ψωριασικό εξάνθημα

TNF Inhibitors in PsA: Summary of Key Data From Placebo-Controlled Phase 3 Trials

Agent (Route)/Dosing Regimen Evaluated	ACR 20 (week 24)	ACR 50 (week 24)	ACR 70 (week 24)	PASI 75 (week 24)	Common Side Effects[2]
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Certolizumab pegol (SC) 400 mg at weeks 0, 2 and 4; then 200 mg every 4 weeks*	64%	44%	28%	62%	Injection-site reactions, infections
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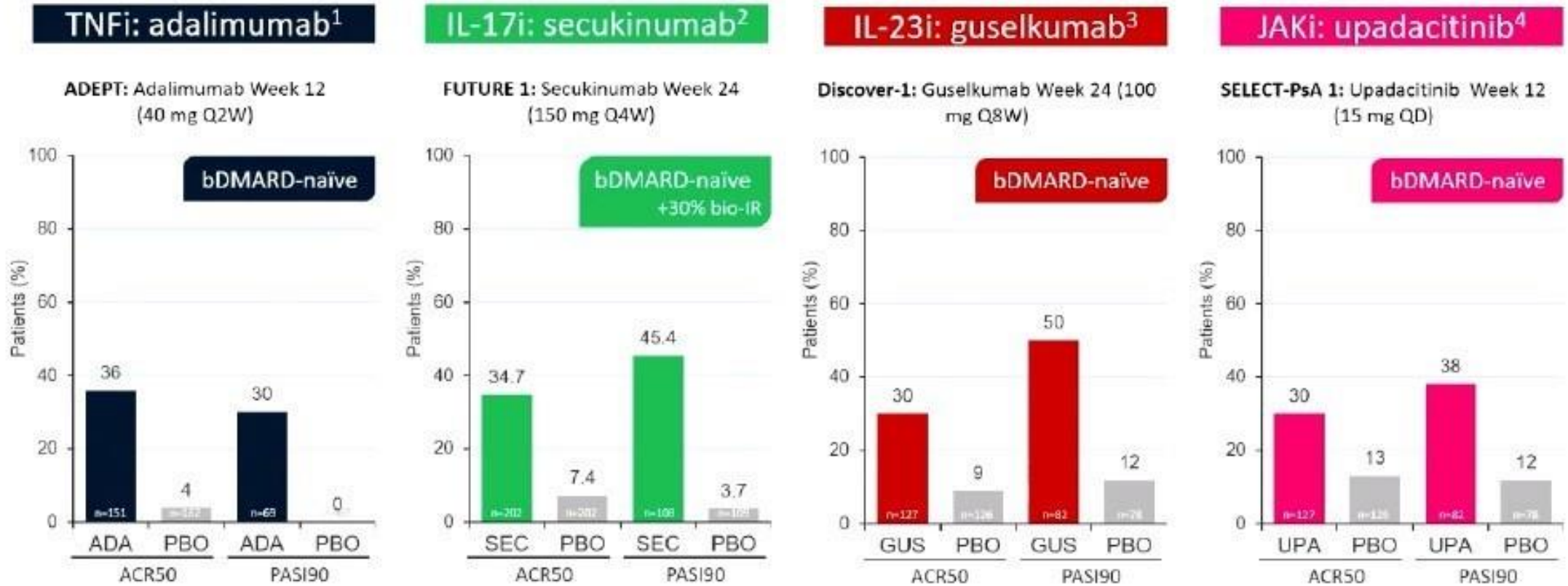
1. D'Angelo S et al. Open Access Rheumatol. 2017;9:21-28;
2. 2. Ritchlin CT et al. N Engl J Med. 2017;376(10):957-970.

Overview of efficacy of some targeted drugs in PsA on joints (ACR50) and skin (PASI90)



Licensed doses for PsA – in major RCTs – not all drugs shown

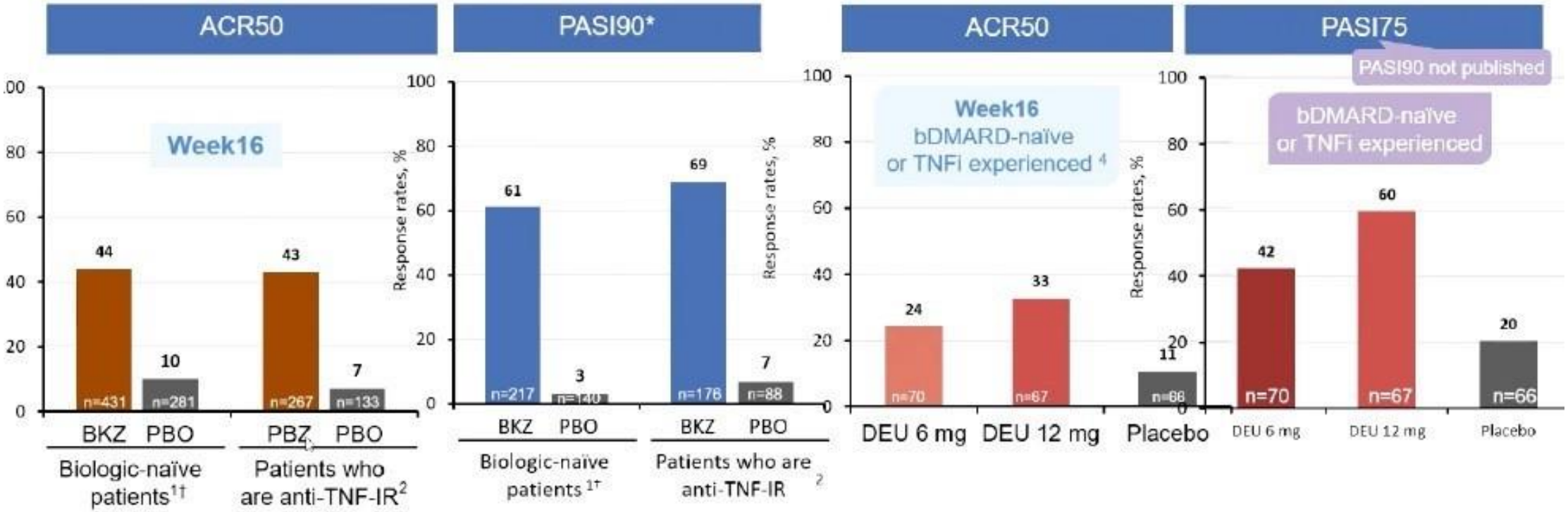
No head-to-head comparisons: Results of individual studies cannot be directly compared, nor conclusions inferred

1. Mease PJ, et al. Arthritis Rheum. 2005;52(10):3279-3289. 2. Mease PJ et al. N Engl J Med 2015; 373:1329-1339; 3. Deodhar A. et al. Lancet 2020;395:1115-1125; 4. McInnes IB et al. N Engl J Med 2021;384(4):1227–1239.

Overview of efficacy of some targeted drugs in PsA on joints (ACR50) and skin (PASI90); drugs not currently licensed

Bimekizumab, IL17 inhibitor (IL-17A & IL-17F)

Deucravacitinib, tsDMARD targeting TYK2

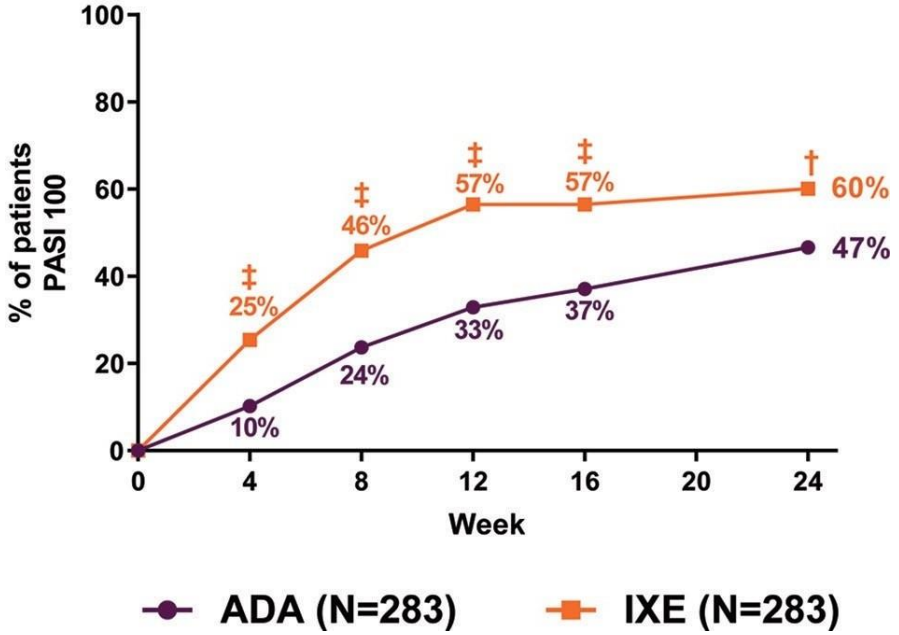


Drugs in clinical development for psoriatic arthritis not currently approved for this indication
No head-to-head comparisons: Results of individual studies cannot be directly compared, nor conclusions inferred

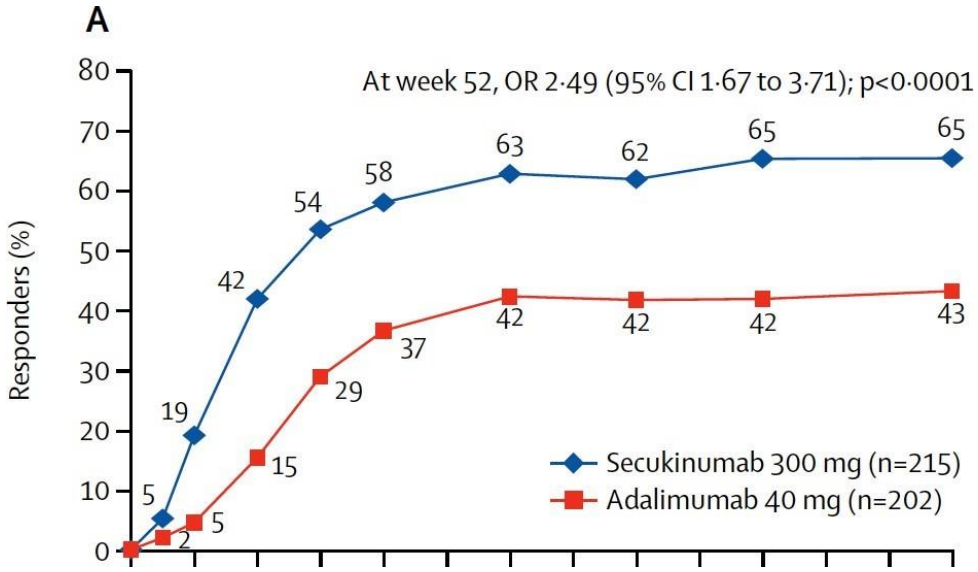
McInnes I, et al. Lancet 2022; Kristensen LE et al. Ann Rheum Dis. 2022 Feb;81(2):225-231. Mease PJ, et al. Ann Rheum Dis 2022;0:1–8. Mease PJ, et al. Ann Rheum Dis 2022;0:1–8

2 head-to-head trials, IL17i vs adalimumab: better efficacy on skin

SPIRIT H2H: ixexizumab vs adalimumab, PASI 100 at 24 w



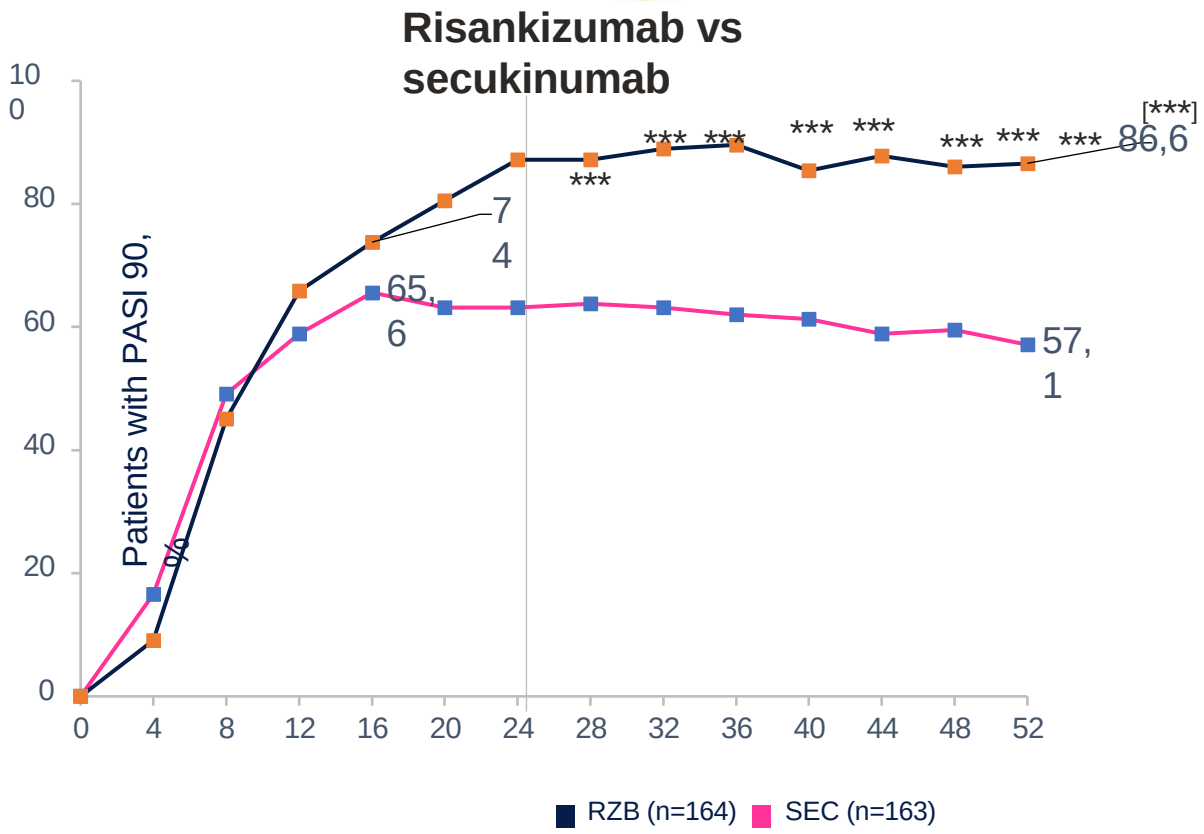
EXCEED: secukinumab vs adalimumab, PASI 90 at 1 year



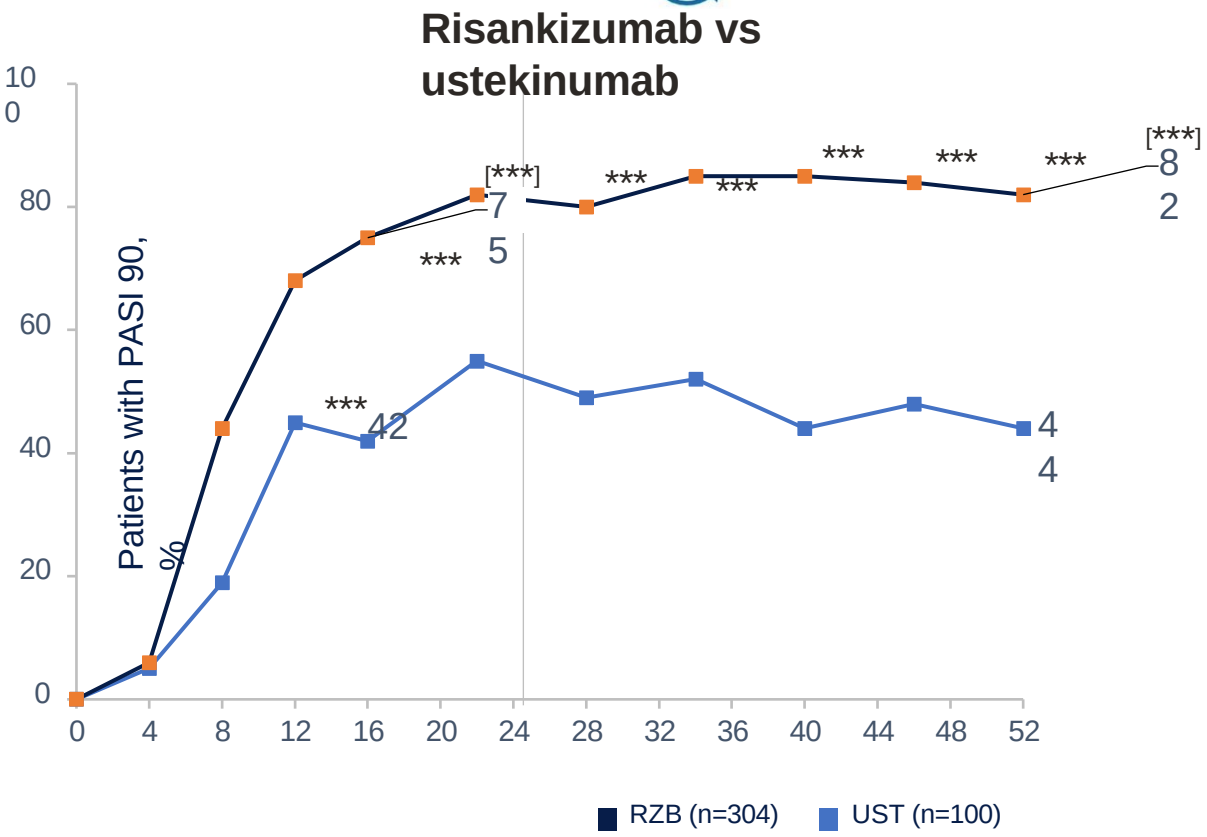
Smolen JS, et al. Ann Rheum Dis. 2020 Jan
McInnes I et al, Lancet. 2020 May

Superior PASI 90 Response of Risankizumab (IL-23i) vs Secukinumab (IL-17i) and Ustekinumab (IL12/23i) in Psoriasis

immerge [1]



ultimma-1 [2]

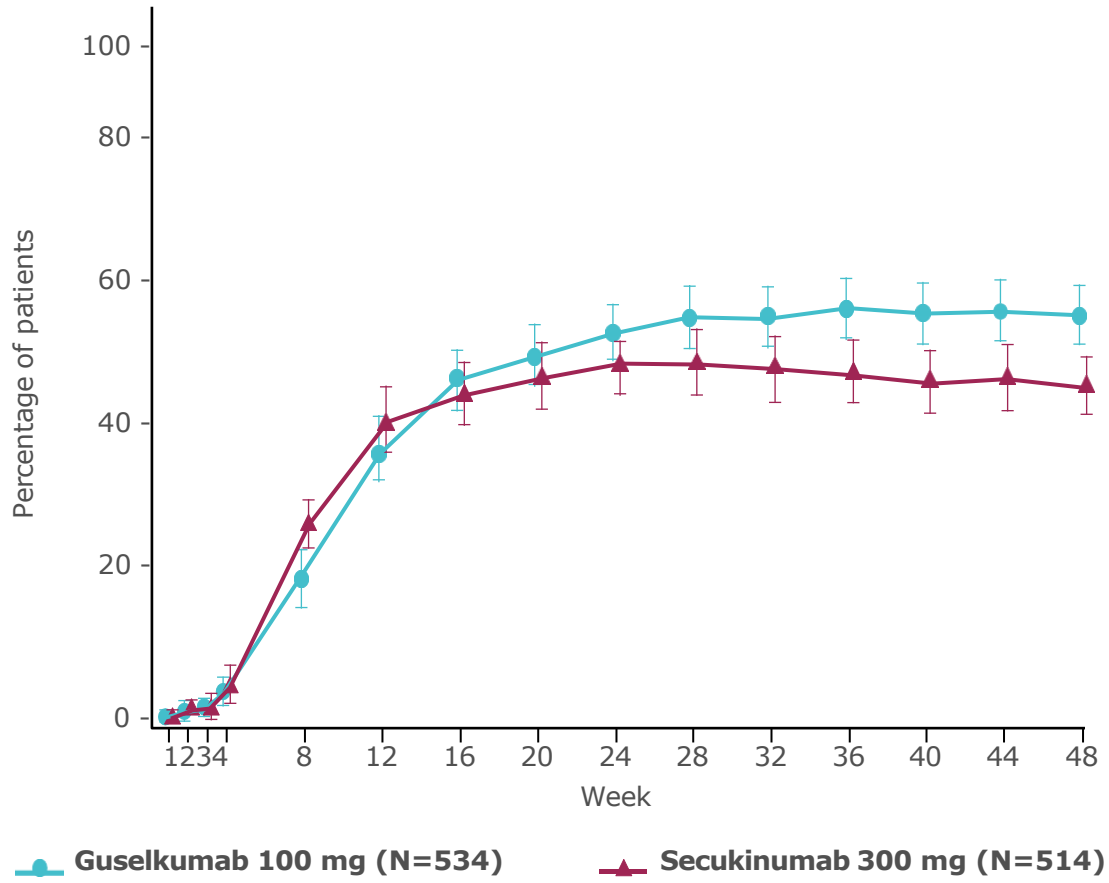


1. Warren RB, et al. Br J Dermatol 2021;184:50–9;
2. Gordon KB, et al. Lancet 2018;392:650-661.

Guselkumab showed superior long-term efficacy based on PASI 90 at week 48 when compared with secukinumab

ECLIPSE

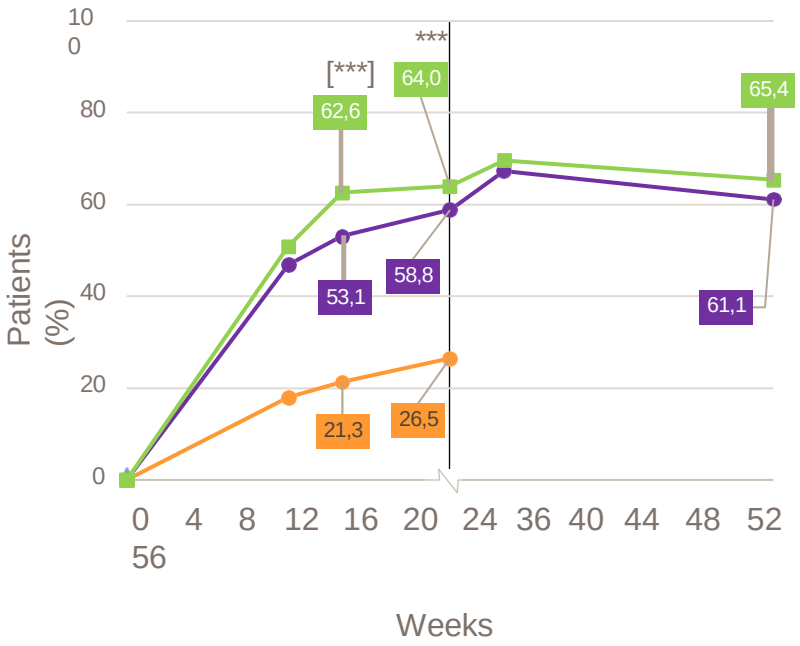
PASI 100 response rates through Week 48 by visit*



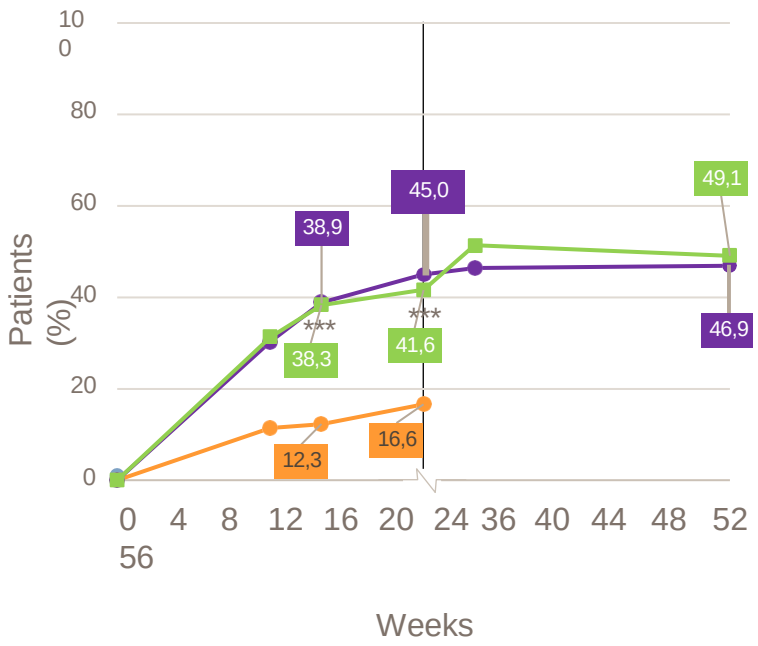
Reich K. et al, Lancet 2019

PASI 75/90/100a responses with upadacitinib over time through Week 56

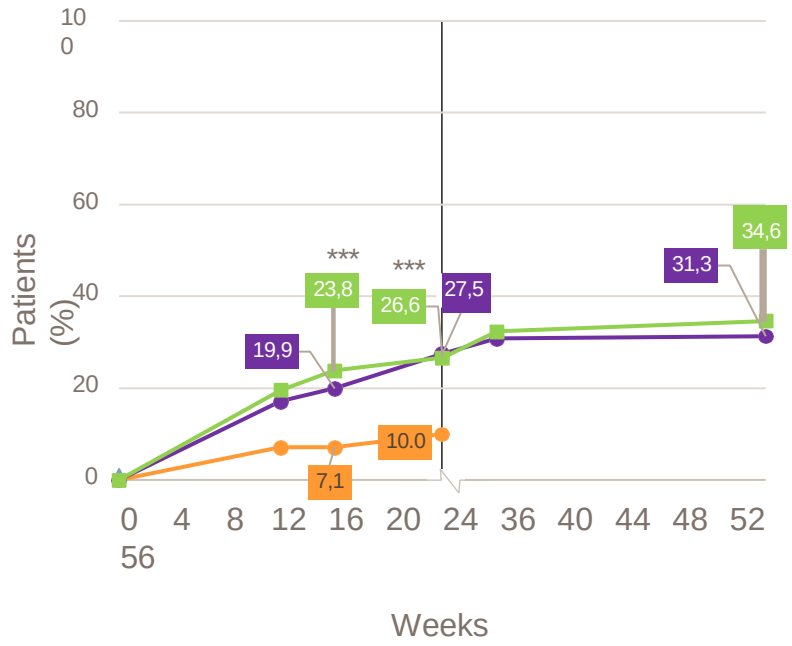
PASI 75[1,2]



PASI 90[1–3]



PASI 100[1,2,4]



PBO (n=211)

UPA 15 mg QD (n=214)

ADA (n=211)

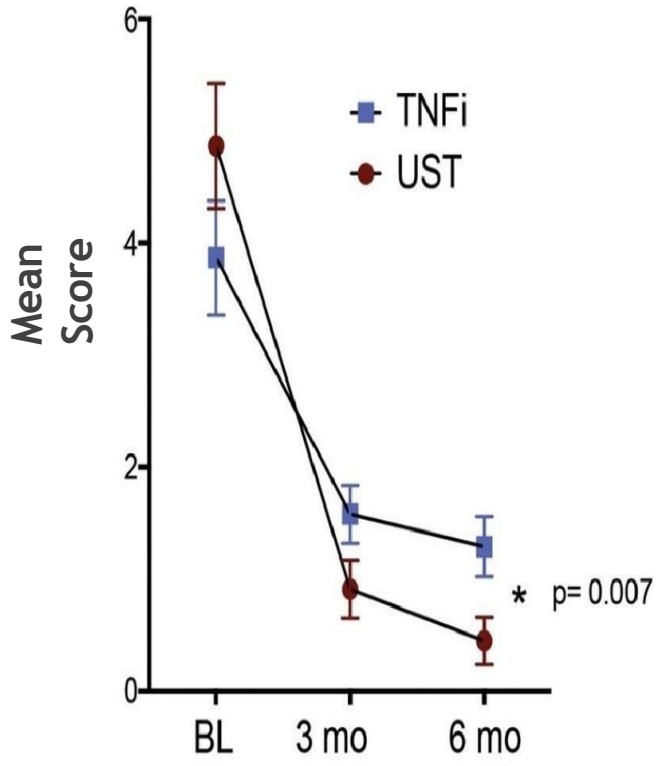
1. McInnes IB et al. N Engl J Med 2021;384(4):1227–1239;
2. McInnes IB et al. RMD Open 2021 [Epub ahead of print].
3. AbbVie. Data on file. RRTI ABVRRTI71420;
4. AbbVie. Data on file. RRTI ABVRRTI71702.

Ενθεσίτιδα

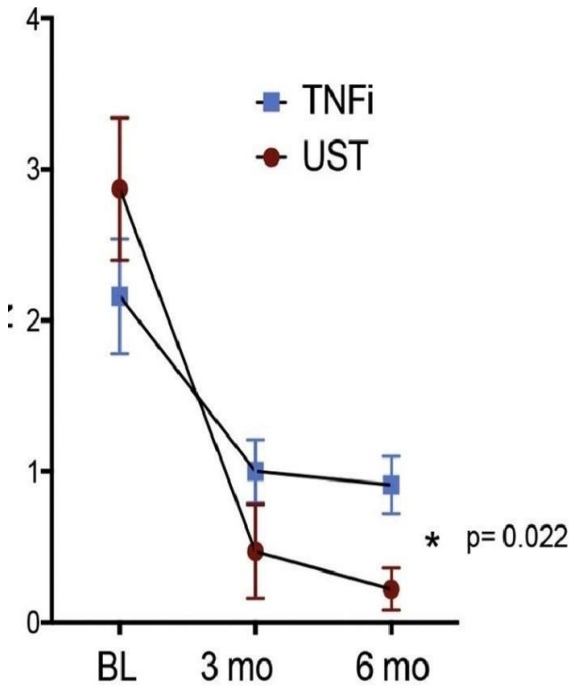
Ustekinumab is superior toTNFi in resolving enthesitis in PsA patients (n=47)

ECLIPSAStudy

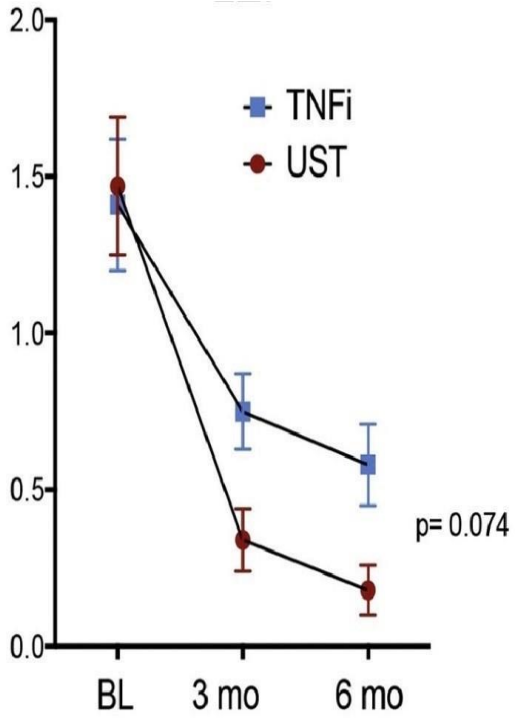
SPARCC



MASES



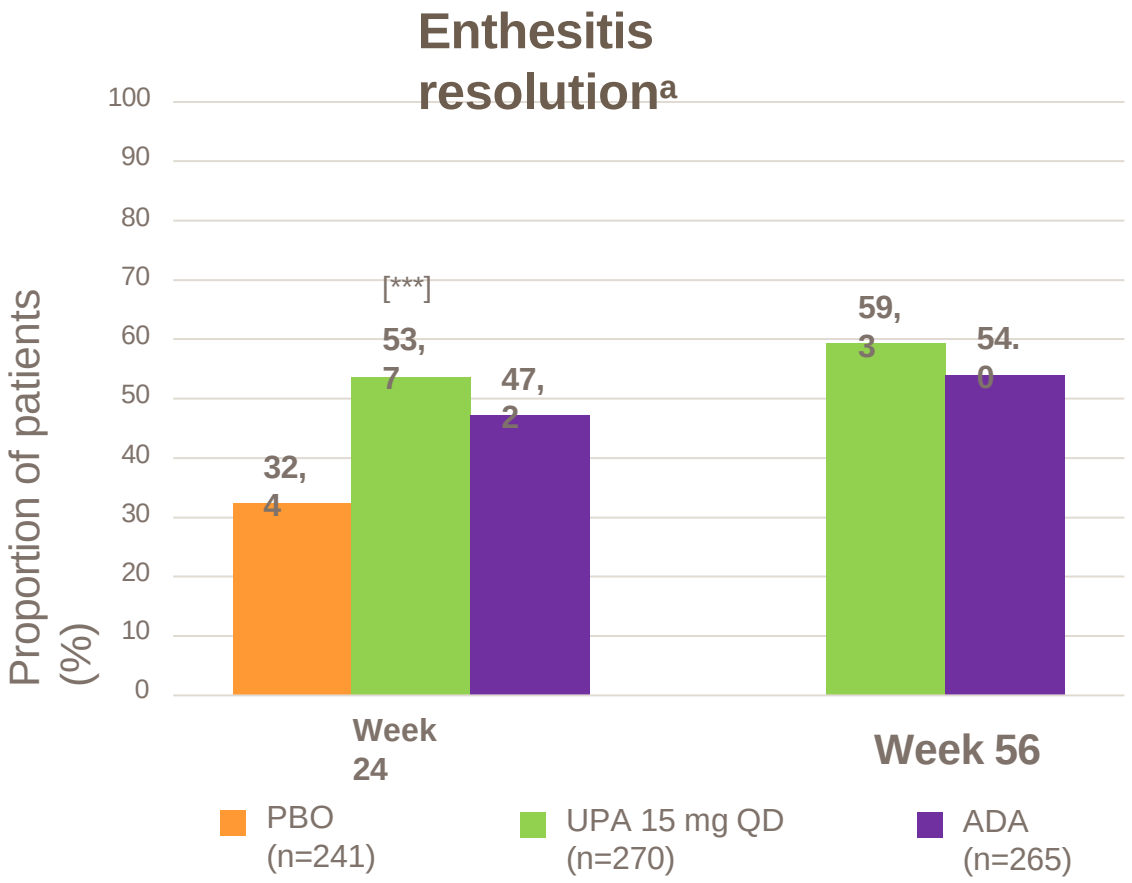
LEI

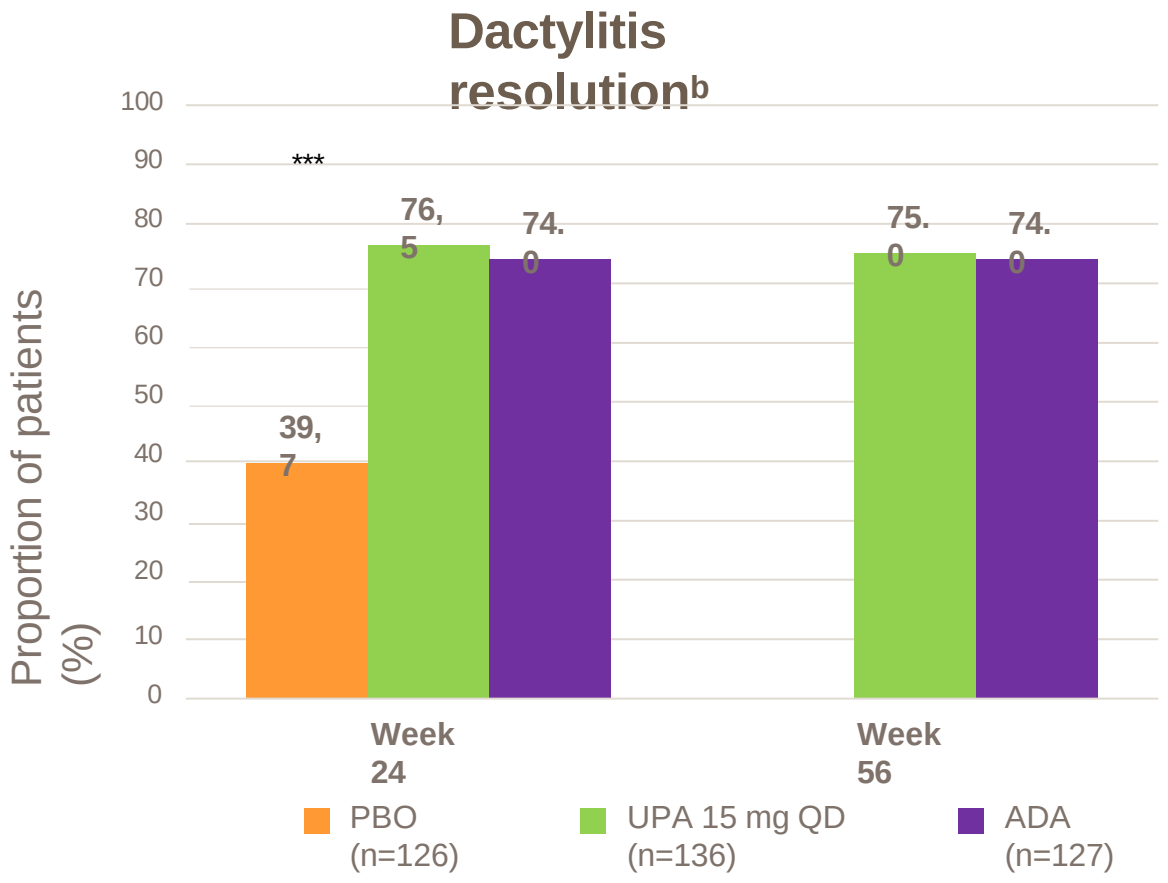


SPARCC, Spondyloarthritis Research Consortium of Canada; MASES, Maastricht Ankylosing Spondylitis Entheses Score; LEI, leeds enthesitis index

Araujo EG et al. ACR 2017 Arthr & Rheum 2018

Resolution of enthesitis and dactylitis at Weeks 24 and 56

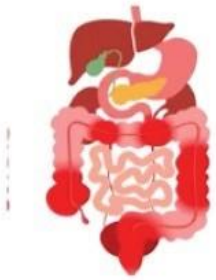




1. McInnes IB et al. N Engl J Med 2021
2. McInnes IB et al. RMD Open 2021

Extra-MSK manifestations influence treatment choice for b/tsDMARDs

Uveitis	**TNFi (monoclonal Ab)**



Inflammatory bowel disease	**TNFi (monoclonal) or IL12/23i or IL23i or JAKi***

Current EMA authorisations in IBD (in green)

DISEASE	IL12/23	IL-23		IL-17	JAKs
Crohn's disease	UST	RZB	GUS (prelim data)	Disease aggavation	UPA
Ulcerative colitis	UST	RZB, GUS (prelim data)			UPA, TOFA, FILGO

*For JAK-inhibitors, caution is needed for patients with risk factors, refer to the EMA guidelines.

Coates LC et al, Nat Rev Rheumatol. 2022 Jun 27 : 1–15.
Gossec L, *et al*. EULAR 2023 (OP)

Adapted from:
1. Schett G, et al. Nat Med. 2013;19(7):822-824; 2.Risankizumab EU Summary of Product Characteristics. Feb 2023; 3. https://news.abbvie.com/news/4. Upadactinib EU Summary of Product Characteristics. April 2023;

GRAPPA 2021 PsA treatment guidelines propose a guide to MOAs according to comorbidities in PsA

Comorbidity	NSAIDs	GCs	MTX and/or LEF	TNFi	IL-17i	IL-12/23i	IL-23i	JAKi	PDE4i
Elevated risk of CVD	Caution							Caution	
Congestive heart failure[a]		Caution		Avoid					
Elevated risk for VTE								Caution	
Obesity			Caution						
Fatty liver disease			Avoid						
Active hepatitis B or C			Avoid	Caution	Caution	Caution	Caution	Caution	Caution
Tuberculosis				Caution	Caution	Caution	Caution	Caution	Caution
History of recent malignancy				Caution	Caution	Caution	Caution	Caution	Caution
MS and/or demyelinating disease				Avoid					
Depression and/or anxiety									Caution

[a]Severe or advanced; class III or IV according to the New York Heart Association (NYHA) Functional Classification.

CVD, cardiovascular disease; GC, glucocorticoid; HIV, human immunodeficiency virus; i, inhibitor; IL, interleukin; JAK, Janus kinase; LEF, leflunomide; MS, multiple sclerosis; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; PDE4, phosphodiesterase 4; PsA, psoriatic arthritis; TNF, tumour necrosis factor; VTE, venous thromboembolism.

Adapted from:

1. Coates LC, et al. Nature Reviews Rheumatol. 2022;18:465-479; 2. Yang K, et al. Am J Clin Dermatol. 2021;22:173-192.

2023 update of the EULAR recommendations for the management of PsA

Target	Disease Domain					
	Arthritis (ACR 70)	Physical function (HAQ)	Skin (PASI 75)	Enthesitis*	Dactylitis*	Radiographic damage (PsA-mSvdHS)
TNF (ADA, CZP, ETN, IFX, GOL)						
IL-17A (IXE, SEC)						
IL-17A/F (BKZ)						
IL-12/23 (UST)						
IL-23-p19 (GUS, RIS)						GUS / RIS
JAK (TOFA, UPA)				TOFA / UPA	TOFA / UPA	TOFA / UPA
CD80/86 (ABA)						
PDE-4 (APR)						

Kershbaumer et al ARD 2024

Ασφάλεια

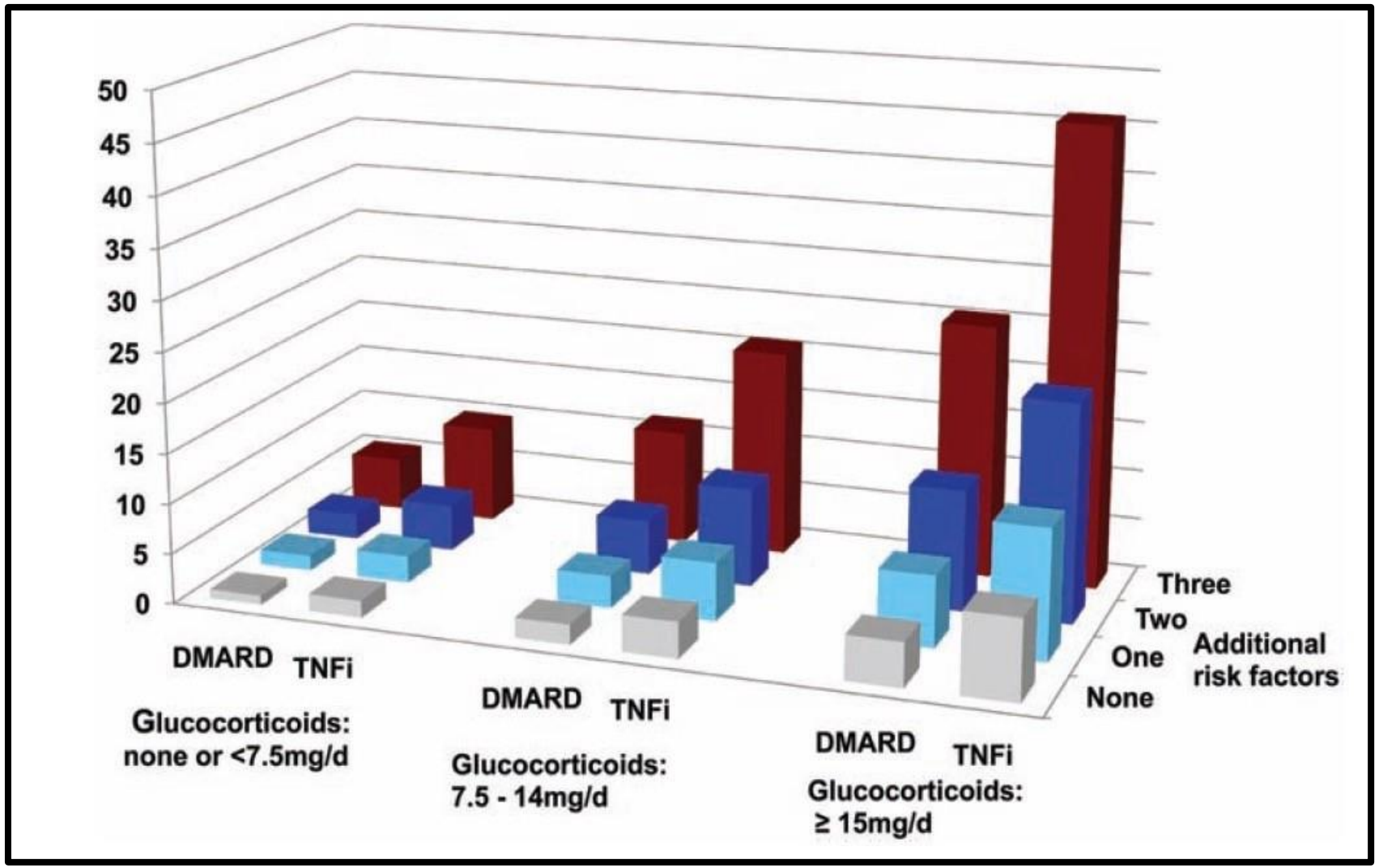
b/tsDMARDs increase the risk of infections

Infection	Risk increase with b/tsDMARDs[1]
Tuberculosis	Risk increase with bDMARDs, particularly TNFi[2]
Herpes Zoster	Risk increase with JAKi [2]
Candidiasis	Risk increase with IL-17i (localised) [2]

Adapted from:
1. Kerschbaumer A, et al. Ann Rheum Dis. 2020;79(6):778-786;
2. Gossec L, et al. . Ann Rheum Dis. 2020;79(6):700–712.

Σοβαρές λοιμώξεις ανά 100 ασθενείς ανά χρόνο σε σχέση με τη θεραπεία και παράγοντες κινδύνου

German Register RABBIT



Strangfeld A et al Ann Rheum Dis 2011

Ανεπιθύμητες ενέργειες Jakinibs

- Infection – equivalent to biologics, including serious and opportunistic infections
- Including: TB, nontuberculous mycobacteria, Candida, *Pneumocystis jirovecii*, Cryptococcus, toxoplasmosis
- Viral infection
  - Herpes zoster – more common than biologics
    - 1.5 to 2 fold higher; more common in Asian populations
    - Related to IFNα antagonism?
    - VZV reactivation also seen with Sifalimumab in SLE
  - Small number of CMV infections

Winthrop KL et al Nat Rev Rheum 2017 Kivotz A. et al Sem Arthr Rheum 2018

Ανεπιθύμητες ενέργειες Jakinibs

- Cytopenias: anemia, leukopenia, neutropenia
  - Jak2inhibition? IL-6?
- DVT– Drug vsClasseffect? Mechanism?

  Yunet al Abstr824 ACR 2018 Desaiet al Abstr L09, ACR 2018
- Increasedlipids
  - Significancefor CVdisease?HDLmay also be increased

    Tayloret al ARD2018
- GIperforation
  - Efficaciousin IBD(?)
- Increasedtransaminases
- Increased CPK
- Increasedcreatinine
  - Decreasedcreatinine clearance, no long term

Winthrop KL et al Nat Rev Rheum 2017

Kivotz A. et al Sem Arthr Rheum 2018

Clinical Management of Herpes Zoster in Patients With Rheumatoid Arthritis or Psoriatic Arthritis Receiving Tofacitinib Treatment

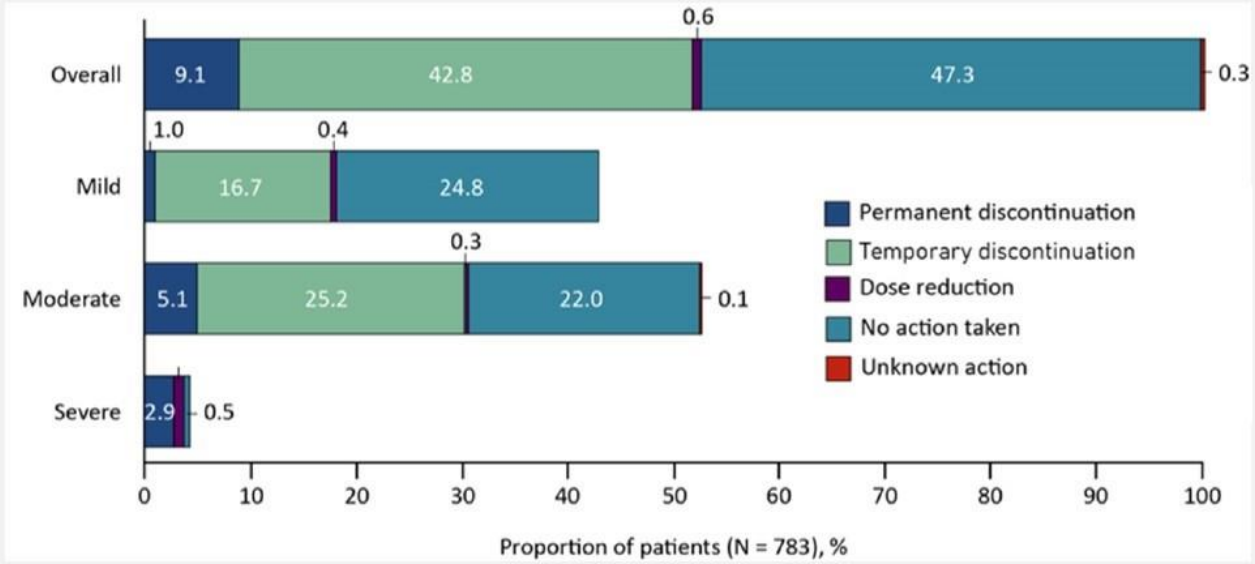
Study design

- Post hoc analysis of data from 21 RA and 3 PsA clinical studies
  - **Phase I:** 2 studies (RA)
  - **Phase II:** 10 studies (RA)
  - **Phase III:** 6 studies (RA), 2 studies (PsA)
  - **Phase III/IV:** 1 study (RA)
  - **LTE:** 2 studies (RA), 1 study (PsA)
- Outcomes of HZ events and TOFA treatment changes were evaluated in response to first and second HZ events

Key results

- HZ events in patients receiving tofacitinib were
  - generally non-serious and mild or moderate in severity
  - clinically manageable with events resolving in most patients

Changes to TOFA treatment due to first HZ event in RA



HZ events in patients with RA receiving tofacitinib were generally nonserious and clinically manageable

Winthrop KL, et al. Rheumatol Ther. 2021

Safety of JAK inhibitors: EMA guidance

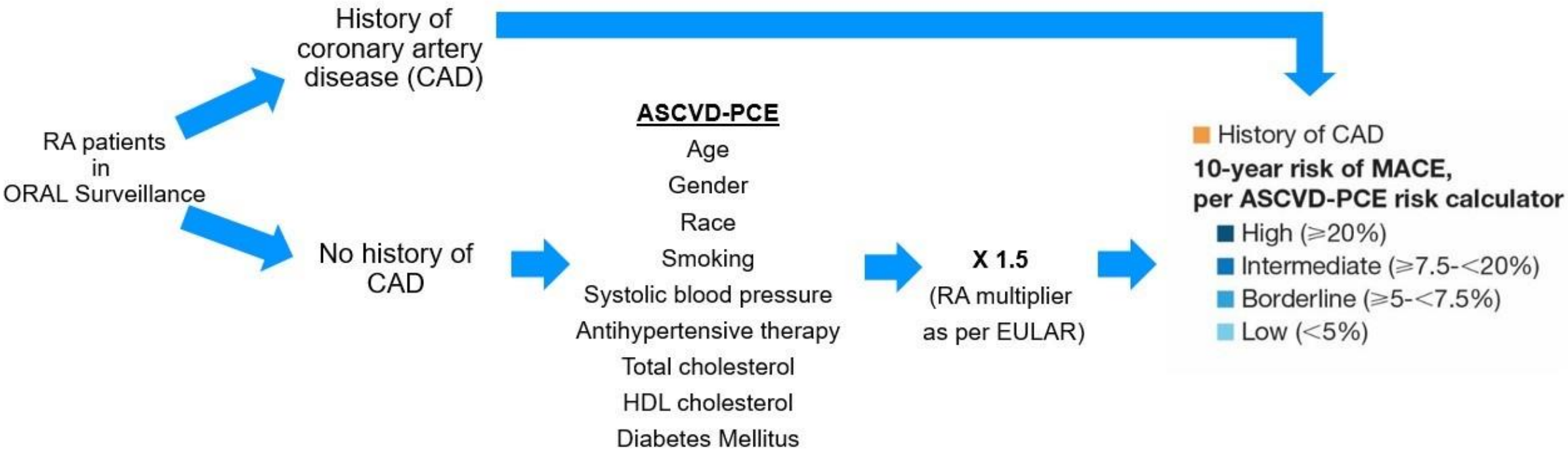
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- An EMA review has found that, compared with TNF-alpha inhibitors, Janus kinase (JAK) inhibitors used to treat chronic inflammatory disorders (rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, ulcerative colitis, atopic dermatitis and alopecia areata) are linked to a higher risk of major adverse cardiovascular events (MACE), venous thromboembolism (VTE), malignancy, serious infections and all-cause mortality.
- EMA concluded that **the identified risks apply to all JAK inhibitors approved for the treatment of chronic inflammatory disorders.**
- These medicines (Xeljanz, Cibinqo, Olumniant, Rinvoq and Jyseleca) should be used in the following patients only if no suitable treatment alternatives are available:
  - those aged 65 years or above,
  - those who are current or past long-time smokers,
  - those with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors,
  - or those with other malignancy risk factors.
- Cautious use is also recommended in patients with known risk factors for VTE other than those listed above.

https://www.ema.europa.eu/en/medicines/human/referrals/janus-kinase-inhibitors-jaki

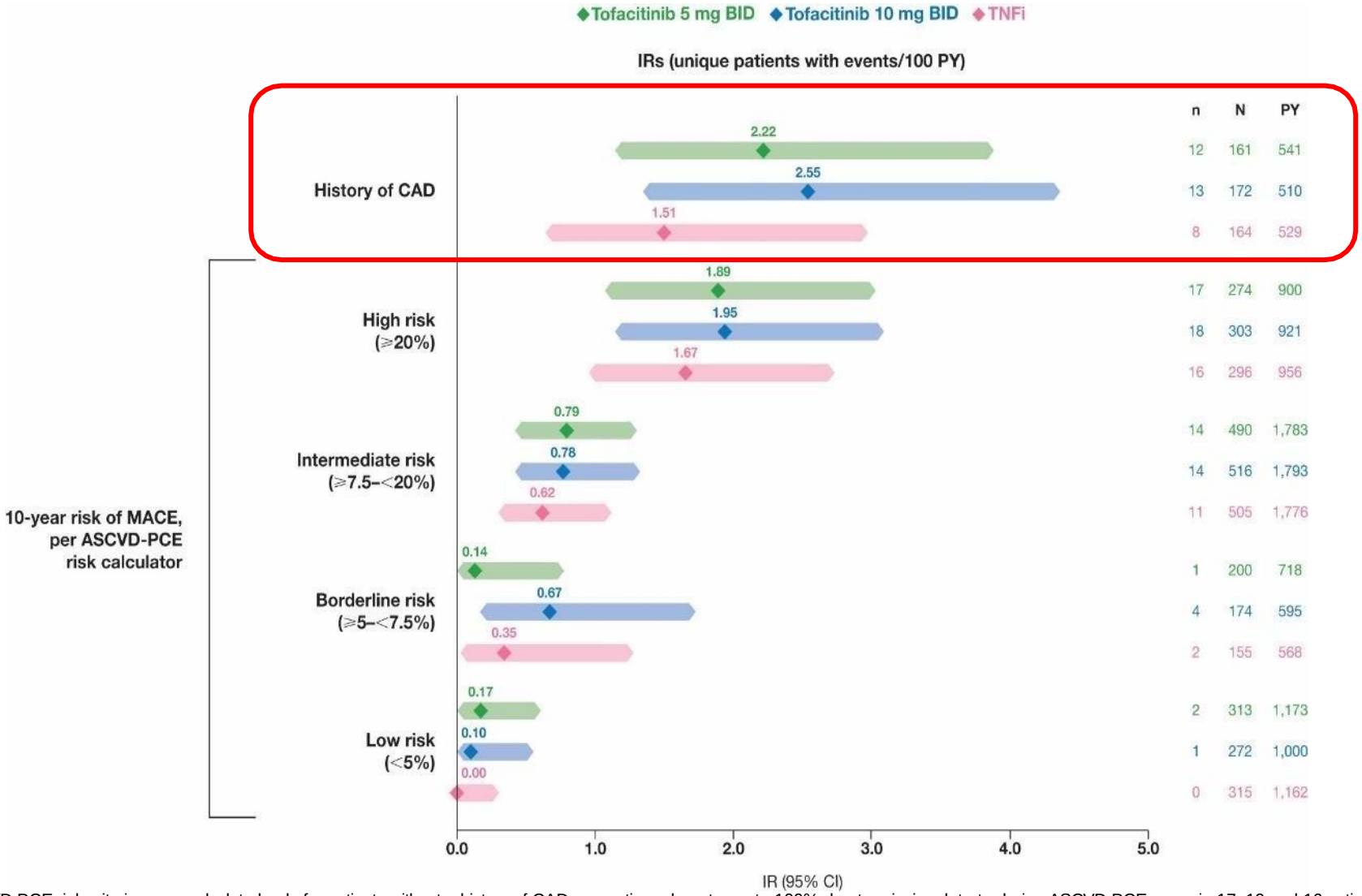
ASCVD-PCE Cardiovascular Risk Scoring

- Applied 10-year atherosclerotic cardiovascular disease (ASCVD)[1] risk estimation with additional EULAR-recommended[2] risk multiplier
  - The scoring method only applies to patients who do not already carry a diagnosis



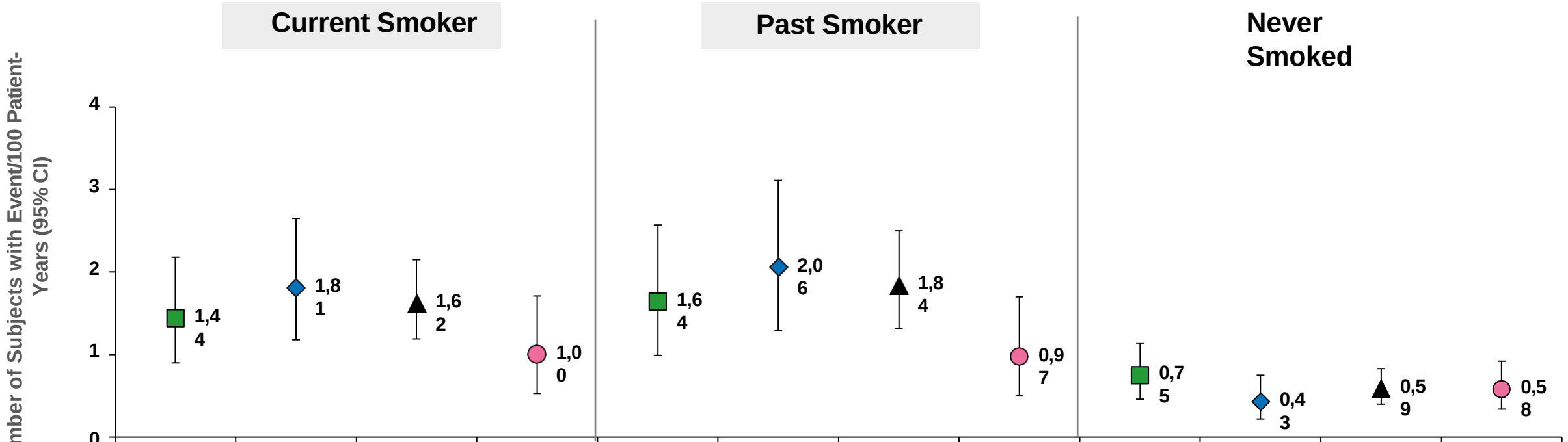
1. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. Arnett DK et al. Circulation 2019;140, 11: e596-e646; 2. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Agca R et al. Ann Rheum Dis. 2017;76:17-28

Across treatment groups, MACE mostly occurred in patients with a history of CAD or at high risk of MACE at baseline



a. 10-year risk of MACE, per ASCVD-PCE risk criteria, were calculated only for patients without a history of CAD; proportions do not sum to 100% due to missing data to derive ASCVD-PCE score in 17, 19 and 16 patients in the tofacitinib 5 mg BID, tofacitinib 10 mg BID, and TNFi treatment groups, respectively; ASCVD-PCE, atherosclerotic cardiovascular disease-pooled cohort equation; BID, twice daily; CAD, coronary artery disease; CI, confidence interval; IR, incidence rate; MI, myocardial infarction; PY, patient-years; TNFi, tumor necrosis factor inhibitor. Data on file. Pfizer Inc, New York, NY. Presented at ACR Convergence 2021, presentation 0958

Incidence Rates of Malignancies (Excluding NMSC) by Smoking Status



	Current Smoker				Past Smoker				Never Smoked			
	Tofa 5 mg	Tofa 10 mg	All Tofacitinib	TNFi	Tofa 5 mg	Tofa 10 mg	All Tofacitinib	TNFi	Tofa 5 mg	Tofa 10 mg	All Tofacitinib	TNFi
n/N	22/411	26/402	48/813	13/353	19/309	22/302	41/611	12/326	21/735	12/752	33/1487	17/772
PY	1526.21	1439.61	2965.82	1299.69	1155.82	1070.15	2225.96	1231.82	2809.45	2801.95	5611.40	2950.79

Data on file. Pfizer Inc, New York, NY. Presented at ACR Convergence 2021, presentation 1940

Incidence of AEs of Special Interest in Tofacitinib PsA program

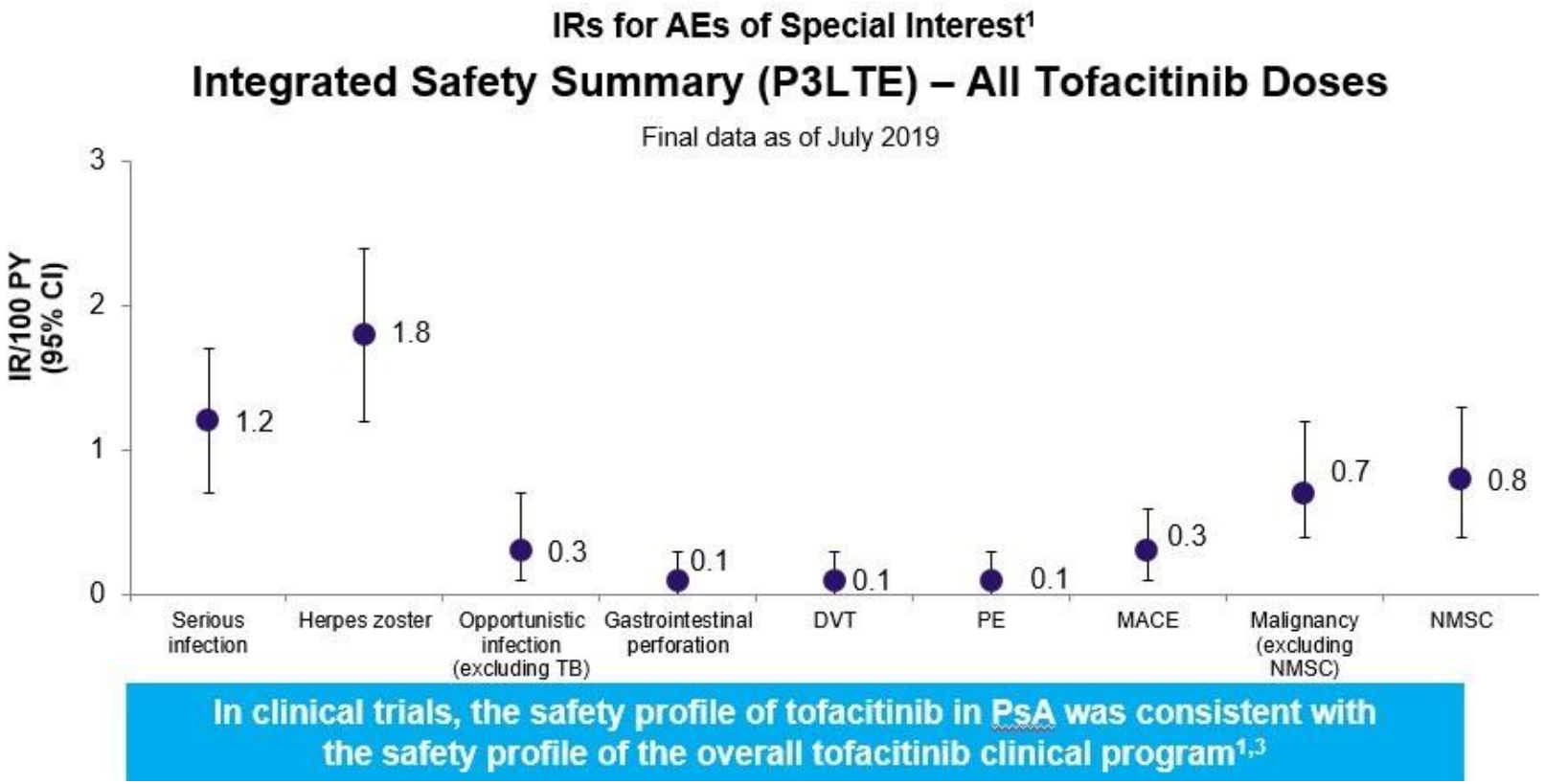
783 patients studied[1]

2038 PY of exposure[1]

PHASE 3

3 clinical trials[2,3†]

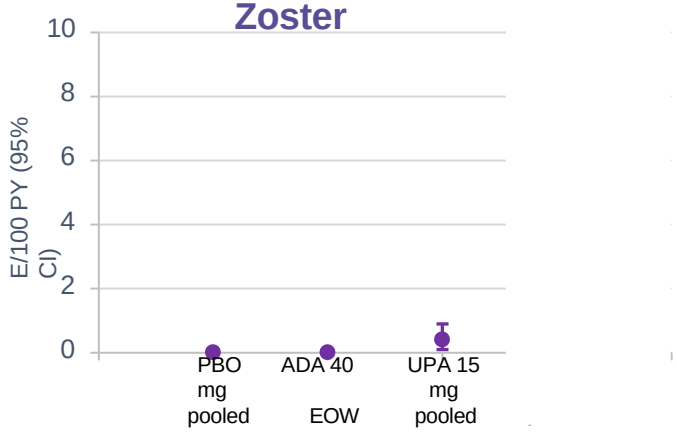
Up to 48 months‡ of observation in the LTE study for safety[4]



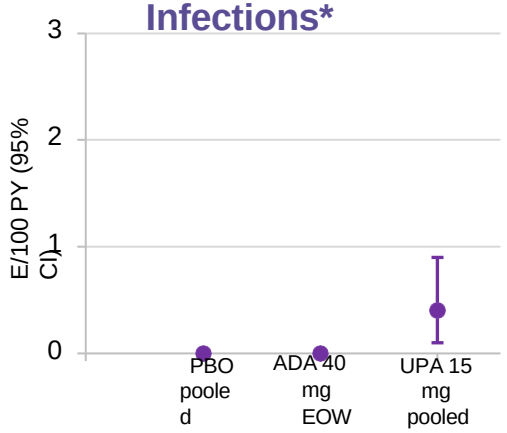
1. Burmester GR, et al. *RMD Open*. 2021;7(2):e001595.
2. Burmester GR, et al. *RMD Open*. 2021;7(2):e001595 (Supplementary).
3. Nash P, et al. *Lancet Rheumatol*. 2021;3(4):e270-e283.

Upadacitinib 15mg and adalimumab had similar safety profiles with the exception of HZ and opportunistic infections up to 3 Years: An Integrated Analysis of Two Pivotal Phase 3 Trials

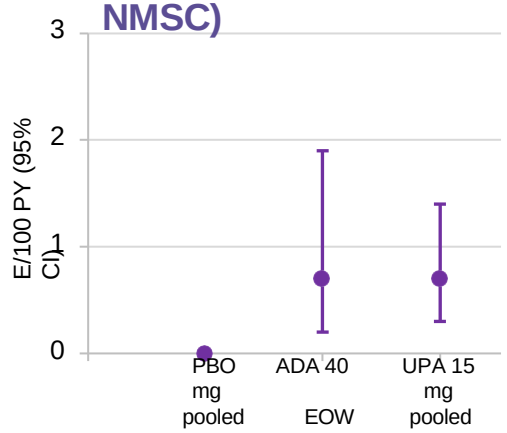
Herpes Zoster



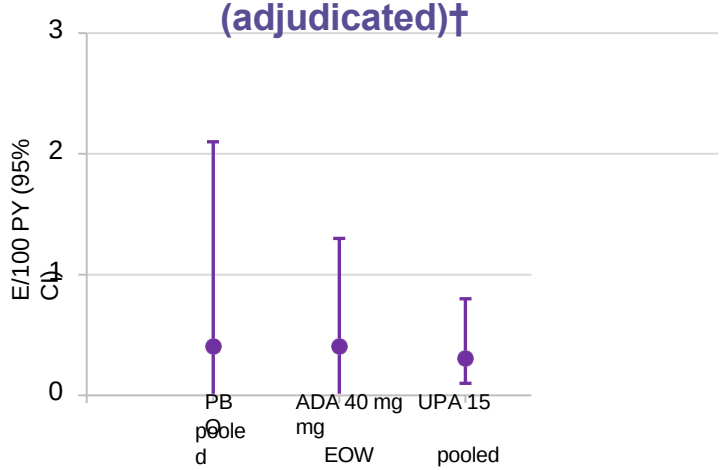
Opportunistic Infections*



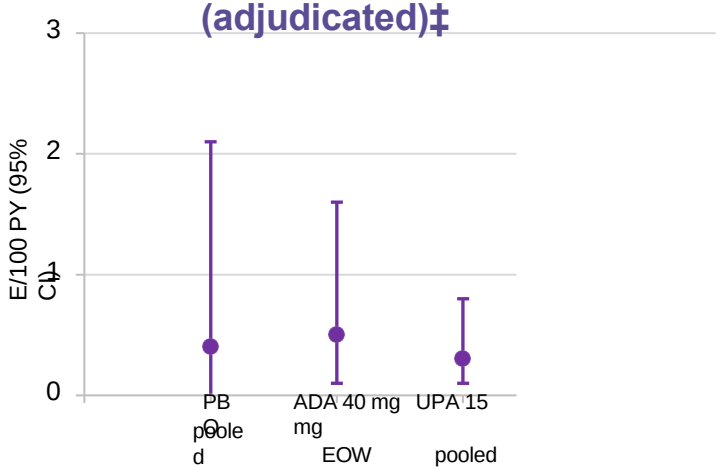
Malignancies (excluding NMSC)



VTE (adjudicated)†

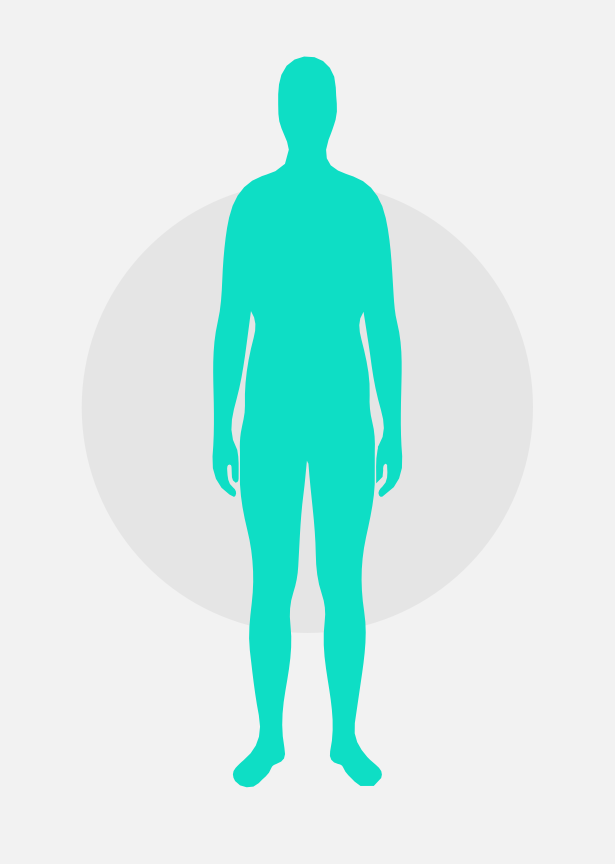


MACE (adjudicated)‡



Burmester G et al Rheumatol Ther. 2022

Περίπτωση #1



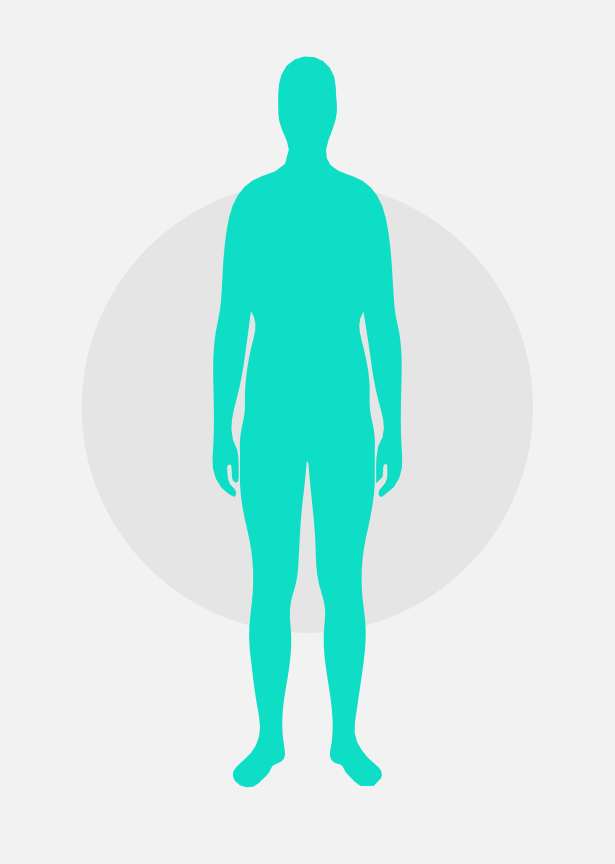
Άνδρας 52 ετών

BMI: 30.8 kg/m2

Κλινικά χαρακτηριστικά		
CRP (mg/L)		**7**
TKE		**30**
TJC/SJC (68/66)		**16/12**
PASI		**4.4**
BSA		**3**
Patient global assessment	(VAS 100 mm)	**75**
Pain VAS (100 mm)		**80**
HAQ-DI		**1.8**
DAS28-CRP		**5.9**
Μικροσκοπική κολίτιδα		

Προηγηθείσα θεραπεία: Ανεπαρκής ανταπόκριση σε MTX 17,5mg/w

Περίπτωση #1



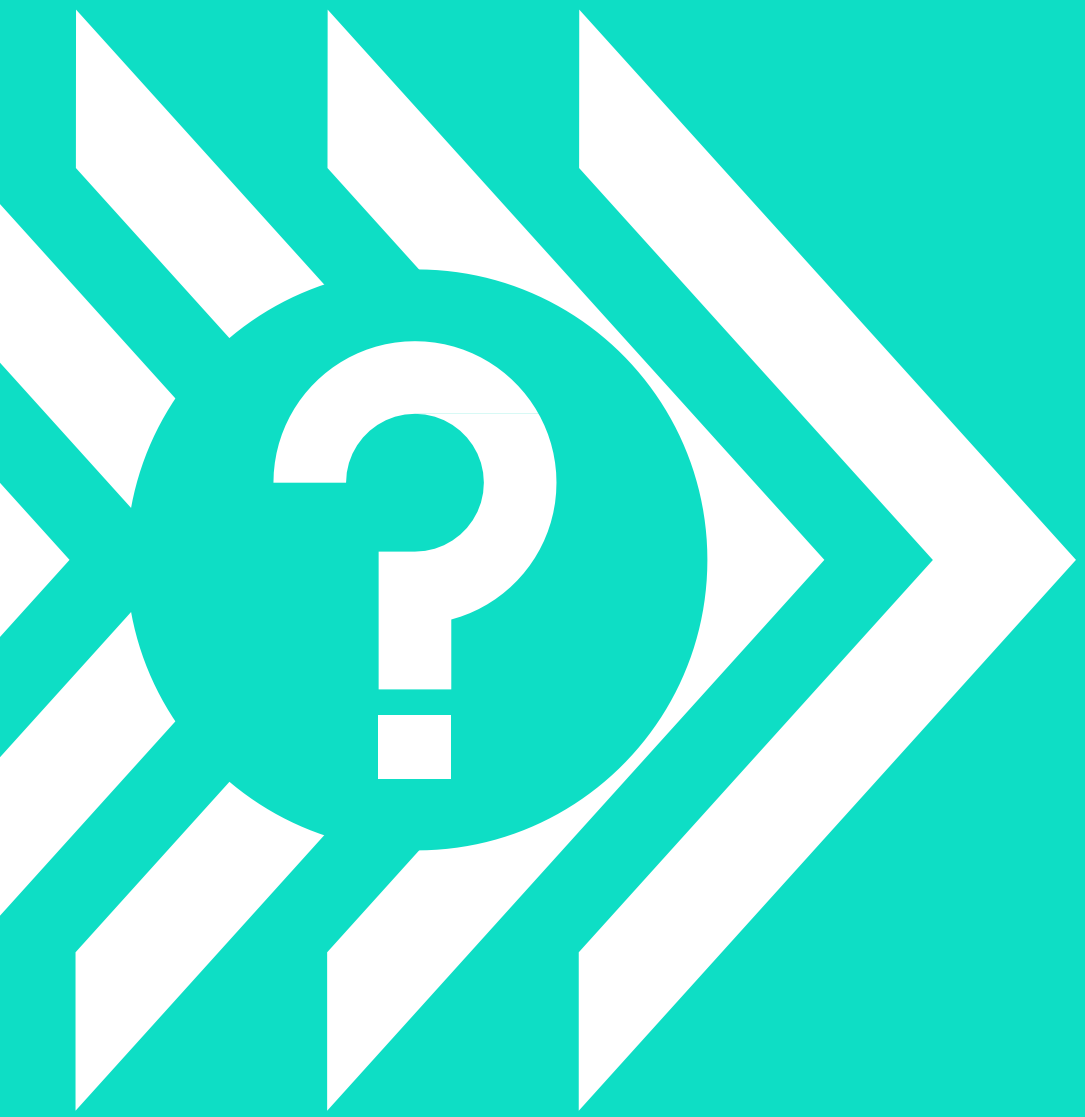
Άνδρας 52 ετών

BMI: 30.8 kg/m2

Κλινικά χαρακτηριστικά		
CRP (mg/L)		**7**
TKE		**30**
TJC/SJC (68/66)		**16/12**
PASI		**4.4**
BSA		**3**
Patient global assessment	(VAS 100 mm)	**75**
Pain VAS (100 mm)		**80**
HAQ-DI		**1.8**
DAS28-CRP		**5.9**
Μικροσκοπική κολίτιδα		

Προηγηθείσα θεραπεία: Ανεπαρκής ανταπόκριση σε MTX 17,5mg/w

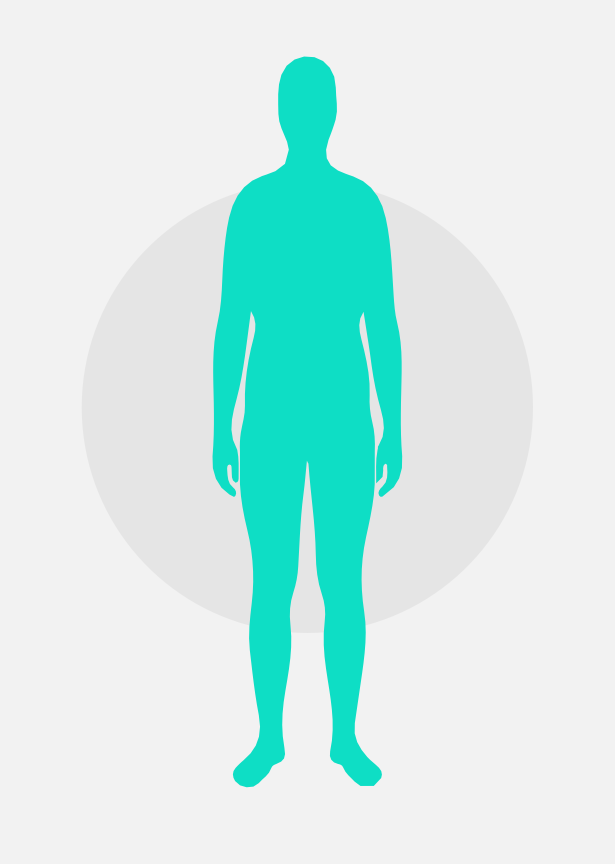
Θεραπευτική αντιμετώπιση Περιστατικού



<u>Προσθήκη</u>

1. **Anti-IL17**
2. **Anti-IL12/23**
3. **JAK inhibitor**
4. **PDE4 inhibitor**
5. **Anti-TNFα**

Περίπτωση #1



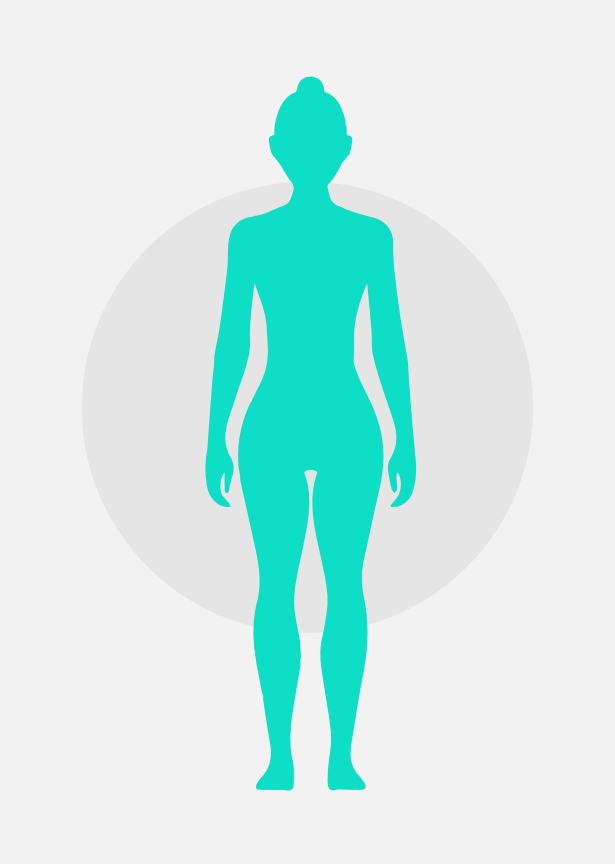
Περιστατικό 1
Μετά από Upadacitinib 15mg/ημέρα (6 έτη)

Άνδρας 52 ετών

BMI: 30.8 kg/m2

Κλινικά χαρακτηριστικά		
CRP (mg/L)		**4**
TKE		**20**
TJC/SJC (68/66)		**1/0**
PASI		**0**
BSA		**0**
Patient global assessment	(VAS 100 mm)	**15**
Pain VAS (100 mm)		**10**
HAQ-DI		**0.7**
DAS28-CRP		**2.3**
Μικροσκοπική κολίτιδα		**(-)**

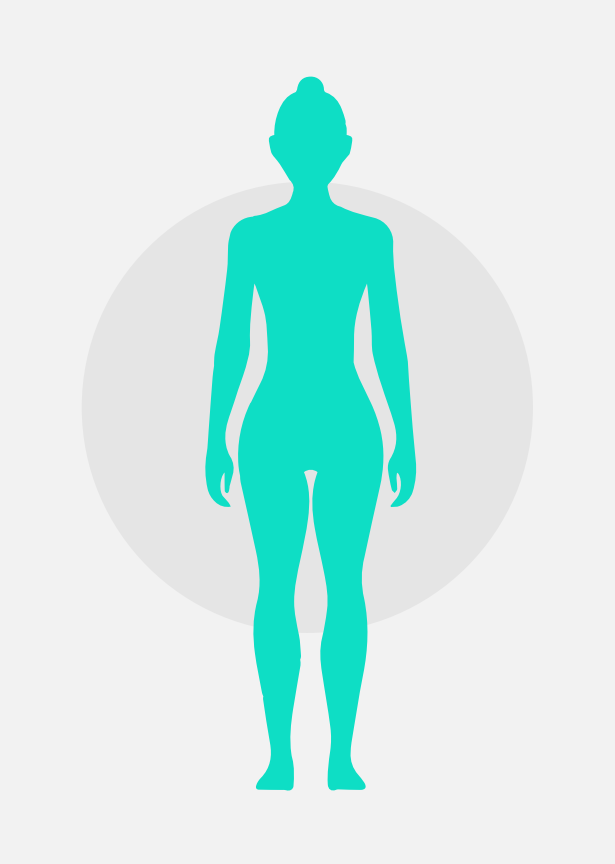
Περίπτωση #2



- Female 45 years old
- Past history: none
- Family history: father with PsA
- Occupation: civil engineer
- Habits: smoker (25pack-years)
- BMI: 29

PASI, Psoriasis Area and Severity Index; TJC, tender joint count; SJC, swollen joint count; BMI, body mass index

Περίπτωση #2

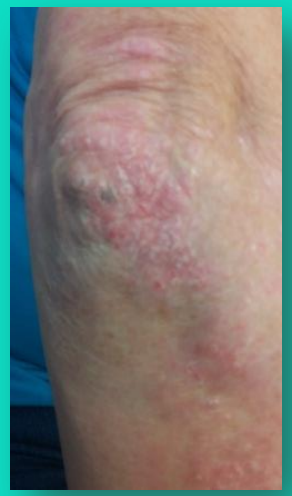


Clinical

2018: Asymmetric oligoarthritis + Psoriasis

- **4 TJC/2 SJC (2017)**

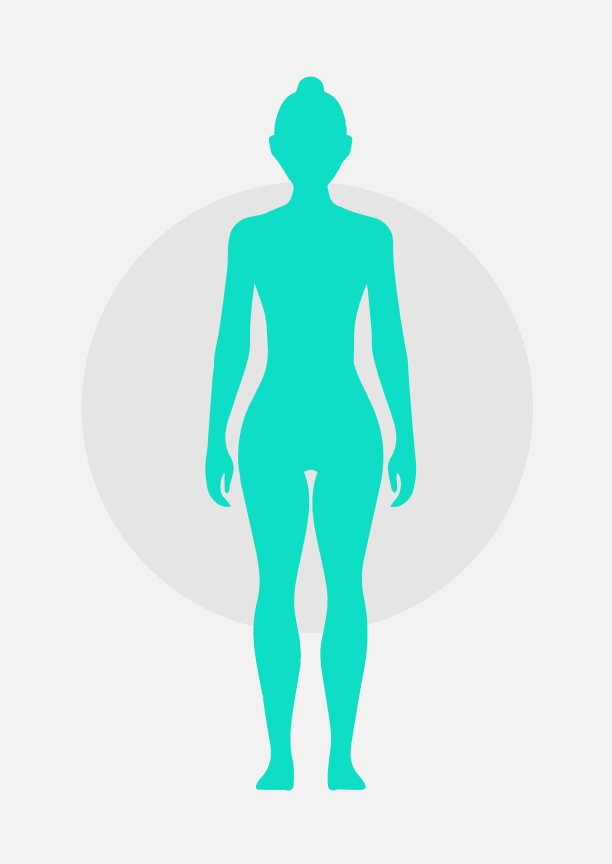
- **Laboratory**
  - **B-27: positive**
  - **ESR: 31 mm/h**
  - **CRP: 0,78 mg/dl**



Courtesy of Dr. Fragkoulis

RF, rheumatoid factor; CRP: C-reactive protein; HLA-B27, Human leukocyte antigen B27

Περίπτωση #2



Treated with

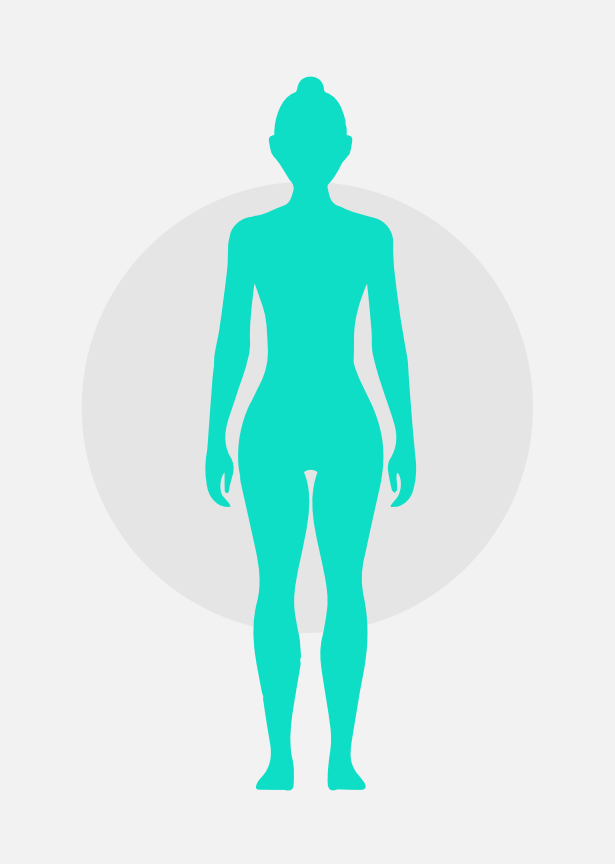
Methotrexate 17.5 mg/week

After couple of months moderate improved

- **But….residual disease (DAPSA: 7.3) plus BSA=6**
- **LFTs**

PASI, Psoriasis Area and Severity Index; DAPSA, disease activity in psoriatic arthritis

Περίπτωση #2



Treated with

Secukinumab

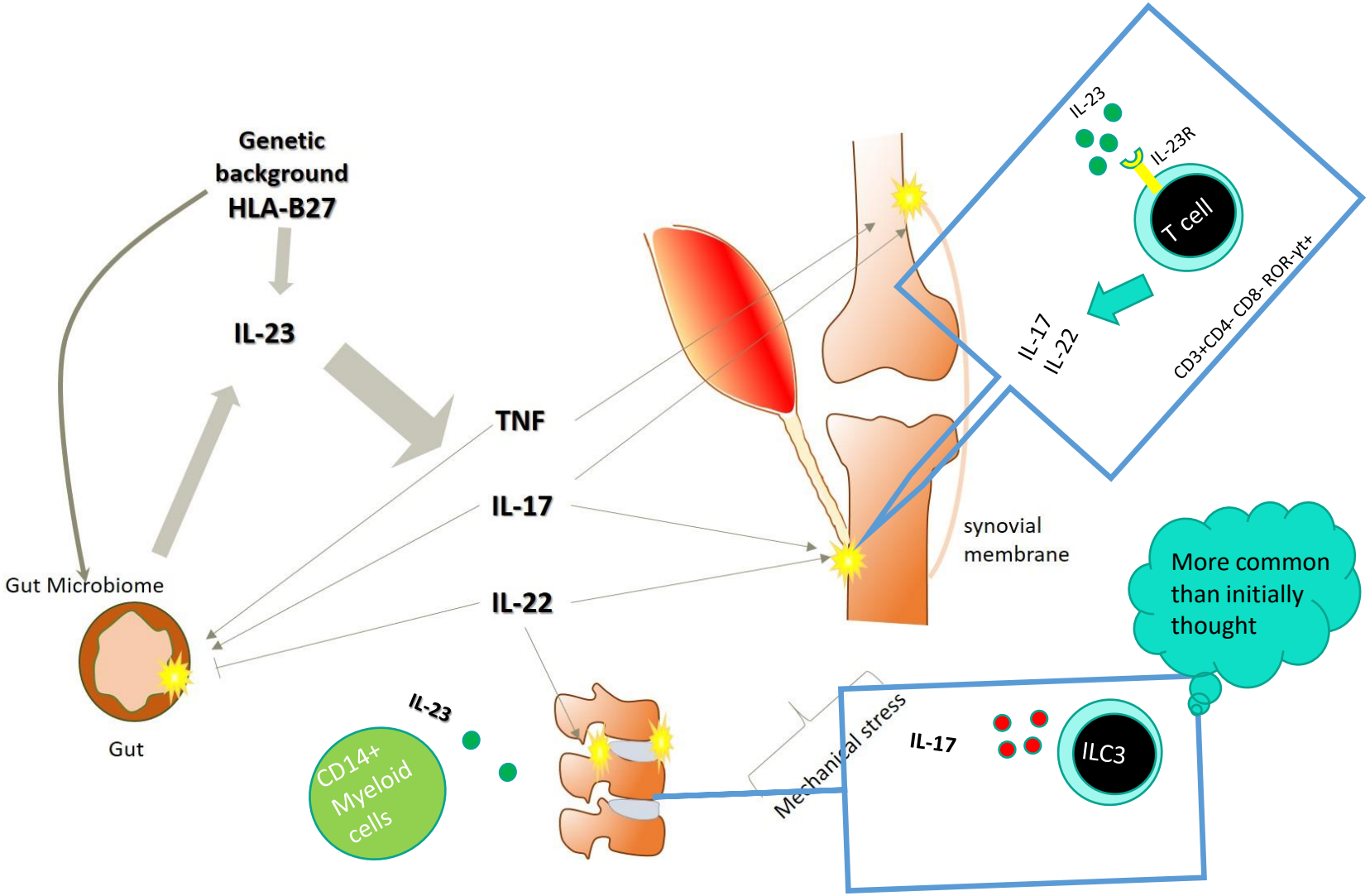
After 6 months

- **Improved**
- **But….diarrheas**
  - **Colonoscopy: IBD- (Crohn's Disease?)**

- **TJC: 2**
- **SJC: 0**
- **DAPSA: 8,1**
- **BSA: 2**
- **LEI: 2**

PASI, Psoriasis Area and Severity Index; DAPSA, disease activity in psoriatic arthritis

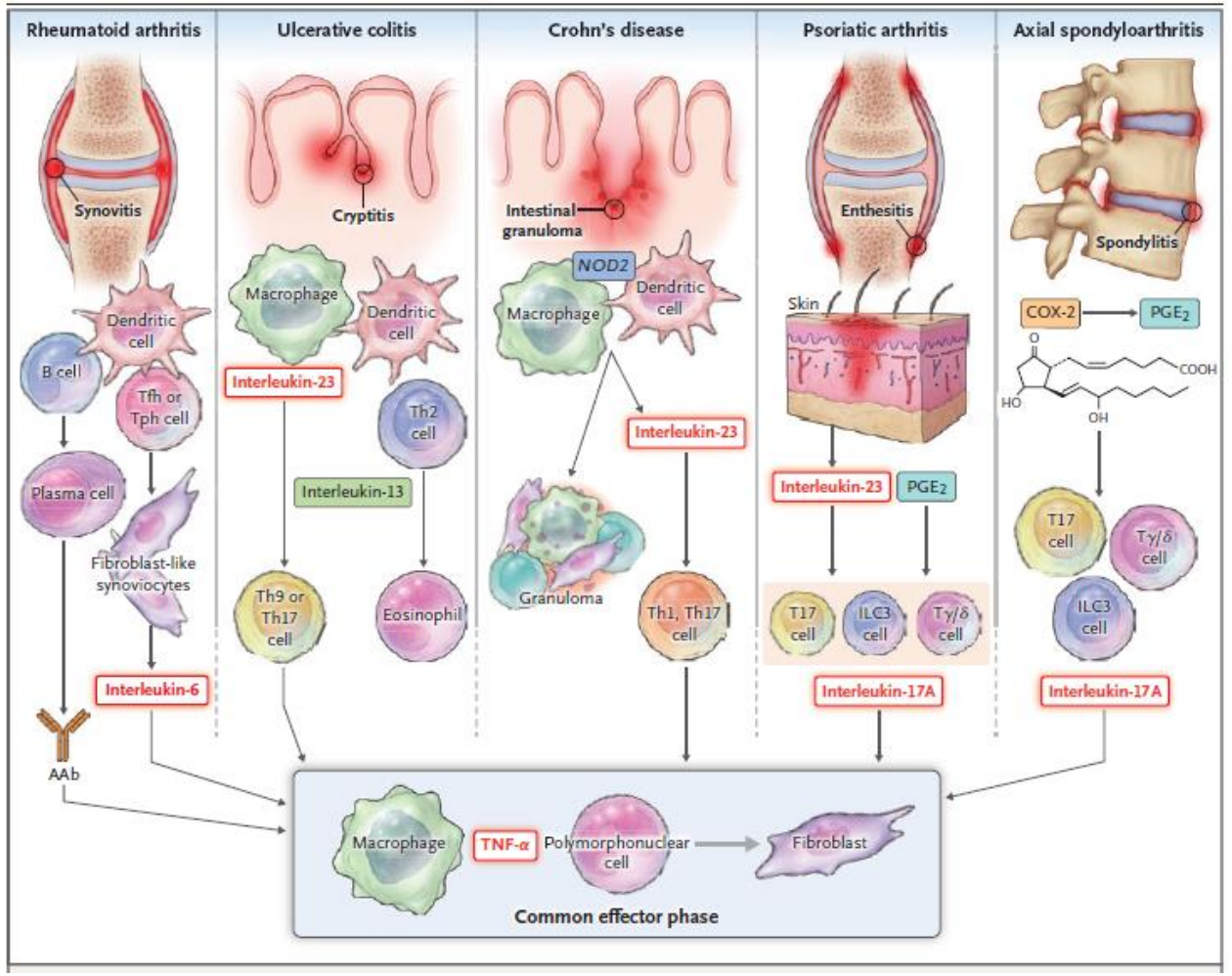
PsA
Pathogenesis overview



McGonagle D et al ARD 2019
Bridgewood et al ARD 2019

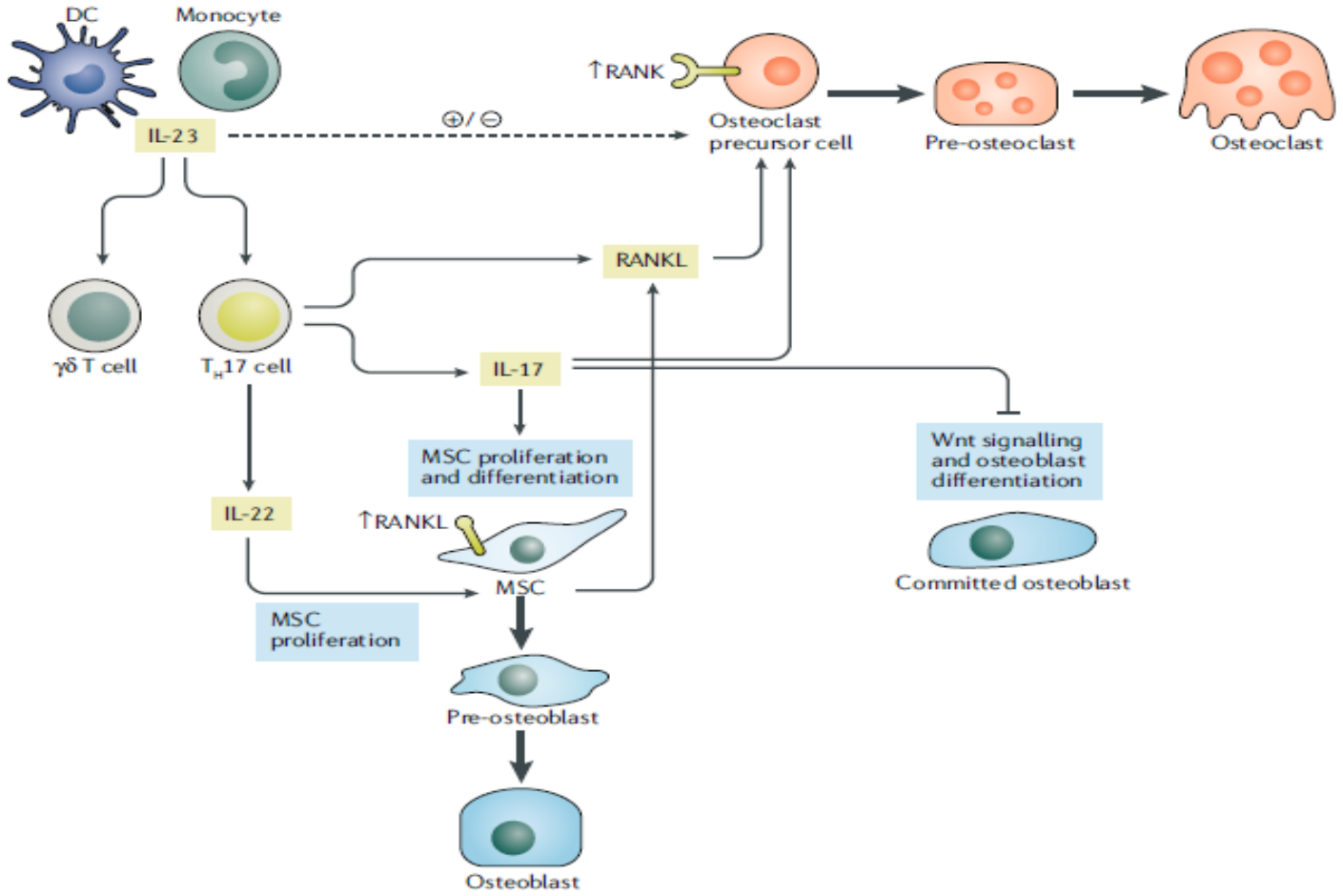
(modif from) Siebert S, Fragoulis GE, McInnes IB EULAR online course 2016
Gravallese and Schett Nat Rev Rheum 2018

Cytokines
Same but different…



Schett G et al. NEJM 2021

Psoriatic arthritis
Pathogenesis



Veale D et al Lancet 2018
Gravallese E & Schett G Nat Rev Rheum 2018

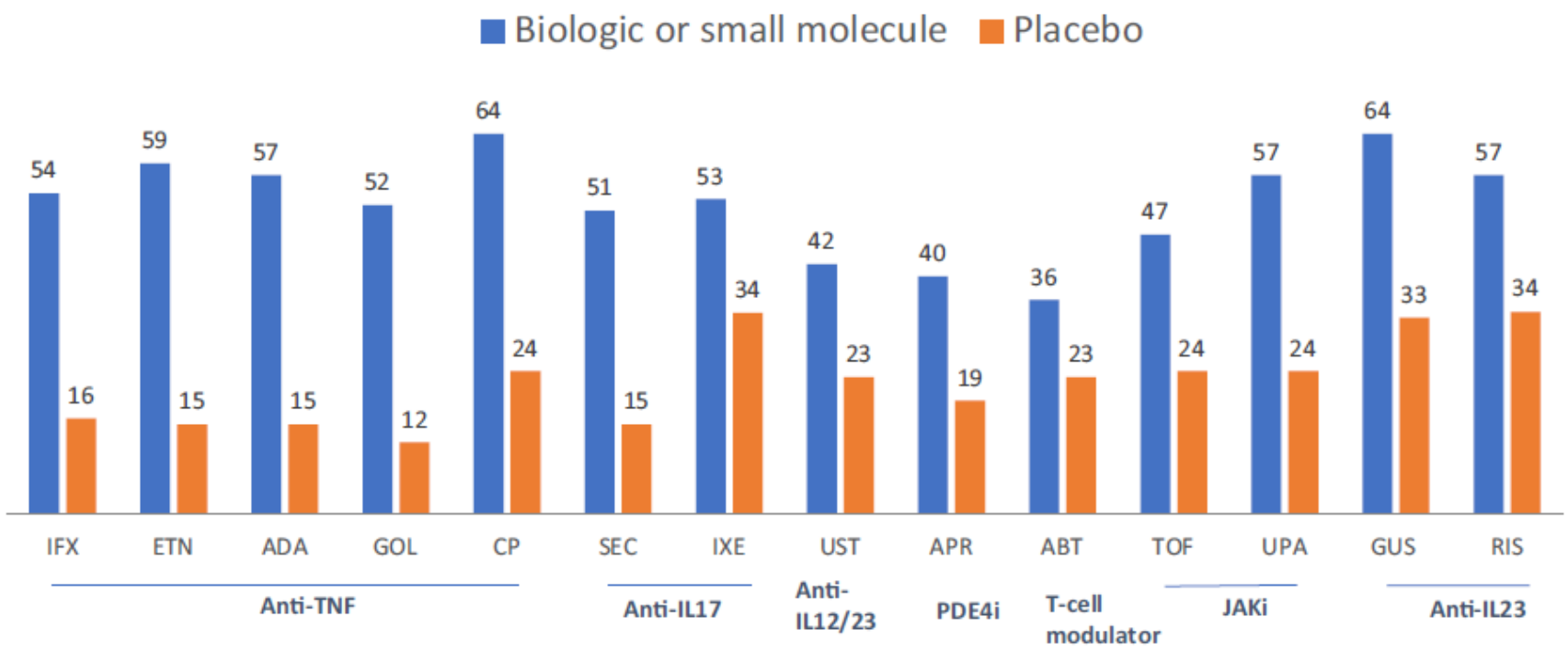
IL-23
Evidence for SpA

- In
  - Entheses
  - Spine
  - Bowel
  - Joints
  - Skin

Speaker's opinion

Biologic and Small-molecule Therapies for PsA: Efficacy Data from Registration Trials

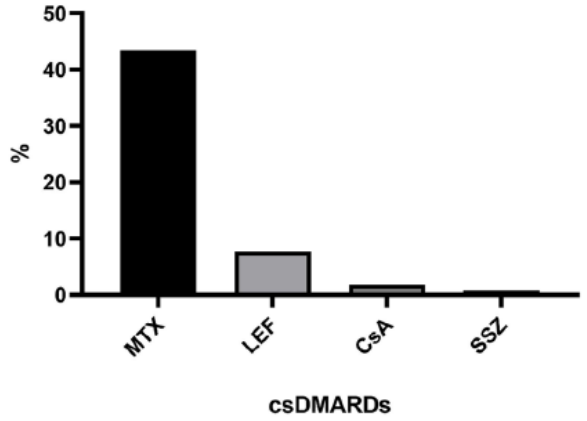
Patients achieving ACR20% Response in Phase 3 PsA Trials

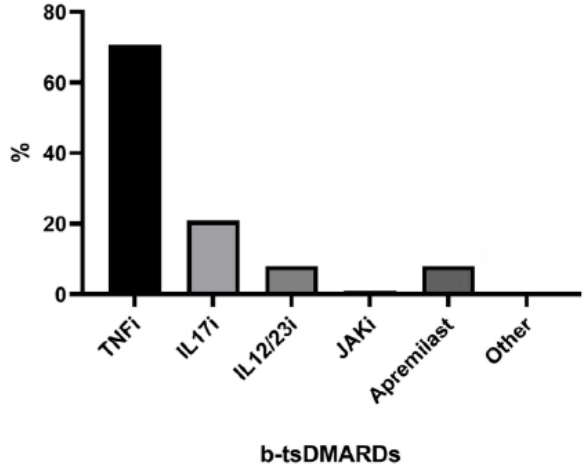


Note: Data are only presented for illustrative purposes and not for direct comparison.

Lubrano et al Rheum Ther 2023
Kumthekar et al Clin Rheum 2023

PsA
Data from Greece



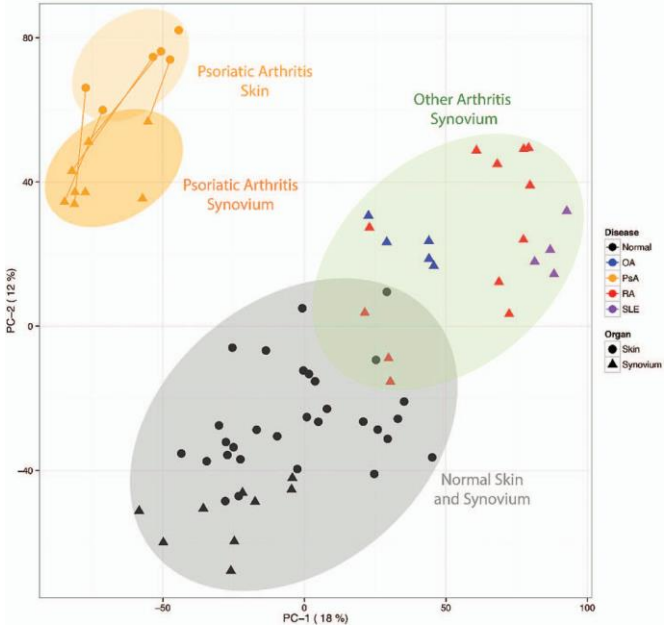


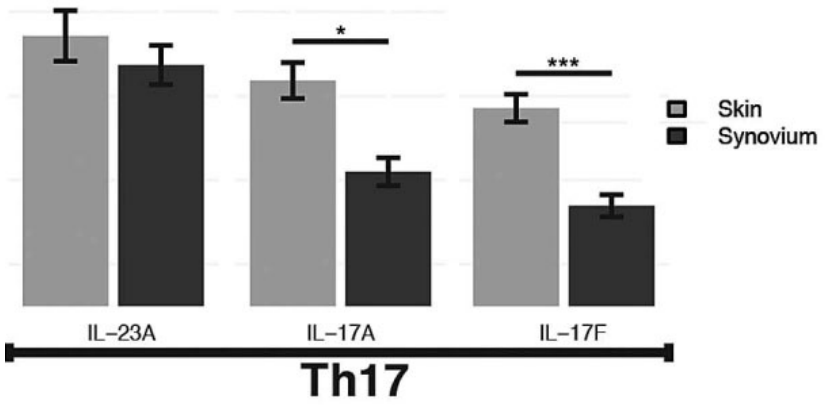
- Among patients treated with biologics, 52.1% were receiving hem as monotherapy
- More patients treated with anti-IL-17 or-12/23 agents received them as monotherapy (64.2%) compared to those on TNFi monotherapy (49.4%, p=0.0001).

Fragoulis et al MJR 2024

Psoriatic arthritis
Synovium Vs Skin

- **Similarities & differences**
  - **TNF pathway, VEGF, TGF-β1 and IL-6**
    - **More activated in synovium**
  - **IL-23/-17 axis**
    - **More active in the skin**

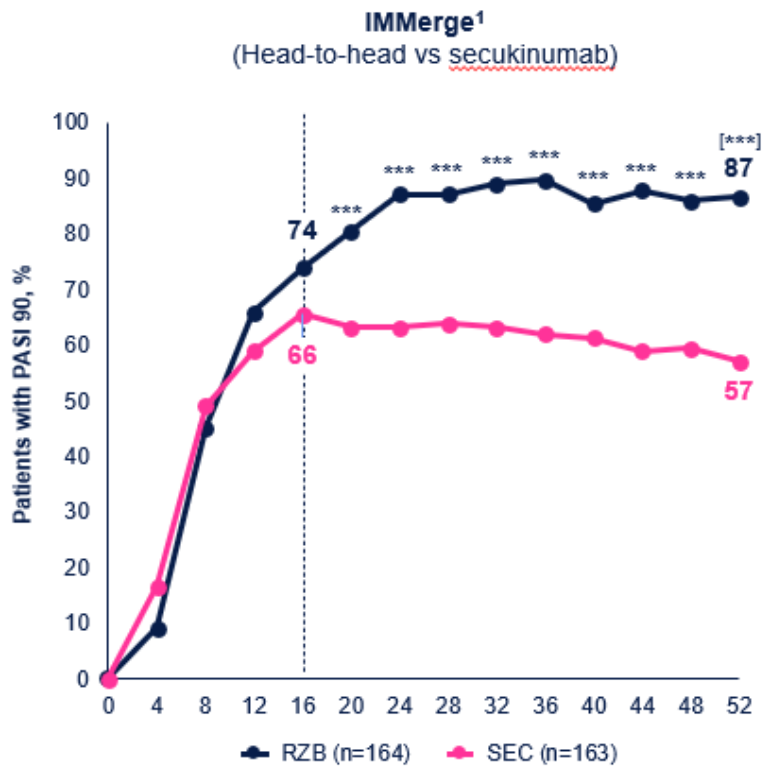


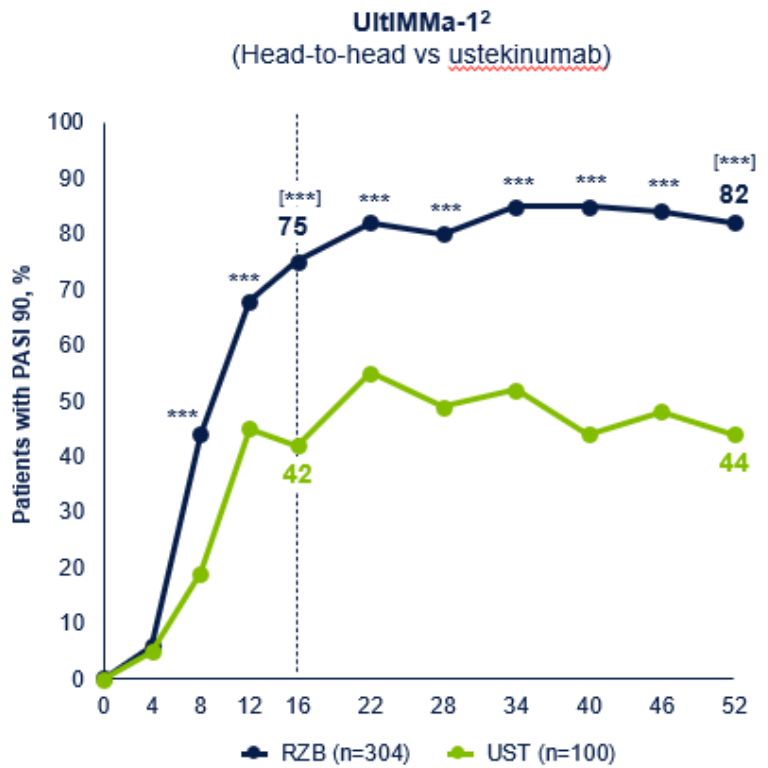


Belasco J et al Arthr Rheum 2015

Psoriatic arthritis – Skin IL-23/IL-17

Superior PASI 90 response vs secukinumab and ustekinumab in psoriasis



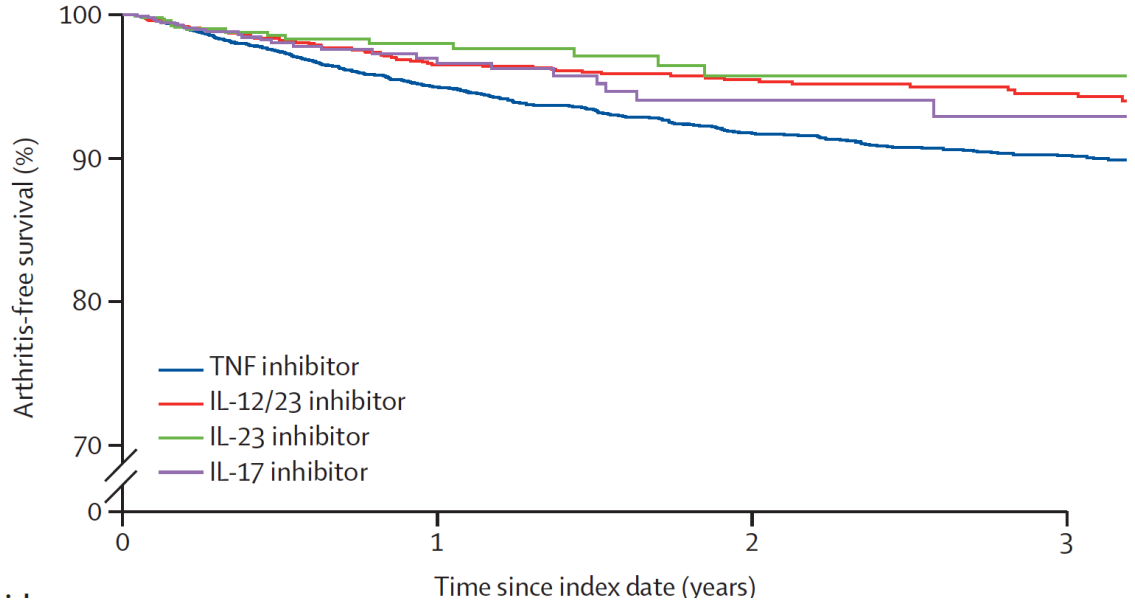


***p≤0.001 vs SEC/UST; Comparisons adjusted for multiplicity [ ]. Co-primary endpoints IMMerge: PASI 90 vs SEC (non-inferiority) at Week 16; PASI 90 vs SEC (superiority) at Week 52. Co-primary endpoints UltIMMa-1: PASI 90 and sPGA (0/1) vs placebo at Week 16. NRI used for missing data. NRI=non-responder imputation; PASI=Psoriasis Area and Severity Index; RZB=risankizumab; SEC=secukinumab; UST=ustekinumab.

1. Warren RB et al. *Br J Dermatol*. 2021;184:50-59. 2. Gordon KB et al. *Lancet*. 2018;392:650-661.

IL-23 inhibitors
Disease interception ?

- USA electronic health records
  - 15.501 PsO patients
    - 6.3% developed PsA
    - cumulative incidence of 2 6 cases per 100 person-years
- Treatment with IL-23i Vs TNFi or IL-17
  - According to first biologic class prescribed
  - associated with ⇩ risk of progression to PsA inflammatory arthritis
    - The results persisted in al 6 sensitivity analyses (e.g other definitions, drug switching etc)



Shikha S. et al, Lancet Rheumatology 2023

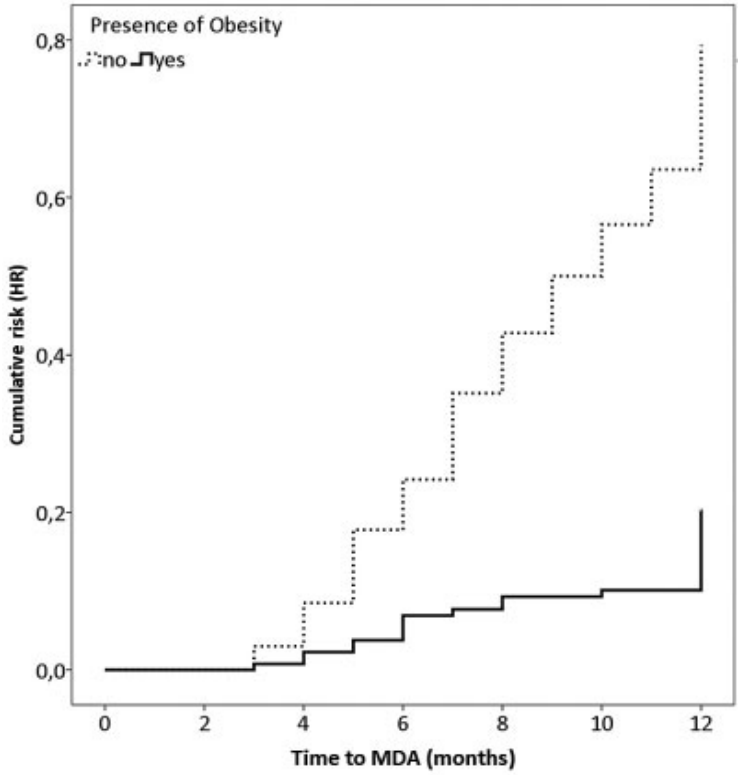
Adipose tissue
An inflammatory tissue

- **Adipose tissue**
  - **Adipocytes + Immune cells (B cells, T cells, Macrophages etc)**
    - **Lean state: homeostatic role**
    - **Obesity: Other cells (e.g Th17) take over**
      - ✓ **Producing inflammatory cytokines (e.g IL-17, TNF etc)**
      - ✓ **Macrophages are polarized towards M1 (more inflammatory..)**
      - ✓ **Alterations in adipokines**

Versini et al Autoimm Rev 2014

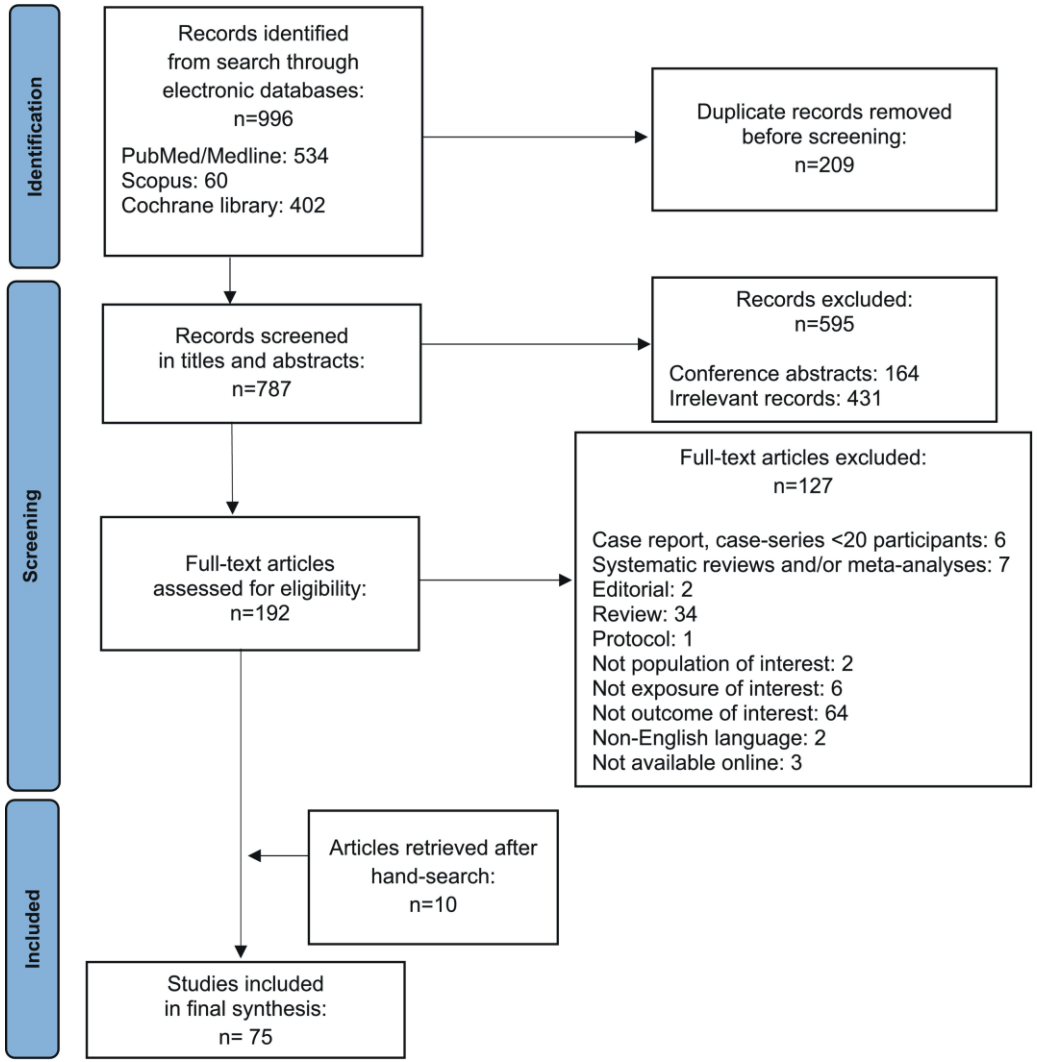
PsA Obesity: difficult to reach and maintain good outcome

- in a prospective study, PsA starting TNFi
  - 135 obese (BMI >30 kg/m2) patients Vs 135 patients of normal weight
  - Follow-up for 24 months
- Obese PsA patients
  - less likely to achieve MDA at month 12
    - [HR] 4.90, 95% confidence interval [95% CI] 3.04–7.87; *P* < 0.001
  - Those who achieve MDA, increased BMI was an adverse prognostic factor for maintaining MDA at month 24
    - HR 2.04, 95% CI 1.015–3.61; (P=0.014)



Fragoulis G et al Ther Adv M. Dis 2018
DiMinno et al Arthr Care & Res 2013

Effect of BMI in treatment efficacy b-ts-DMARDs



- Effect more pronounced for TNFi across IA
- IL 17i and IL-23i: less affected

Drug category	RA	PsA	SpA
Abatacept			
JAK inhibitors			
IL-17 inhibitors			
IL-23 inhibitors			
IL-6R inhibitors			
Rituximab			
TNF inhibitors			

Gialouri et al Autoimmunity Reviews 2023

Psoriatic arthritis
IBD

- 1.2% of PsO
- ~3% of PsA (mainly CD)
  - Possibly higher in those with PsA-axial
  - Few are known for subclinical inflammation

- Inflammatory bowel disease
  - Risk Ratio
    - Vs Healthy: 2.96 (1.40 - 6.00)
    - Vs Psoriasis 3.60 (1.83 – 7.10)

Charlton R et al Ann Rheum Dis 2018
McDonough E et al J Rheum 2014
Khraishi M et al Clin Rheum 2014
Husted JA et al Arthritis Care and Res 2014
Kimball AB J Am Acad Dermatol. 2008
Krishnadas R Brain Behav Immun 2016
Nikiphorou E, Fragoulis GE Ther Adv Musculoskelet Dis. 2018
Fragoulis GE et al Ther Adv Musc Dis 2020
Alinaghi et al J Crohns Colitis 2020
Jadon et al ARD 2017
Fragoulis et al Clin Exp Rheum 2022

AxSpA
IBD Treatment

Approved Drugs	
Ulcerative colitis	**Crohn's Disease**
TNFi	
Infliximab	Infliximab
Adalimumab	Adalimumab
Golimumab	Certolizumab
IL-23i	
Ustekinumab	Ustekinumab
Risankizumab (pre-reg)	Risankizumab
Guselkumab (pre-reg)	
JAKi	
Upadacitinib	Upadacitinib
Tofacitinib	

Whitlock SM et al J Am Acad Derm 2018
Feagan BG et al Lancet 2017

Serious Infections

- **23.333 PsA 11.457 axSpA patients**
- **Serious infections: 1.09/100py similar between PsA and AxSpA**
  - PsA (0.96 per 100 PY 95% CI 0.69 to 1.28)
  - axSpA (1.09 per 100 PY 95% CI 0.76 to 1.46).
- **Non-serious infections: 53.0/100 PY**
  - PsA (54.08 (95% CI 40.96 to 68.99, I2=98%))
  - axSpA (58.02 per 100 PY (95% CI 44.79 to 72.94, I2=98%))

In PsA patients (IRs) for Serious Infections

TNFi 1.36 per 100 PY (95% CI 0.72 to 2.16, I2=55%)
IL-17i 0.97 per 100 PY (95% CI 0.49 to 1.57, I2=47%)
JAKi 1.51 per 100 PY (95% CI 0.00 to 14.74, I2=31%)
IL-23i 0.29 per 100 PY (95% CI 0.00 to 1.03, I2=15%)
PDE4 0.38 per 100 PY (95% CI 0.00 to 1.19, I2=0%)

In axSpA patients,
TNFi 1.24 per 100 PY (95% CI 0.78 to 1.77, I2=28%)
IL-17i 1.20 per 100 PY (95% CI 0.59 to 1.96, I2=40%)
JAKi 1.28 per 100 PY (95% CI 0.00 to 13.77, I2=0%)
with JAKi

ORIGINAL RESEARCH

Incidence of infections in patients with psoriatic arthritis and axial spondyloarthritis treated with biological or targeted disease-modifying agents: a systematic review and meta-analysis of randomised controlled trials, open-label studies and observational studies

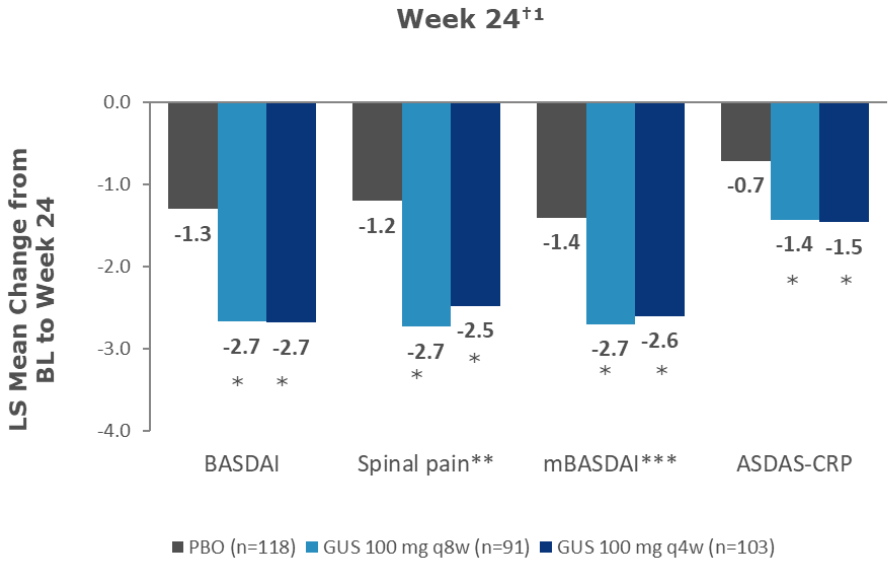
Ustekinumab in Axial PsA
Data from Psummit-1 & 2

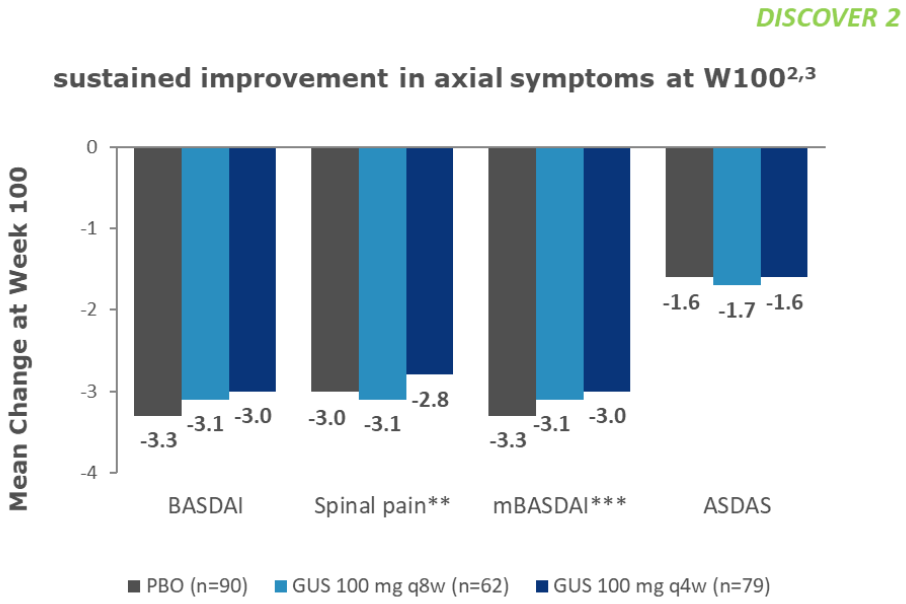
- **Pooled data from PSUMMIT 1 & 2**
  - **the presence of spondylitis at baseline was based solely on the treating physician's assessment**
- **Week 24**
  - **mean changes were larger in UST Vs PBO**
  - **mBASDAI (−2.09 vs −0.59).**
  - **⇧ proportions of UST Vs PBO achieved ASDAS clinically important improvement**
    - **decrease ≥ 1.1; 49.6% vs 12.7%; nominal p<0.05**

Helliwell PS et al, RMDOpen 2020

Guselkumab in Axial PsA
Data from Discover 1-2

- ***n=312***
- ***Axial involvement: sacroiliitis at baseline and either a history of imaging confirmation or pelvic x-ray at screening (post-hoc)***
- ***30% were HLA-B27 + (Results irrespective to B27 status)***





Mease et al, (2021); Lancet Rheumatol
Adapted, with permission from Mease et al. Abstract Supplement ACR Convergence 2021. Arthritis Rheumatol 73:1–4204

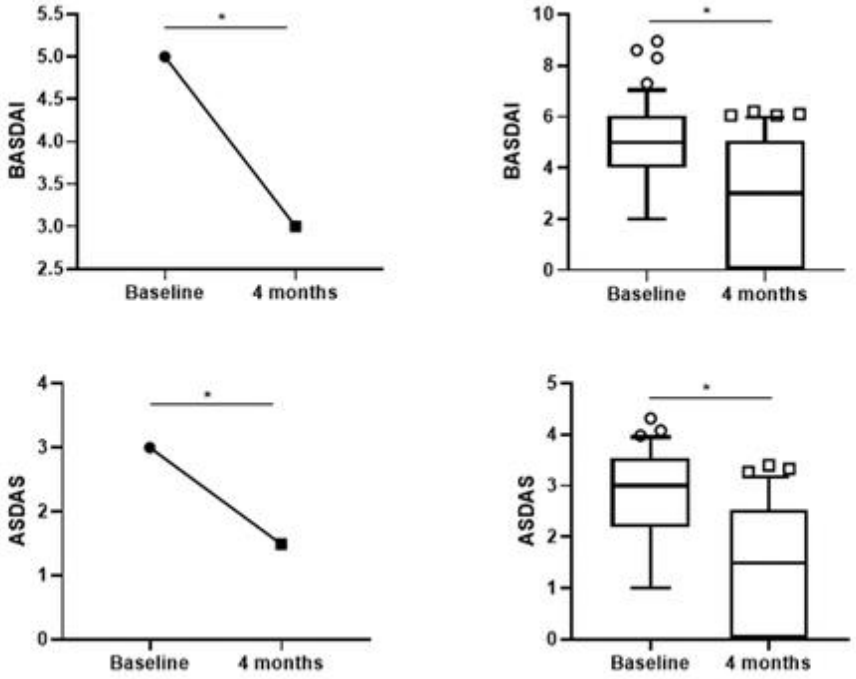
IL-23
Axial-PsA

- Axial-PsA differs from AS
- IL-23i promising for PsA-Axial
- Waiting for results

Gialouri CG et al, Mediterr J Rheumatol. 2022

IL-23 in PsA
Real-life data

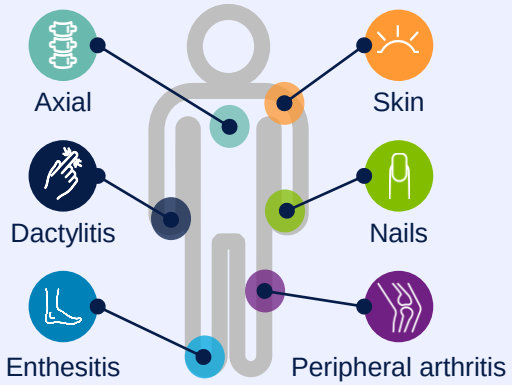
- 67 PsA patients with axial involvement (Subjective + XR OR MR)
  - Received anti-IL-23 for 4 months
  - In 27 patients
    - MRIs before and after
  - Significant BASDAI and ASDAS improvement
  - MRI: ⇩ > 0.80 score SI was observed in 70.3% of pts
    - Paralleled clinical improvement



Ruscitti et al Rheumatology (Oxf) 2024

IL-23 in PsA

Efficacy across all PsA domains[1-3]



Efficacy across patient groups[4]

Disease Characteristics
# of active joints
Baseline hsCRP
PsA duration

Prior Biologic Use
Prior Biologic Use

Baseline Demographics
Age, Sex, BMI, Race

Concomitant Medication Use
Baseline concomitant csDMARD

Superior skin clearance in PsO[5,6]

Superior PASI 90 response and skin clearance vs secukinumab

Patients with PASI 90 at Week 52 (%)

Patients with sPGA 0 or 1 at Week 52 (%)

Superior PASI 90 response and skin clearance vs ustekinumab

Patients with PASI 90 at Week 52 (%)

Patients with sPGA 0 or 1 at Week 52 (%)

BMI=body mass index; csDMARD=conventional synthetic disease-modifying antirheumatic drug; hsCRP=high sensitive c-reactive protein; PASI=psoriasis activity severity index; PsA=psoriatic arthritis; PsO=psoriasis; SEC=secukinumab; sPGA=static Physician's Global Assessment; UST=ustekinumab.

1. Kristensen LE et al. *Rheumatology (Oxford)*. 2022 Oct 25; Online ahead of print. **2.** Kristensen LE et al. *J Eur Acad Dermatol Venereol*. 2022 May;36(5):e389-e392. **3.** Kristensen LE et al. POS1524; presented at EULAR 2023. **4.** Merola JF et al. POS1032; presented at EULAR 2022. **5.** Warren RB et al. *Br J Dermatol*. 2021;184:50-59. **6.** Gordon KB et al. *Lancet*. 2018;392:650-661.

Thank You

Please complete the evaluation form