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Advancing Oral Therapies in Psoriasis: Targeted Innovation for Improved Disease Control and Patient Adherence

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Disclosures

James Krueger, MD, PhD: Consultant (ongoing)—AbbVie, Amgen, Bristol Meyers Squibb, Celgene, Celltrion, Dermavant, Genentech, Incyte, Intercept, Janssen, Lilly, Novartis, Pfizer, Prometheus, Regeneron Pharmaceuticals Inc., Roche, Roivant, RWE, Sanofi, Takeda, Target

Brad P. Glick, DO, MPH, FAAD: Advisory Board (ongoing)—AbbVie, Amgen Inc., Arcutis Biotherapeutics, Bristol Myers Squibb, Dermavant Sciences Inc., Dermira Inc., Eli Lilly and Company, Galderma, Incyte, Janssen Pharmaceuticals, LEO Pharma, Novartis, Ortho Dermatologics, Pfizer Inc., Regeneron P; consultant (ongoing)—AbbVie, Amgen Inc., Arcutis Biotherapeutics, Bristol Myers Squibb, Dermavant Sciences Inc., Dermira Inc., Eli Lilly and Company, Galderma, Incyte, Janssen Pharmaceuticals, LEO Pharma, Novartis, Ortho Dermatologics, Pfizer Inc., Regeneron P; grant/research support (ongoing)—AbbVie, Amgen Inc., Arcutis Biotherapeutics, Bristol Myers Squibb, Dermavant Sciences Inc., Dermira Inc., Eli Lilly and Company, Galderma, Incyte, Janssen Pharmaceuticals, LEO Pharma, Novartis, Ortho Dermatologics, Pfizer Inc., Regeneron P; Speakers' Bureau (ongoing)—AbbVie, Amgen Inc., Arcutis Biotherapeutics, Bristol Myers Squibb, Dermavant Sciences Inc., Dermira Inc., Eli Lilly and Company, Galderma, Incyte, Janssen Pharmaceuticals, LEO Pharma, Novartis, Ortho Dermatologics, Pfizer Inc., Regeneron P

Learning Objectives

- Assess current unmet needs in managing moderate-to-severe PsO, including the implications of under-treatment, nonadherence, comorbid conditions, and the need for more effective and tolerable therapies
- Describe the pathophysiology of PsO, with a focus on the role of the JAK/STAT signaling pathway and the relevance of targeting JAKs and TYK2 for disease management
- Evaluate the clinical evidence supporting current and emerging oral therapies for moderate-to-severe PsO, including head-to-head comparisons and long-term efficacy and safety data
- Identify appropriate candidates for oral therapies and create individualized treatment strategies that reflect patient preferences, therapeutic efficacy, and safety considerations

PsO = psoriasis.

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Psoriasis Overview: Unmet Needs Remain

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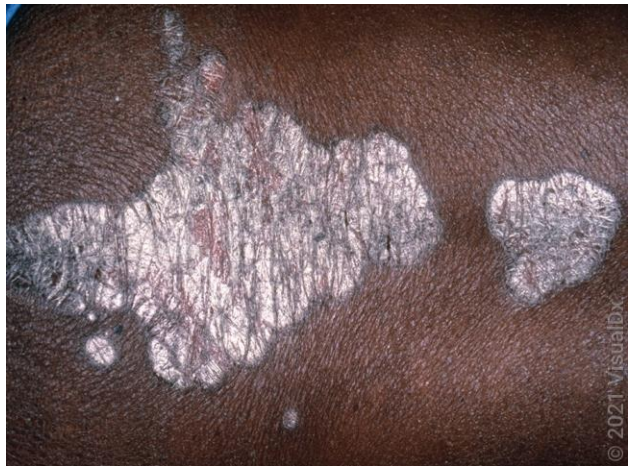
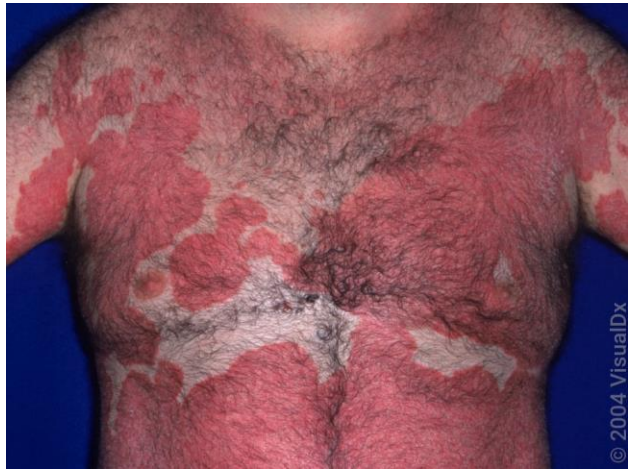
Psoriasis: Epidemiology and Disease Burden

- Chronic immune-mediated disease affecting ~2-3% of adults worldwide (125M)
  - Bimodal distribution (2 peaks: ~16-22 years and ~55-60 years)
- Up to 30% develop psoriatic arthritis over time
- High impact on QoL comparable to diabetes, cancer, and CVD
- Significant work productivity loss, psychosocial burden, and stigma



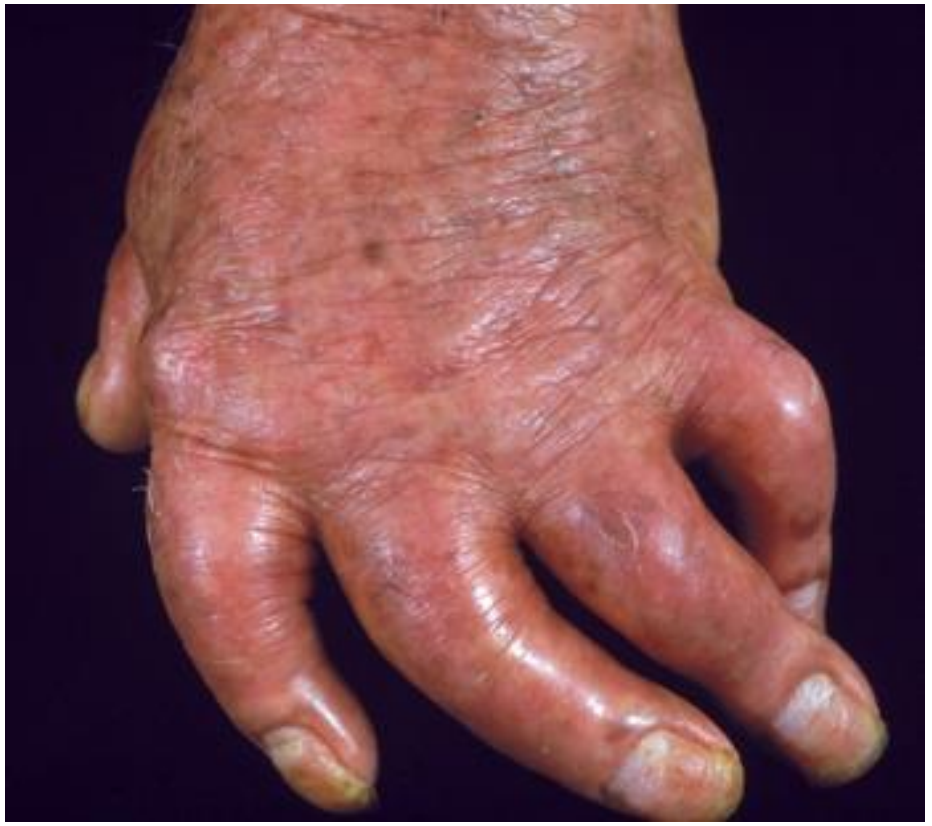


QoL = quality of life; CVD = cardiovascular disease.

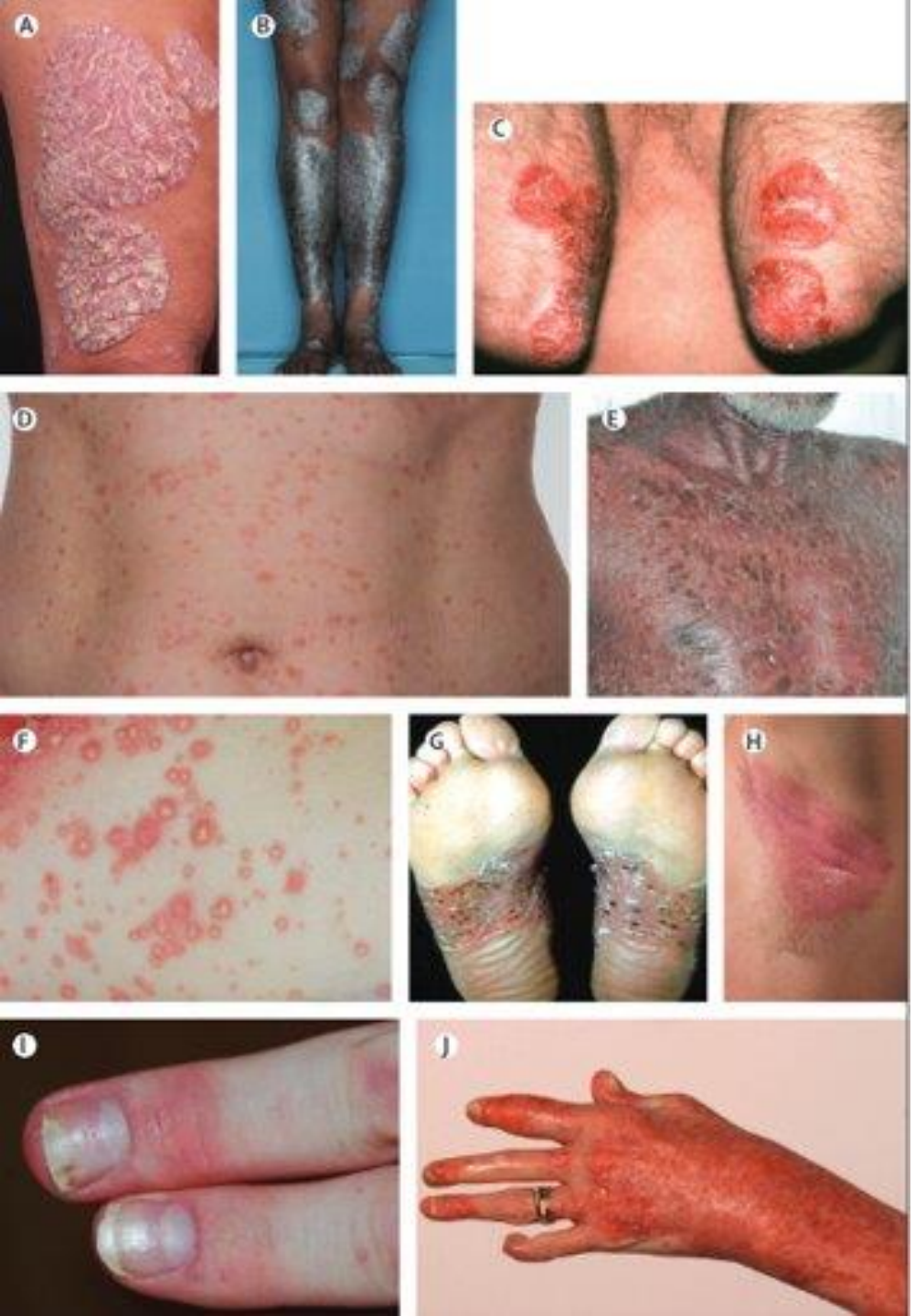
Griffiths CEM, et al. *Lancet*. 2021;397(10281):1301-1315. National Psoriasis Foundation (NPF) [www.psoriasis.org]. Accessed January 22, 2026. https://www.psoriasis.org/psoriasis-statistics. Parisi R, et al. *J Invest Dermatol*. 2013;133(2):377-385. Rapp SR, et al. *J Am Acad Dermatol*. 1999;41(3 Pt 1):401-407.

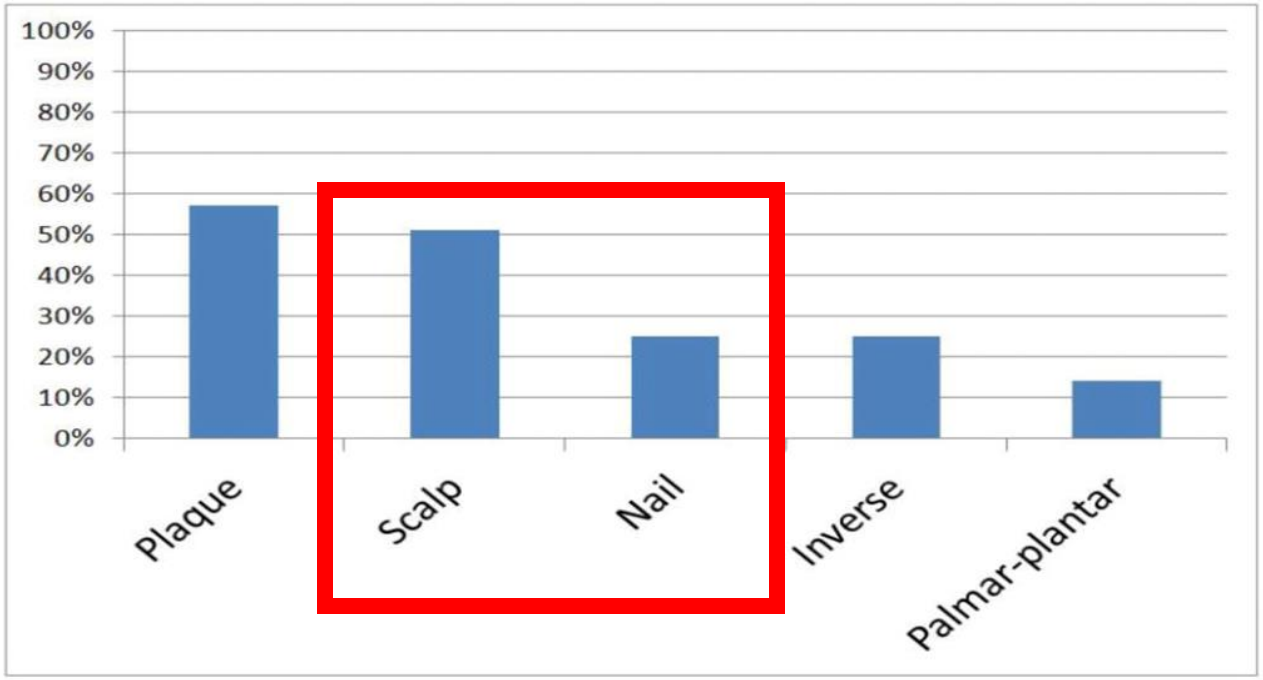
Psoriatic Disease

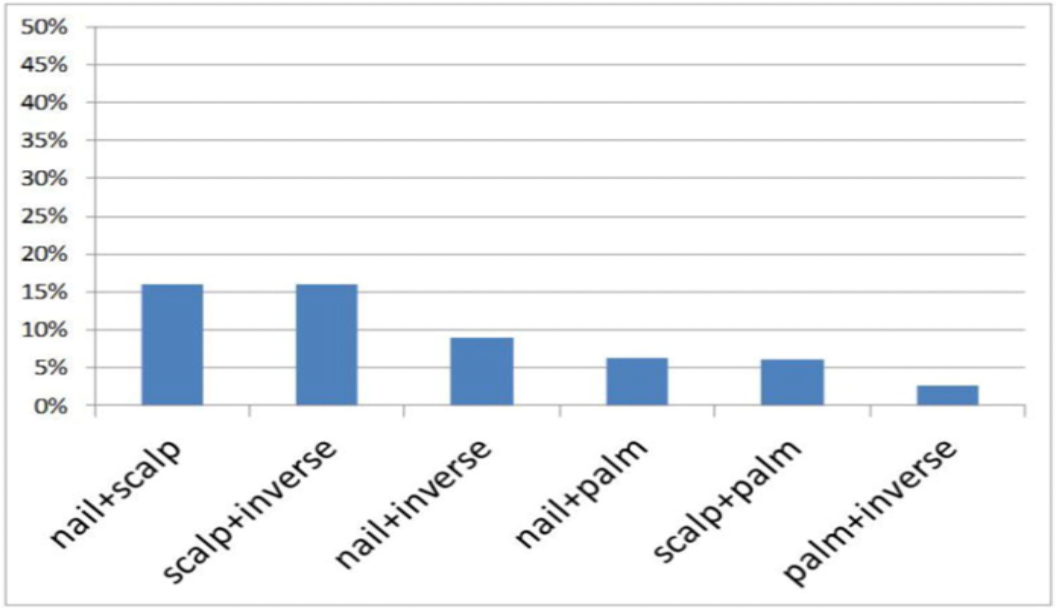
- Multiple important PsO comorbidities
  - Psoriatic arthritis
  - Inflammatory bowel disease
  - Cardiovascular disease
  - Metabolic syndrome
  - Diabetes mellitus
  - Obesity
  - Dyslipidemia
  - Hypertension
  - Psychiatric comorbidities
- Comorbidities impact therapeutic selection and choice



Griffiths CEM, et al. *Lancet*. 2021;397(10281):1301-1315.

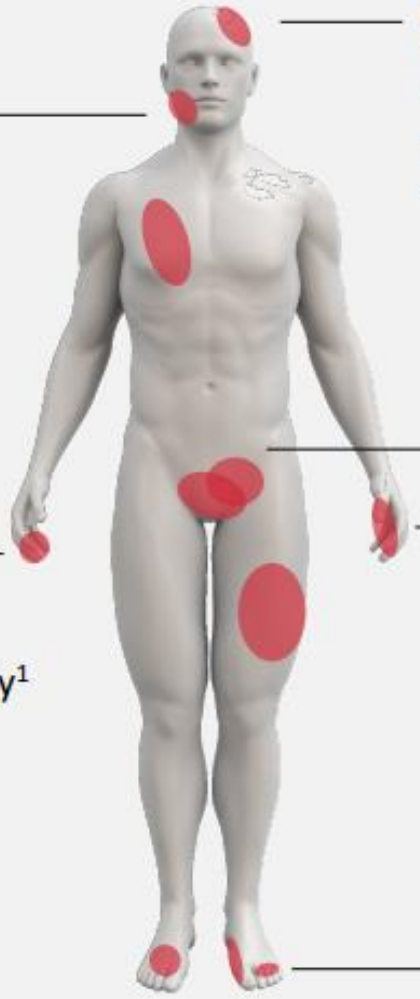






Merola JF, et al. *Clin Exp Dermatol*. 2016;41(5):486-489. Griffiths CEM, et al. *Lancet*. 2021;397(10281):1301-1315.

High-Impact Areas Bring Clinical Challenges and Greater Burden



FACE

25%–50%[1,2]

- Highly visible area[1]
- May affect chewing or swallowing[1]

SCALP

45%–80%[1-4]

- Highly visible, may cause embarrassment[1,5]
- May cause itching and bleeding[1,5]

NAIL

22%–55%[1-4]

- Increased absenteeism and lack of productivity[1]
- Affects dexterity and daily activities[1]

GENITALS

25%–40%[1,2]

- Pain and emotional burden[6]
- Negatively affects sexual health[6]

PALMOPLANTAR

12%–37%[1,2]

- Causes pain/soreness[3]
- Hinders mobility and daily activities[8,9]

1. Merola JF, et al. *Dermatol Ther*. 2018;31(3):e12589. 2. Horner ME, et al. *Dermatol Ther (Heidelb)*. 2024;14(1):187-199. 3. Augustin M, et al. *Br J Dermatol*. 2019;181(2):358-365. 4. Bhutani T, et al. *The Psoriasis and Psoriatic Arthritis Pocket Guide: Treatment Algorithms and Management Options*. 9th ed. Last updated March 2025. Accessed May 2025. https://www.psoriasis.org/the-pocket-guide. 5. Sampogna F, et al. *Acta Derm Venereol*. 2014;94(4):411-414. 6. Meeuwis KAP, et al. *J Dermatolog Treat*. 2018;29:754-760. 7. Callis Duffin K, et al. *Dermatology*. 2021;237(1):46-55. 8. Pettey AA, et al. *J Am Acad Dermatol*. 2003;49(2):271-275. 9. Chung J, et al. *J Am Acad Dermatol*. 2014;71(4):623-632.

Recategorization of Psoriasis Severity (IPC)

- Candidate for a topical therapy
- Candidate for a systemic therapy

PERSONALIZED AND PRECISION ASSESSMENTS

Systemic-eligible is defined as

- BSA of at least 10%

OR

- Disease involving special sites (scalp, palms/soles, nails, genitals, face)

OR

- Failure of topical therapy

BSA = body surface area.

International Psoriasis Council [www.psoriasiscouncil.org]. Last updated June 11, 2025. https://psoriasiscouncil.org/ipc-news/ipc-disease-severity-reclassification-global-traction.

HEALTH POLICY & PRACTICE

International Psoriasis Council psoriasis disease severity reclassification: Update on validity, acceptance, and implementation

Bruce E. Strober, MD, PhD,[a] Andrew Blauvelt, MD, PhD,[b] Peter CM. van de Kerkhof, MD, PhD,[c] Álvaro González-Cantero, MD, PhD,[d,e] Mona El-Kalioby, MSc, MD,[f] Cesar Gonzalez, MD,[g] Benjamin Hidalgo Matlock, MD,[h,i] Filip Rob, MD, PhD,[j] Pravit Asawanonda, MD, MSc, DSc,[k] Rudi Chandra, MD,[l] Julia-Tatjana Maul, MD,[m,n] Tiago Torres, MD, PhD,[o] and Lone Skov, MD, PhD[p]

HEALTH POLICY & PRACTICE

Clarifying psoriasis disease severity: A position statement from the National Psoriasis Foundation Medical Board

Andrew Blauvelt, MD, MBA,[a] Ronald Prussick, MD,[b] Joseph F. Merola, MD, MMSc,[c] Mona Shahriari, MD,[d] Jennifer Cather, MD,[e] Guy S. Eakin, PhD,[f] Leah McCormick Howard, JD,[f] Mark G. Lebwohl, MD,[g] April W. Armstrong, MD, MPH,[h] and Kristina Callis Duffin, MD[i]

Strober BE, et al. *J Am Acad Dermatol*. 2025;93(4):1154-1157. Blauvelt A, et al. *J Am Acad Dermatol*. 2025:S0190-9622(25)03487-5 [Epub ahead of print].

Why Oral Targeted Therapy Improves Outcomes

- Selective intracellular pathway inhibition
- PDE4: broad cytokine modulation
- TYK2: targeted IL-23/IL-12 signaling
- JAK: multi-cytokine control in selected patients
- Rapid onset and convenient dosing
- No injections or cold-chain storage
- Improved adherence and patient satisfaction
- Useful as bridge, maintenance, or early systemic therapy

IL = interleukin.

Armstrong AW, et al. *Dermatol Ther (Heidelb)*. 2024;14(2):421-439.

Current Challenges in Psoriasis Management

- Undertreatment common even in moderate-to-severe disease
- Treatment nonadherence driven by inconvenience, tolerability, and patient preferences
- Mismatch between physician-defined success and patient expectations
- Need for durable, effective, and convenient systemic options

Feldman SR, et al. *J Dermatol Treat*. 2022;33(3):1511-1520.

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Selecting Oral Systemic Therapy

Dermatol Ther (Heidelb) (2024) 14:421–439
https://doi.org/10.1007/s13555-023-01089-6

ORIGINAL RESEARCH

Evaluating Treatment Choice in Patients with Moderate to Severe Psoriasis in the United States: Results from a US Patient Survey

April W. Armstrong · Sayeli Jayade · Sanika Rege · Namita Joshi · Vardhaman Patel · Samaneh Kalirai · Daniel Wolin · Kimberly Boyle · Dipen Patel · Lauren Seigel

JOURNAL OF DERMATOLOGICAL TREATMENT
2024, VOL. 35, NO. 1, 2339440
https://doi.org/10.1080/09546634.2024.2339440

RESEARCH ARTICLE

Tradeoffs and decision-making in moderate to sev injectable treatments: data from patients and der

Saxon D. Smith[a†], Simon Fifer[b], Meredith Edwards[c], Anne W Bronwyn West[b] and Lynda Spelman[e]

Bottom Line:

Armstrong AW, et al. *Dermatol Ther (Heidelb)*. 2024;14(2):421-439. Smith SD, et al. *J Dermatolog Treat*. 2024;35(1):2339440.

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Pathophysiology and Newer Ways to Target Inflammation

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Chief Executive Officer, The Rockefeller University Hospital
New York City, New York

Psoriasis Pathophysiology: Chronic Activation of Type 3 Immunity (Typified by Type 17 T Cells)

Initiated by genetic susceptibility and environmental triggers

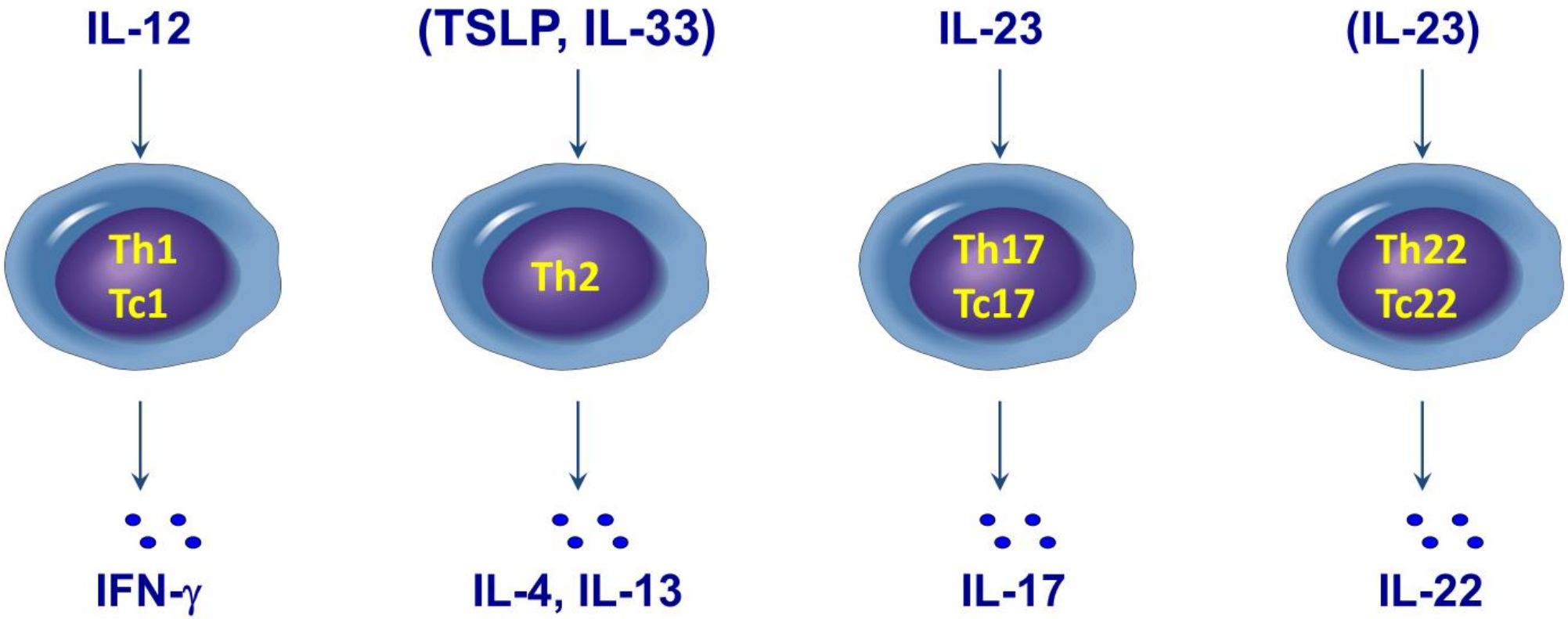
Activation of dendritic cells that overproduce IL-23 and synthesize IL-12

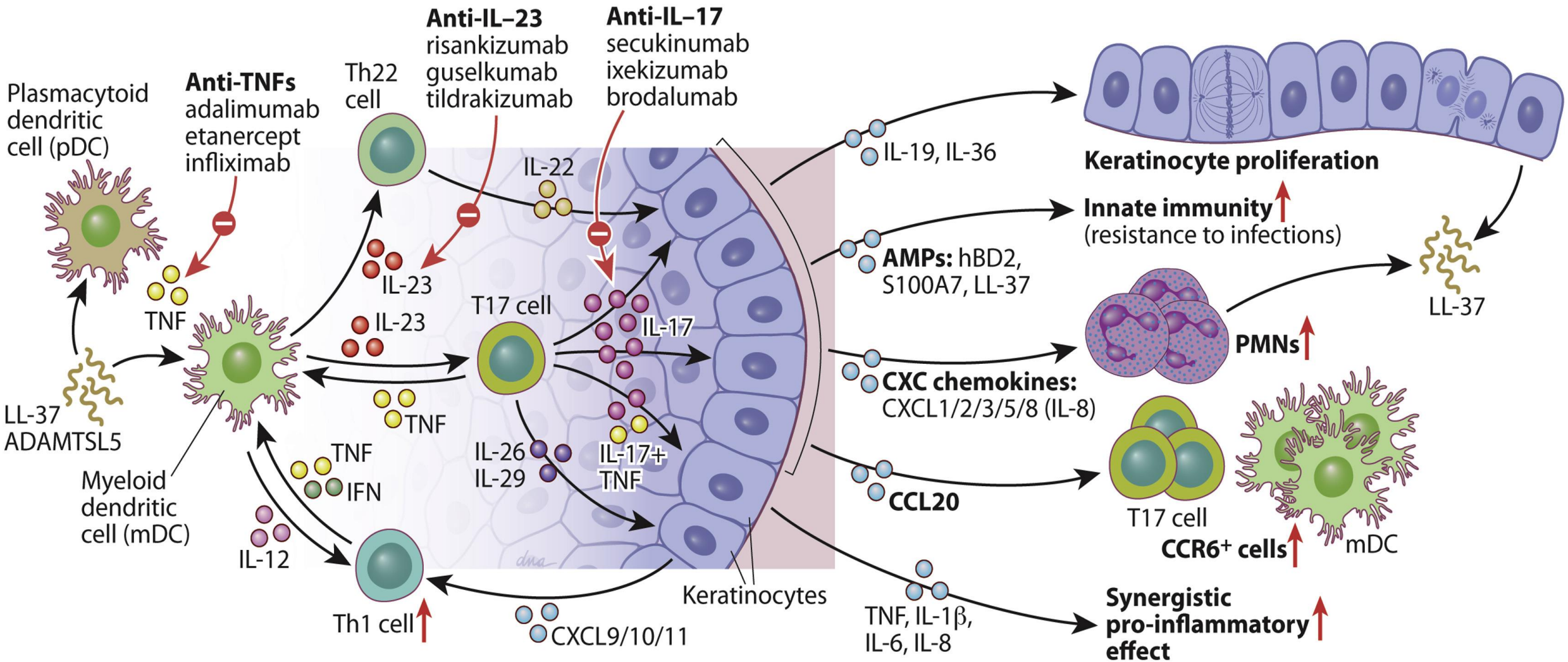
IL-23 induces pathogenic type 17 T cells that make large amounts of IL-17A and IL-17F
(IL-12 and IL-23 receptors critically dependent on specific JAK/STAT pathways)

Type 3 immunity has massive stimulation of the epidermis to produce cytokines and chemokines that mediate anti-microbial immunity, inflammation, and epidermal hyperplasia

Kim J, Krueger JG. *Annu Rev Med*. 2017:68:255-269.

Polar T-Cell Subsets

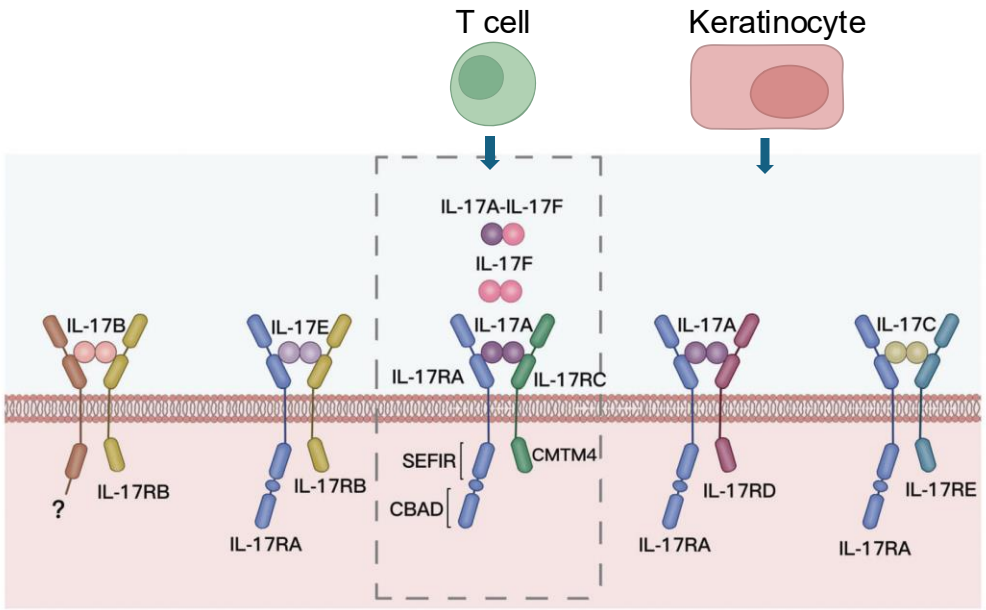




Hawkes JE, et al. *J Allergy Clin Immunol*. 2017;140(3):645-653.

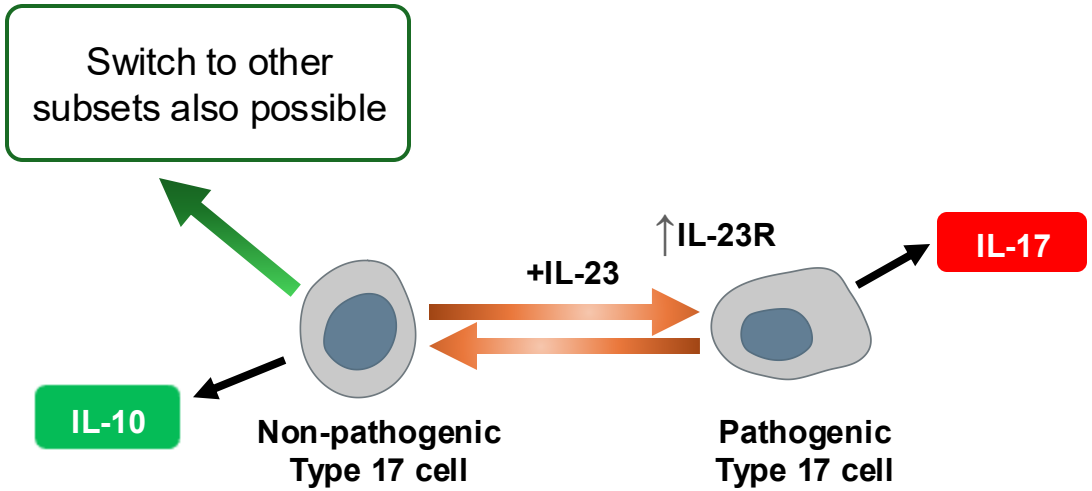
IL-17 Cytokine Family and T17 Cell Plasticity

The IL-17 family consists of six structurally related cytokines[1]



- **IL-17A and IL-17F** are the most related IL-17-family cytokines, and both are **produced mainly by T cells**
- IL-17RC is primarily expressed in non-hematopoietic epithelial cells and mesenchymal cells, which restricts IL-17A signaling to these two cell types

Plasticity of type T17 cells[2,3]



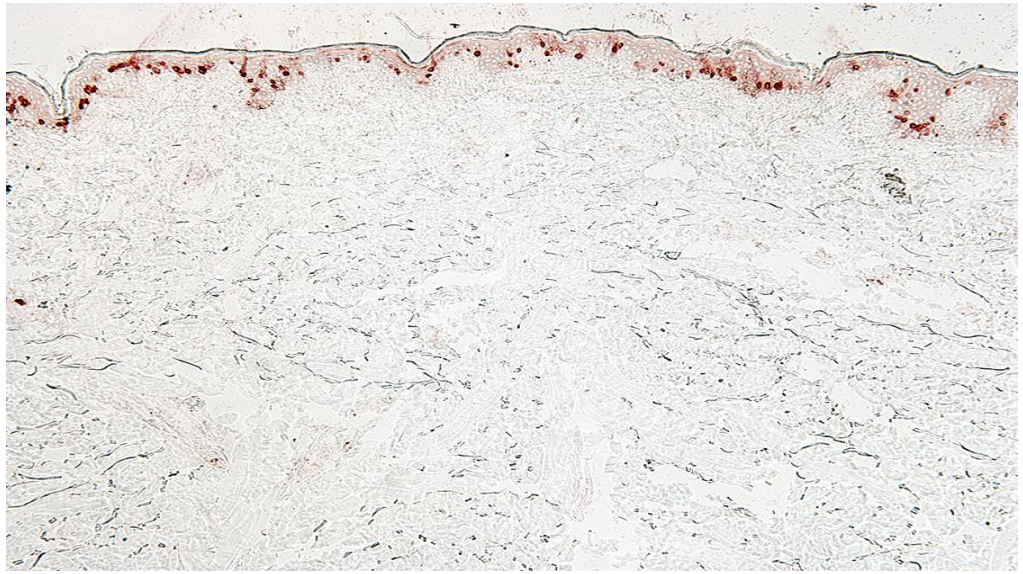
CBAD = C/EBPβ-activation domain; CMTM = chemokine-like factor (CKLF)-like MARVEL transmembrane domain-containing family; R = receptor; SEFIR = SEF/IL-17 receptor-like domain; T17 = T helper 17.

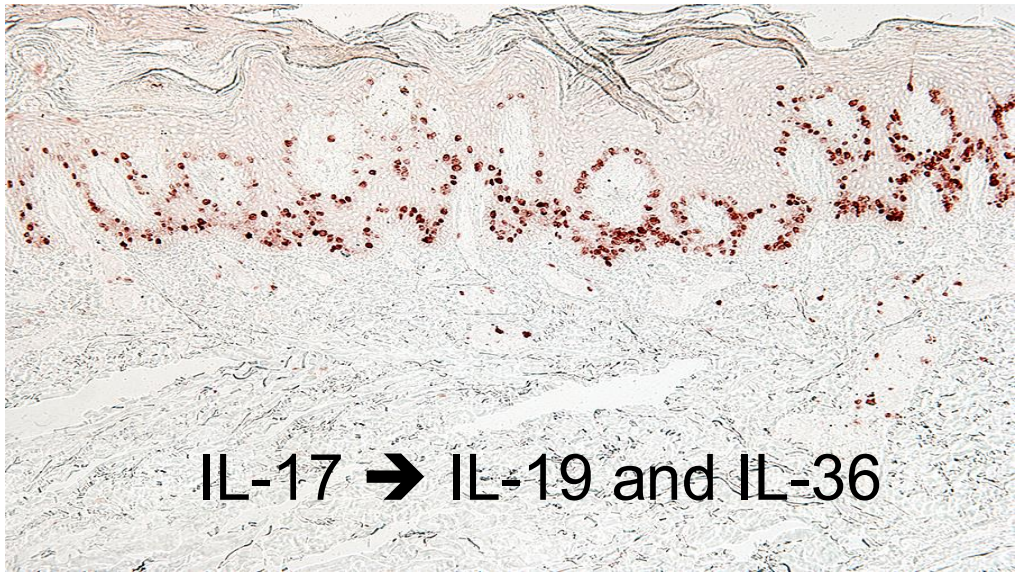
1. Huangfu L, et al. *Signal Transduct Target Ther*. 2023;8(1):402. 2. Wu X, et al. *Front Immunol*. 2018;9:1112. 3. Lee Y, et al. *J Clin Immunol.* 2014;34(Suppl 1):56-60.

NON-LESIONAL

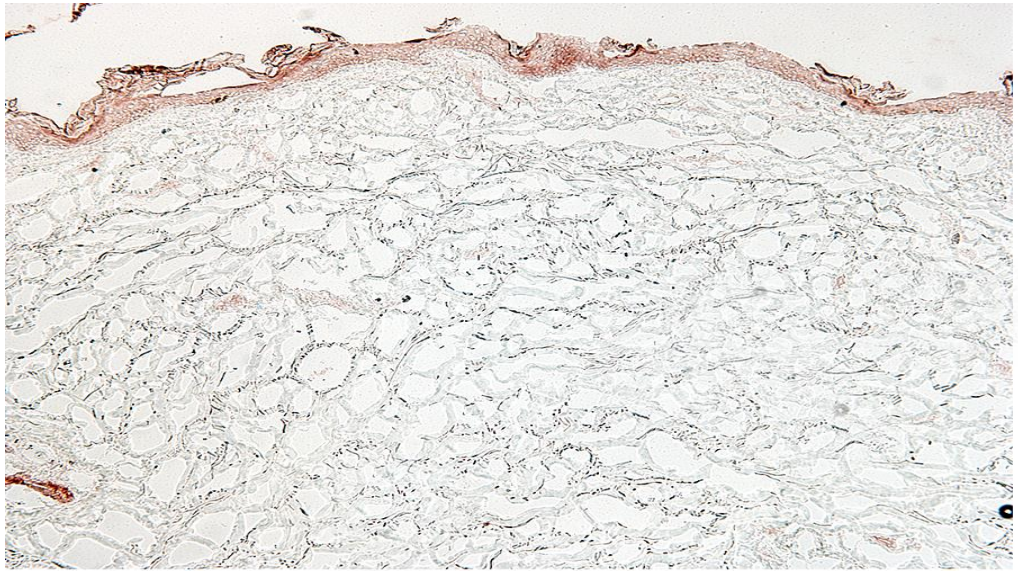
LESIONAL

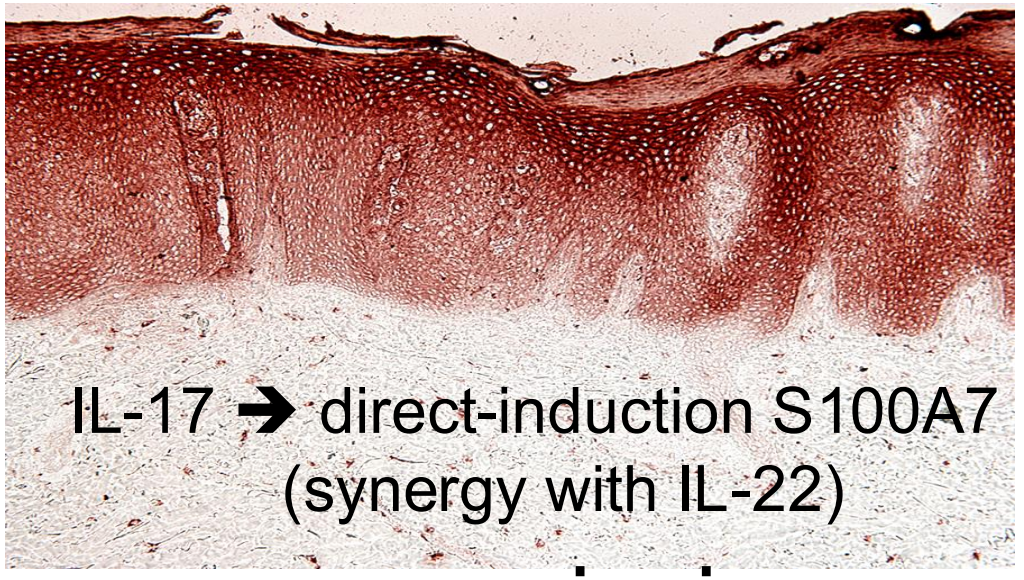
Ki-67





S100A7





psoriasin

Krueger Laboratory Archive.

NON-LESIONAL

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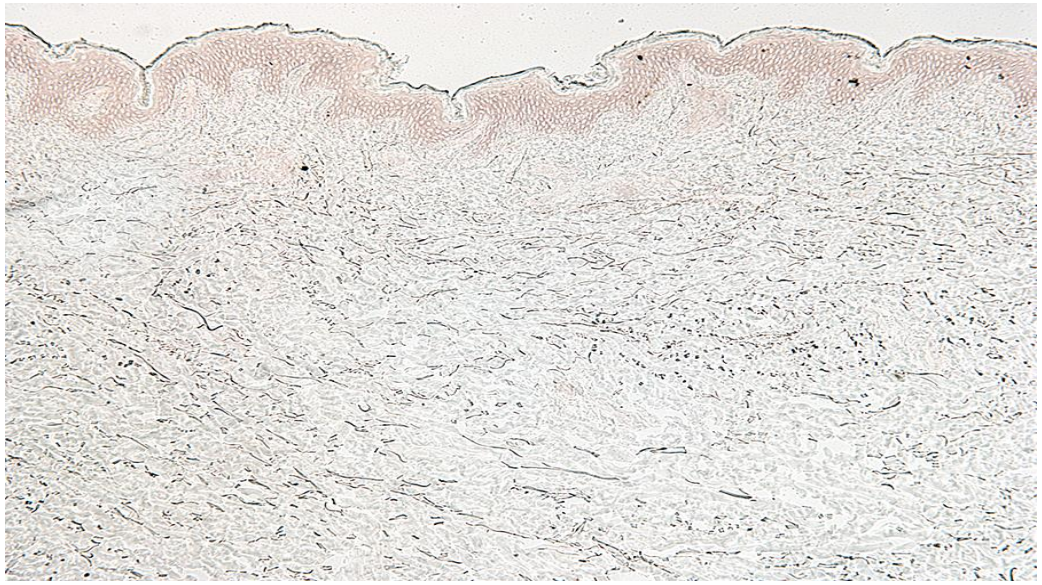
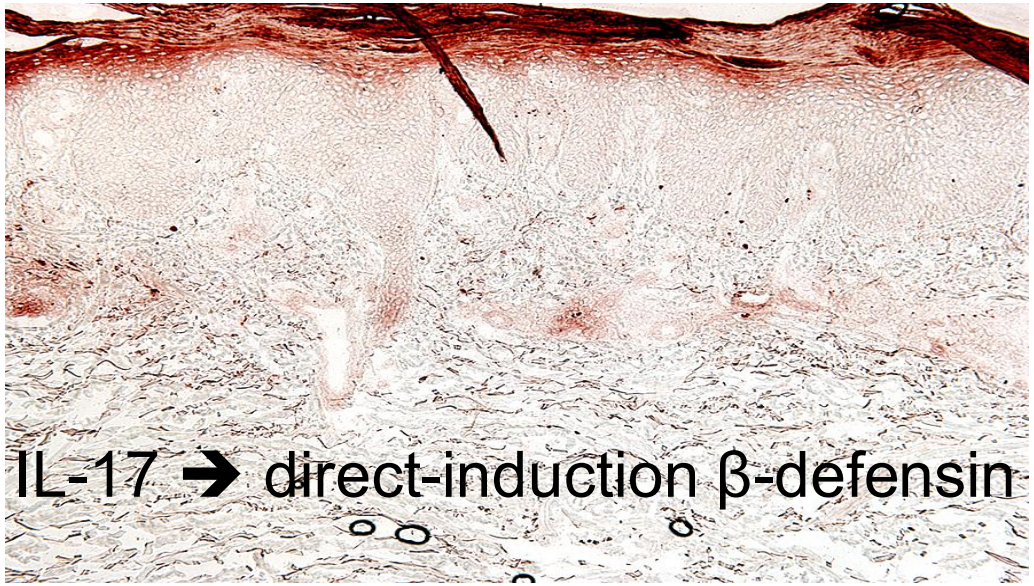
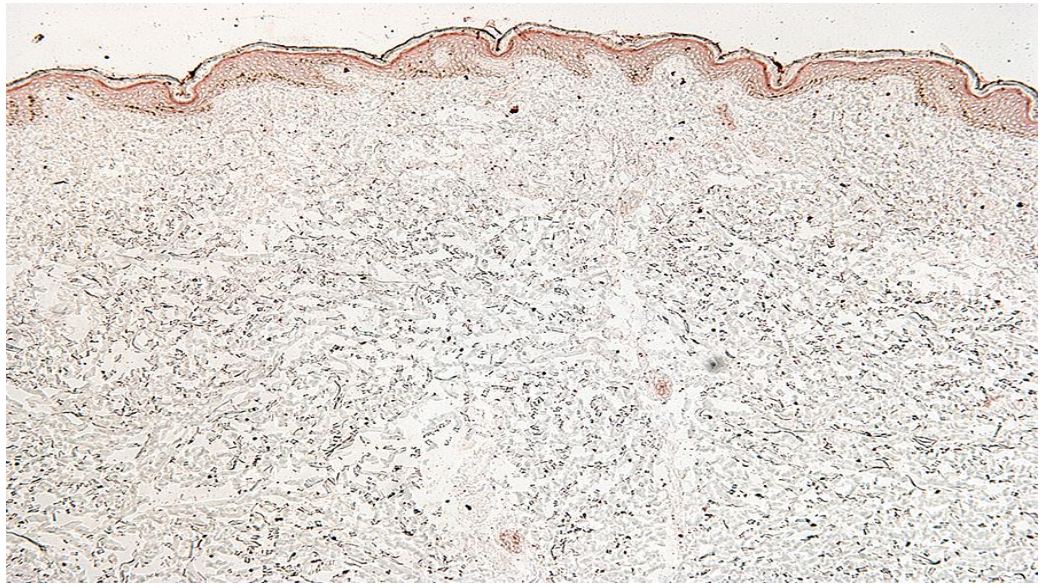
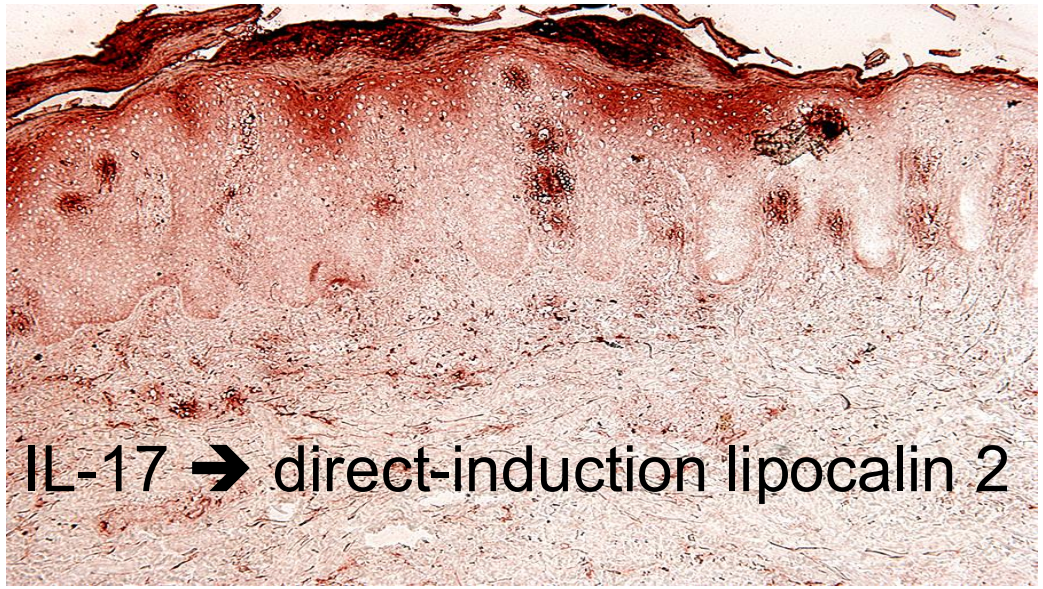
HBD-2



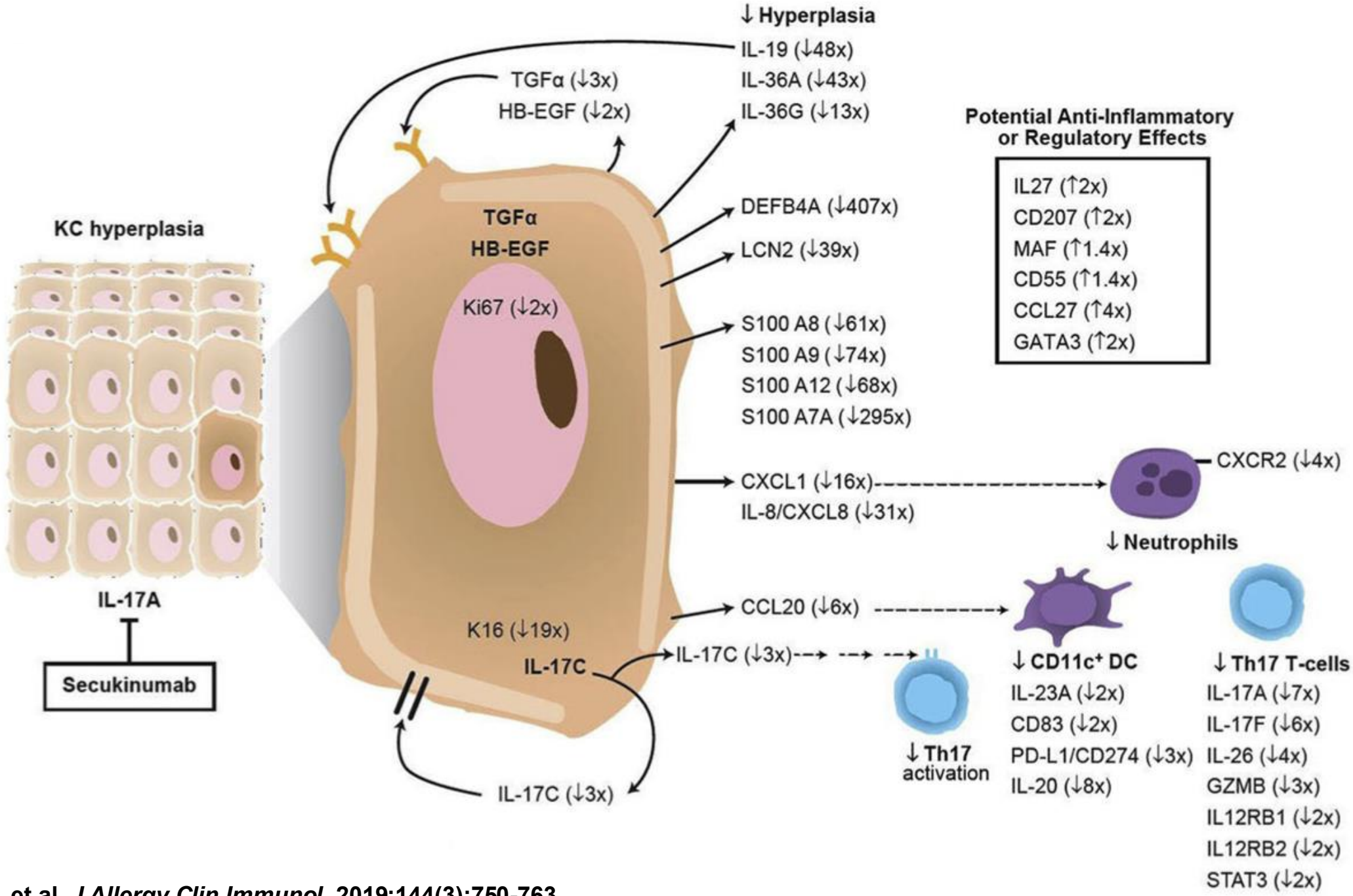


LCN-2

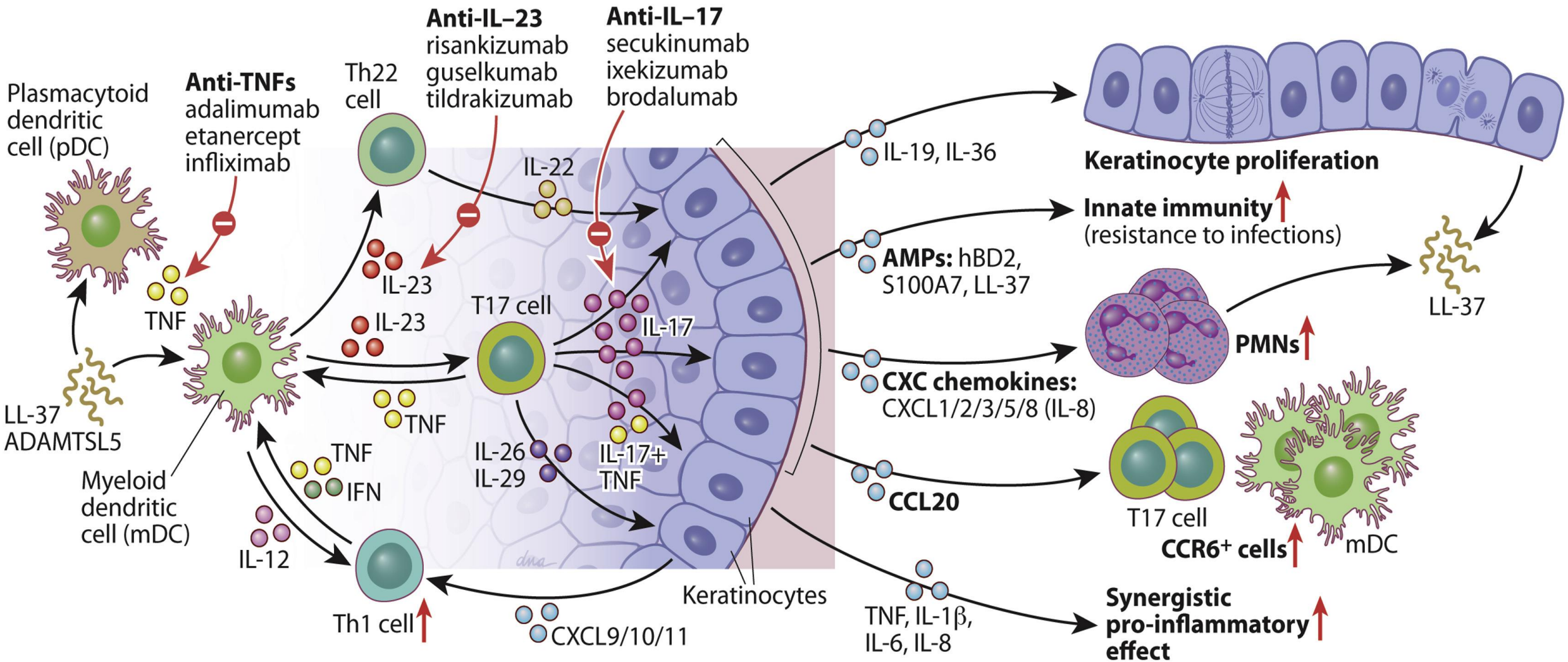




Krueger Laboratory Archive.

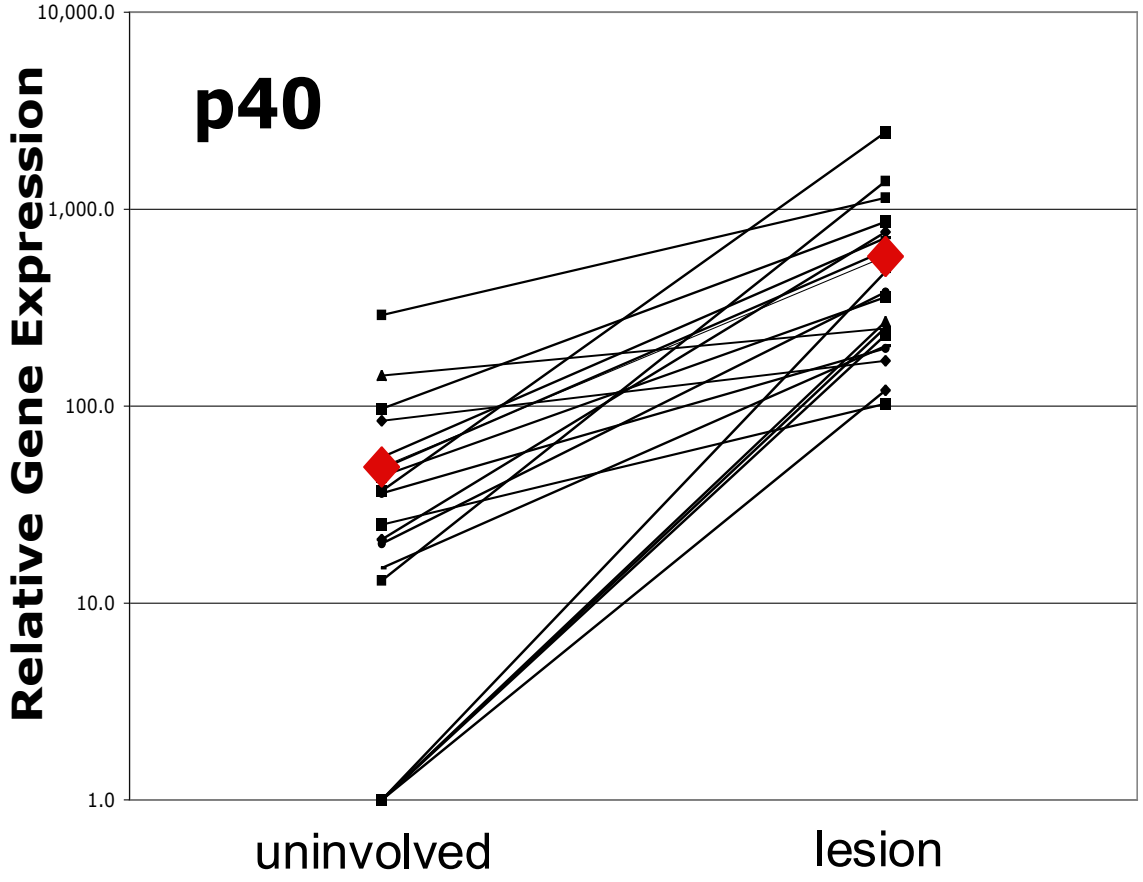


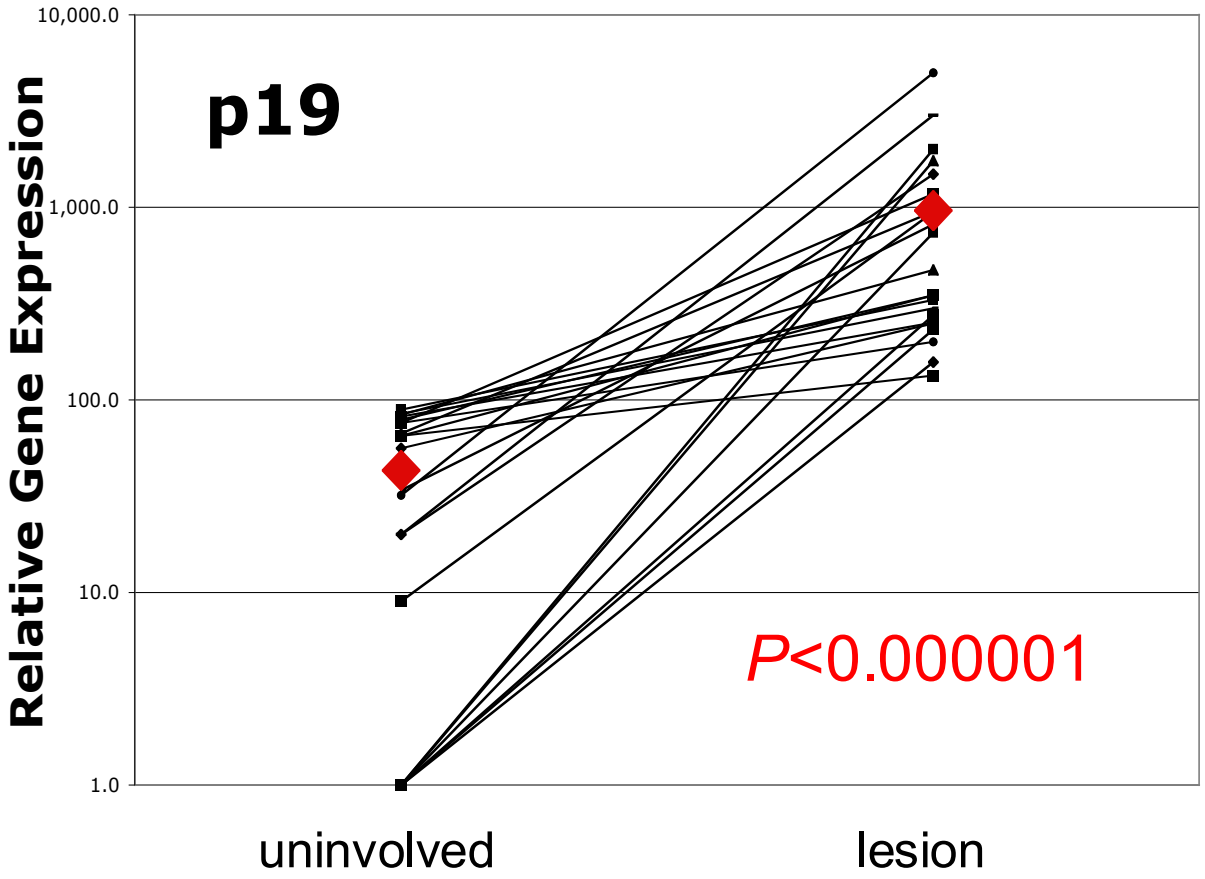
Krueger JG, et al. *J Allergy Clin Immunol*. 2019;144(3):750-763.



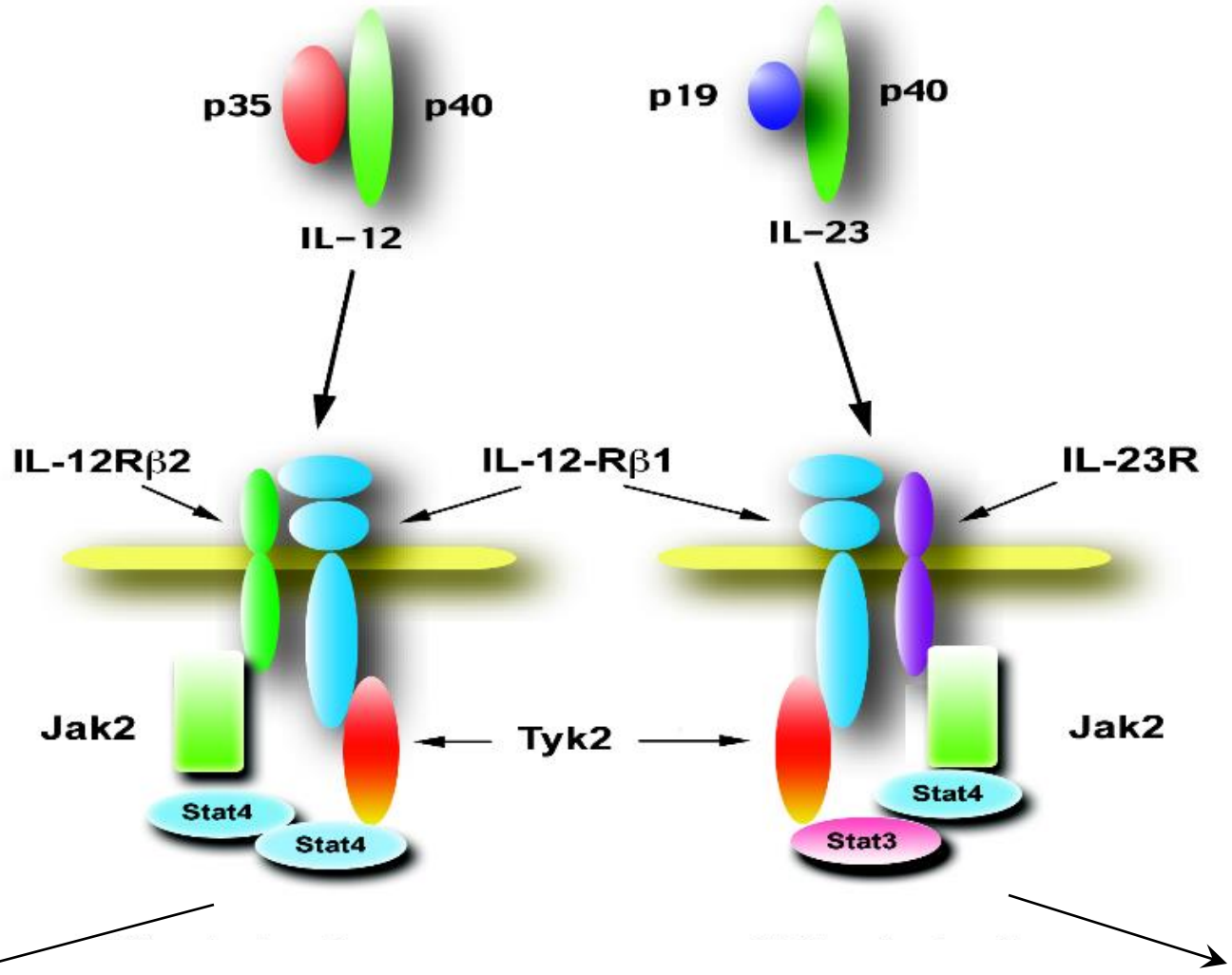
Hawkes JE, et al. *J Allergy Clin Immunol*. 2017;140(3):645-653.

Consistent Up-Regulation of p40 and p19 mRNAs (IL-23 Subunits) in Psoriasis Plaques, as Detected by Real-Time RT-PCR (Normalized to HARP mRNA)





In this work, IL-23 synthesis traced back to CD11c+ DCs.
mRNA = messenger RNA; RT-PCR = reverse transcription polymerase chain reaction; HARP = hyperacute response protein.
Lee E, et al. *J Exp Med*. 2004;199(1):125-130.



JAK/STAT signaling transduces cytokine signals, promoting a Th17 response that drives inflammation.

γ-interferon (Th1/Tc1)

IL-17A or IL-17F (Th17/Tc17)

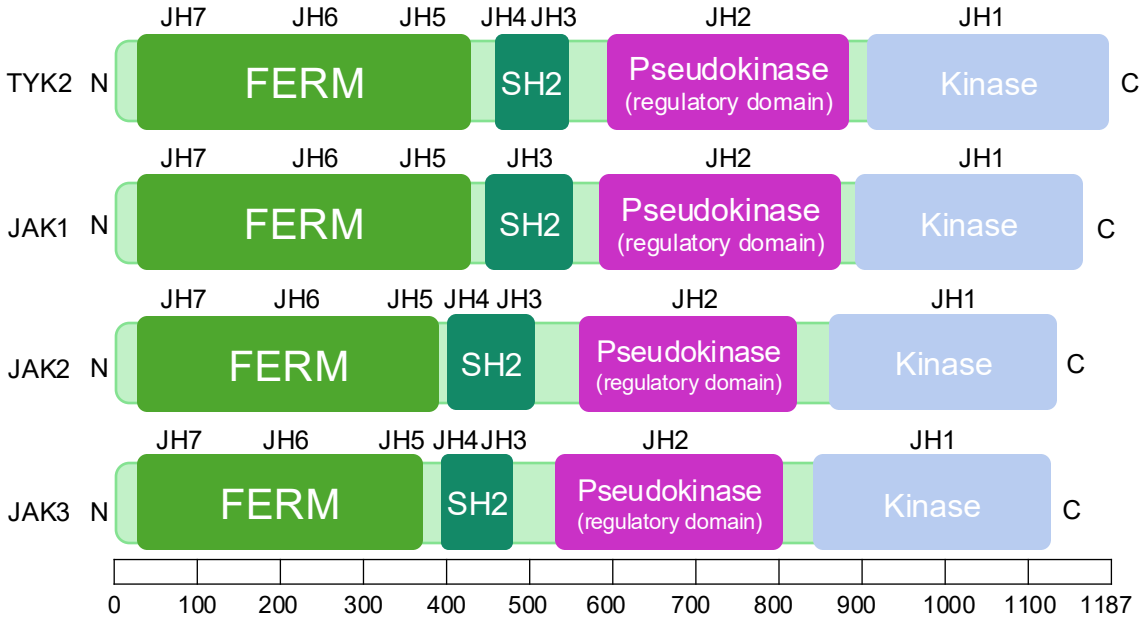
Genetic Association between TYK2 and Psoriasis

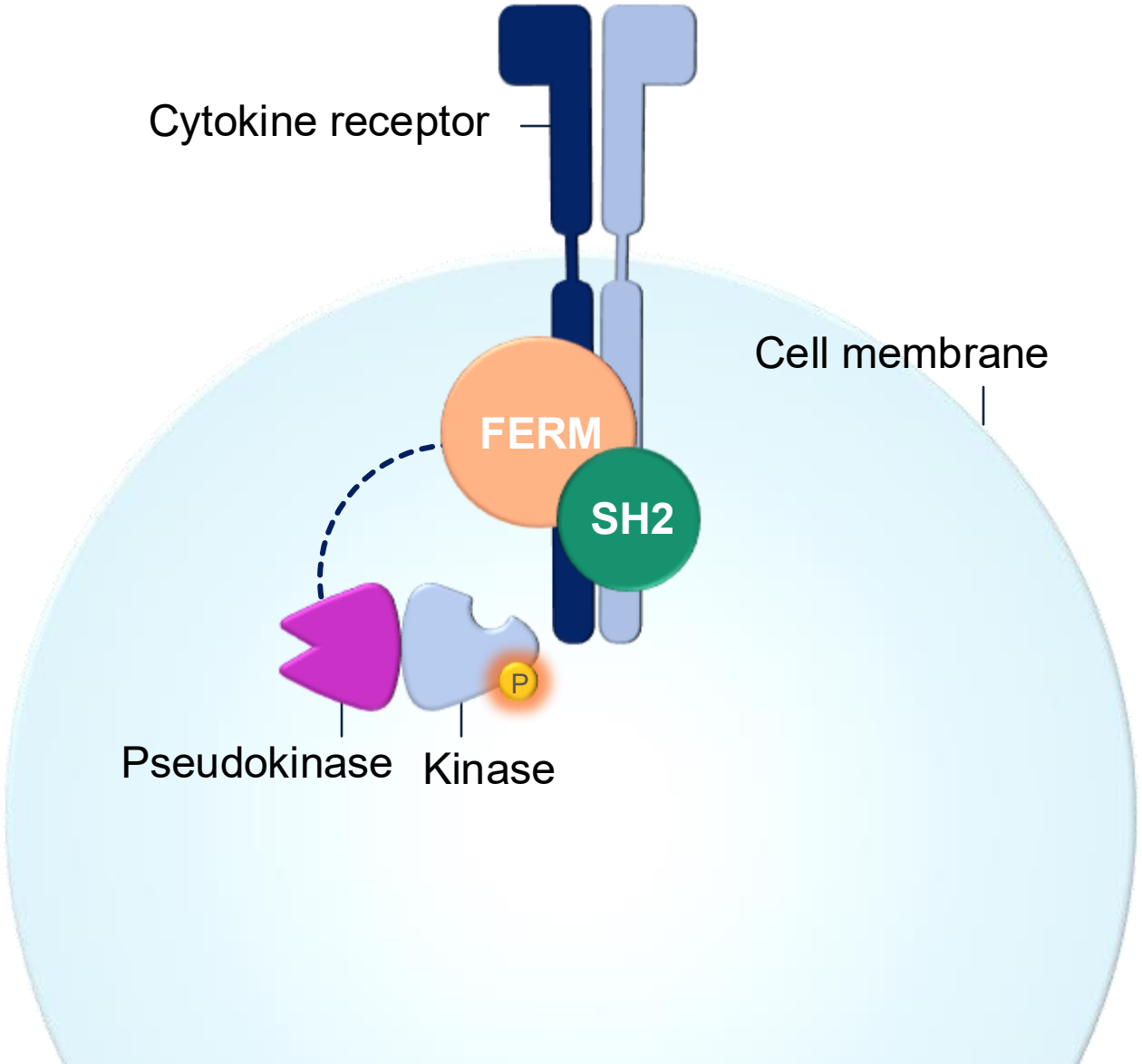
- Studies have shown genetic associations between members of the JAK-STAT pathway and PsO susceptibility
- The single nucleotide polymorphism (SNP) rs34536443 in TYK2 has been associated with PsO susceptibility
- Homozygous mutation in this SNP results in near complete loss of function of TYK2 and is protective against PsO
- Does not appear to be associated with increased risk of infection, cardiovascular disease, malignancy

TYK = tyrosine kinase.

Patel HA, et al. *Int J Mol Sci*. 2023;24(15):12310. Elyoussfi S, et al. *Expert Rev Clin Pharmacol*. 2023;16(6):549-558. Dai B, et al. *Psoriasis (Auckl)*. 2025;15:361-372. Mehrotra S, et al. *J Invest Dermatol*. 2025:S0022-202X(25)00531-7.

Janus Kinase Family: JAK1, JAK2, JAK3, and TYK2 (Tyrosine Kinase 2)

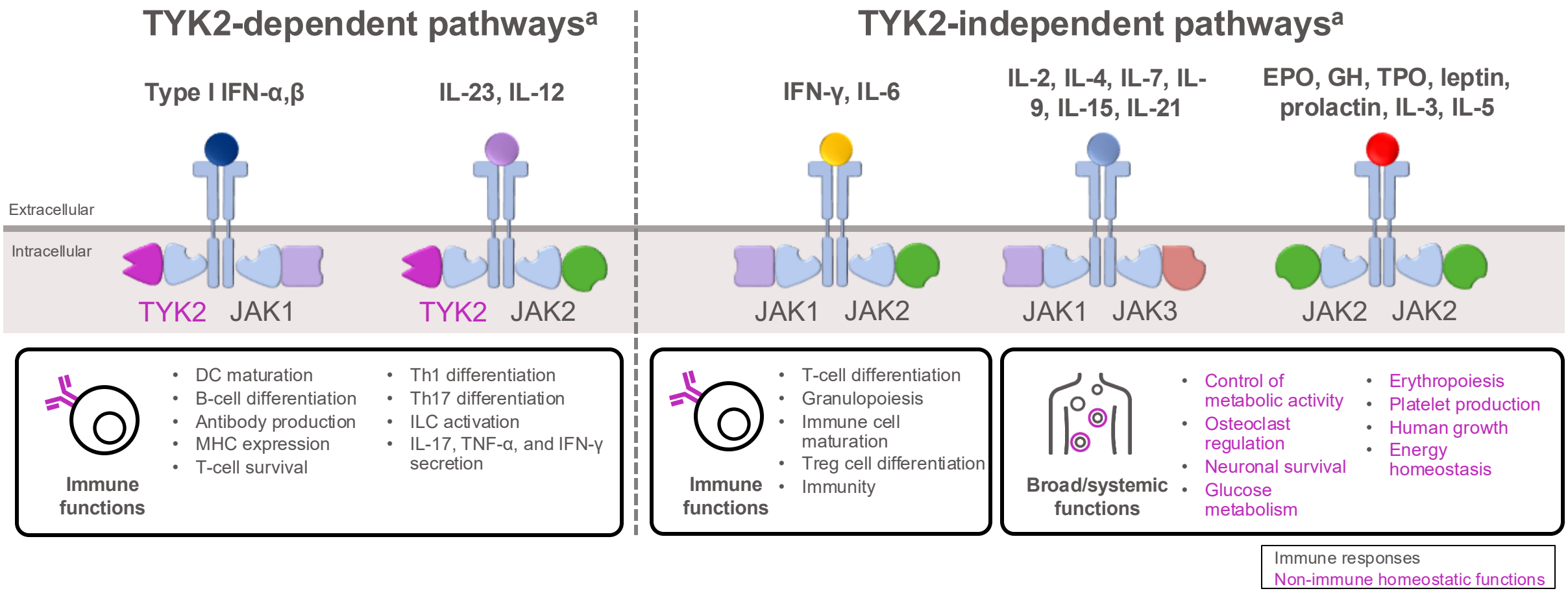




C = C terminus; JH = Janus kinase homology; N = N terminus; P = phosphate.
Adapted with permission from *Cancers (Basel)*[3] and *Immunotherapy*.[5]

1. Banerjee S, et al. *Drugs*. 2017;77(5):521-546. 2. Tokarski JS, et al. *J Biol Chem*. 2015;290(17):11061-11074. 3. Borcherding DC, et al. *Cancers (Basel)*. 2021;13(16):4171. 4. Zhou Y, et al. *Front Immunol*. 2022;13:884399. 5. Gonciarz M, et al. *Immunotherapy*. 2021;13(13):1135-1150.

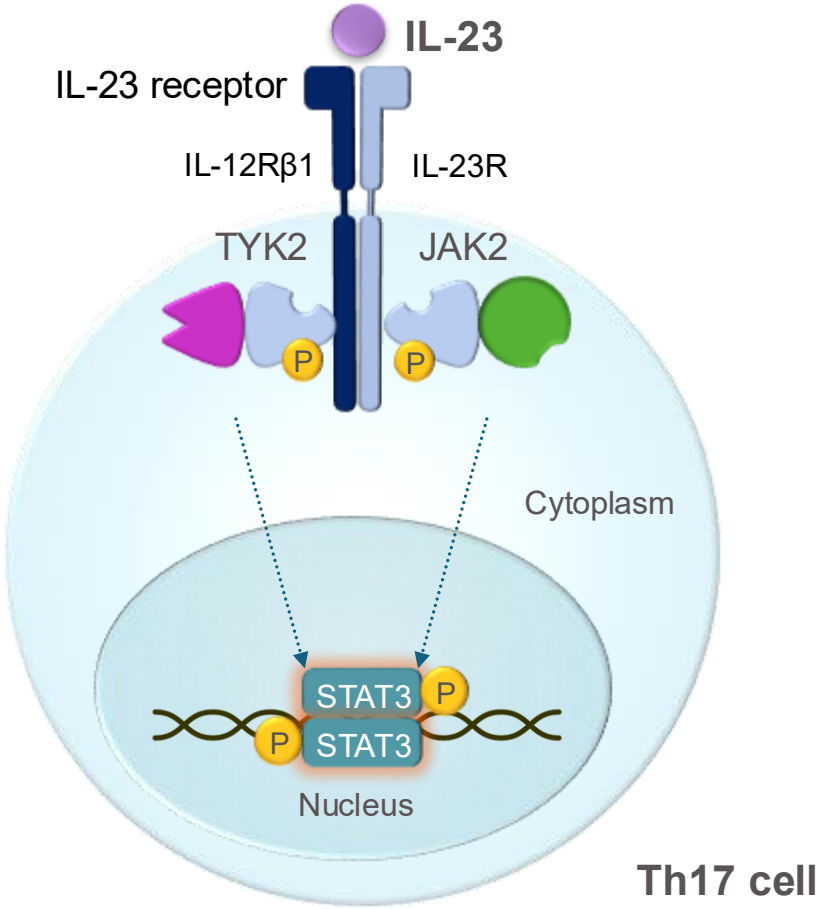
TYK2-Mediated Signals Affect Immune Responses, while JAK1-, JAK2-, and Jak3-Mediated Signals Affect Both Broad Functions and Immune Responses[1-28]



[a]Please note that this list of cytokines modulated by different JAK/JAK and TYK2/JAK pairs is not exhaustive. Certain cytokines might also be mediated by JAK and TYK2 trimers.[1,27]
Adapted with permission from *Immunotherapy*.[29]
EPO = erythropoietin; GH = growth hormone; IFN = interferon; ILC = innate lymphoid cell; MHC = major histocompatibility complex; Th = T helper cell; TNF = tumour necrosis factor; TPO = thrombopoietin; Treg = T regulatory.

1. Banerjee S, et al. *Drugs*. 2017;77(5):521-546 2. Zhang P, et al. *J Exp Med*. 1998;188(6):1173-1184. 3. Diehl S, Rincón M. *Mol Immunol*. 2002;39(9):531-536. 4. Kopf M, et al. *Nature*. 1994;368(6569):339-342. 5. Glund S, Krook A. *Acta Physiol (Oxf)*. 2008;192(1):37-48. 6. Gao Y, et al. *J Clin Invest*. 2007;117(1):122-132. 7. Sun L, et al. *Oncotarget*. 2017;8:40065-40078. 8. Giliani S, et al. *Immunol Rev*. 2005;203:110-126. 9. Karasuyama H, et al. *J Exp Med*. 1988;167(4):1377-1390. 10. Sonoda Y. *Leuk Lymphoma*. 1994;14(3-4):231-240. 11. Ebbo M, et al. *Nat Rev Immunol*. 2017;17(11):665-678. 12. Fallon PG, et al. *Immunity*. 2002;17(1):7-17. 13. Kitagawa Y, Sakaguchi S. *Curr Opin Immunol*. 2017;49:64-70. 14. Krolopp JE, et al. *Front Physiol*. 2016;7:626. 15. Dougan M, et al. *Immunity*. 2019;50(4):796-811. 16. Zeigler BM, et al. *Dis Model Mech*. 2010;3(11-12):763-772. 17. Staerk J, Constantinescu SN. *JAKSTAT*. 2012;1(3):184-190. 18. Lu M, et al. *Signal Transduct Target Ther*. 2019;4:3. 19. Jiang L, et al. *J Biol Chem*. 2008;283(42):28066-28073. 20. Simmons DP, et al. *J Immunol*. 2012;188(7):3116-3126. 21. De Groof A, et al. *Rheumatology (Oxford)*. 2020;59(3):668-677. 22. Eloranta ML, Rönnblom L. *J Mol Med (Berl)*. 2016;94(10):1103-1110. 23. Floss DM, et al. *Cells*. 2020;9(10):2184. 24. Ishizaki M, et al. *Int Immunol*. 2014;26(5):257-267. 25. Aggarwal S, et al. *J Biol Chem*. 2003;278(3):1910-1914. 26. Geremia A, et al. *J Exp Med*. 2011;208(6):1127-1133. 27. Baker KF, Isaacs JD. *Ann Rheum Dis*. 2018;77(2):175-187. 28. Clark JD, et al. *J Med Chem*. 2014;57(12):5023-5038. 29. Gonciarz M, et al. *Immunotherapy*. 2021;13(13):1135-1150.

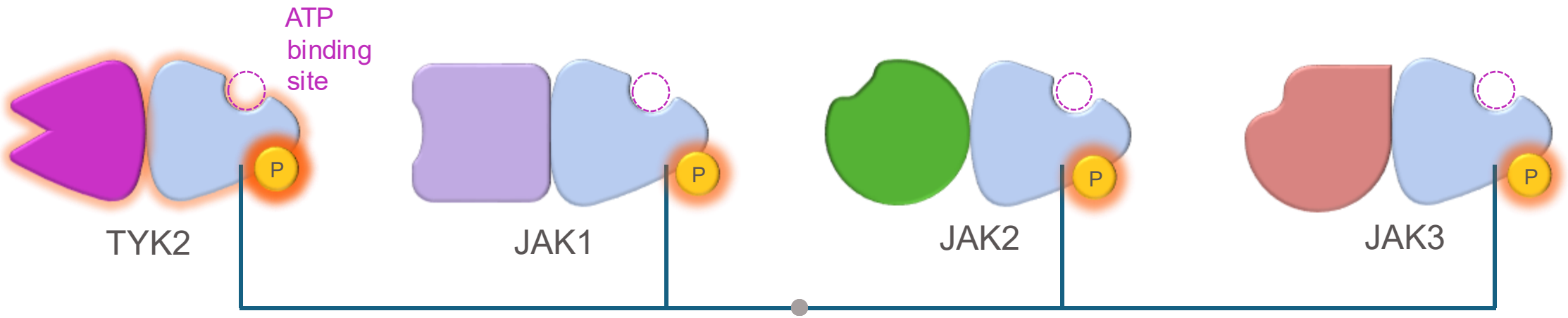
TYK2 and Its Partner JAK Kinase Activate STAT Proteins, Eventually Leading to Altered Gene Transcription[1-7]



P = phosphate; R = receptor.

1. Baker KF, Isaacs JD. *Ann Rheum Dis*. 2018;77(2):175-187. 2. Delgoffe GM, Vignali DAA. *JAKSTAT*. 2013;2(1):e23060. 3. Harden JL, et al. *J Autoimmun*. 2015;64:66-73. 4. Di Cesare A, et al. *J Invest Dermatol*. 2009;129(6):1339-1350. 5. Hawkes JE, et al. *J Allergy Clin Immunol*. 2017;140(3):645-653. 6. Morris R, et al. *Protein Sci*. 2018;27(12):1984-2009. 7. Seif F, et al. *Cell Commun Signal*. 2017;15(1):23.

TYK2 and JAK1/2/3 Possess a Conserved Active Site and a Differentiated Regulatory Domain[1,2]



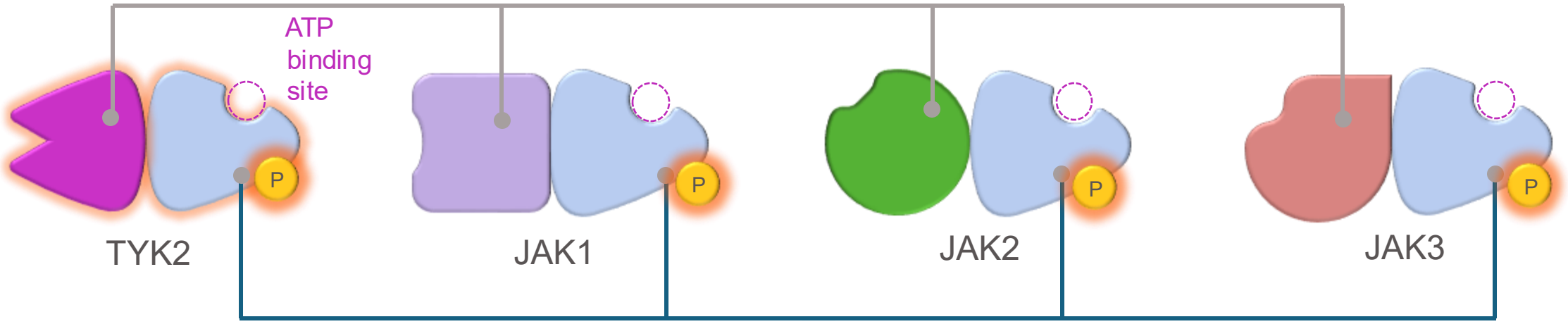
Active domain: **Structurally similar** across family members

ATP = adenosine triphosphate.

1. Banerjee S, et al. *Drugs*. 2017;77(5):521-546. 2. Tokarski JS, et al. *J Biol Chem*. 2015;290(17):11061-11074.

TYK2 and JAK1/2/3 Possess a Conserved Active Site and a Differentiated Regulatory Domain[1,2]

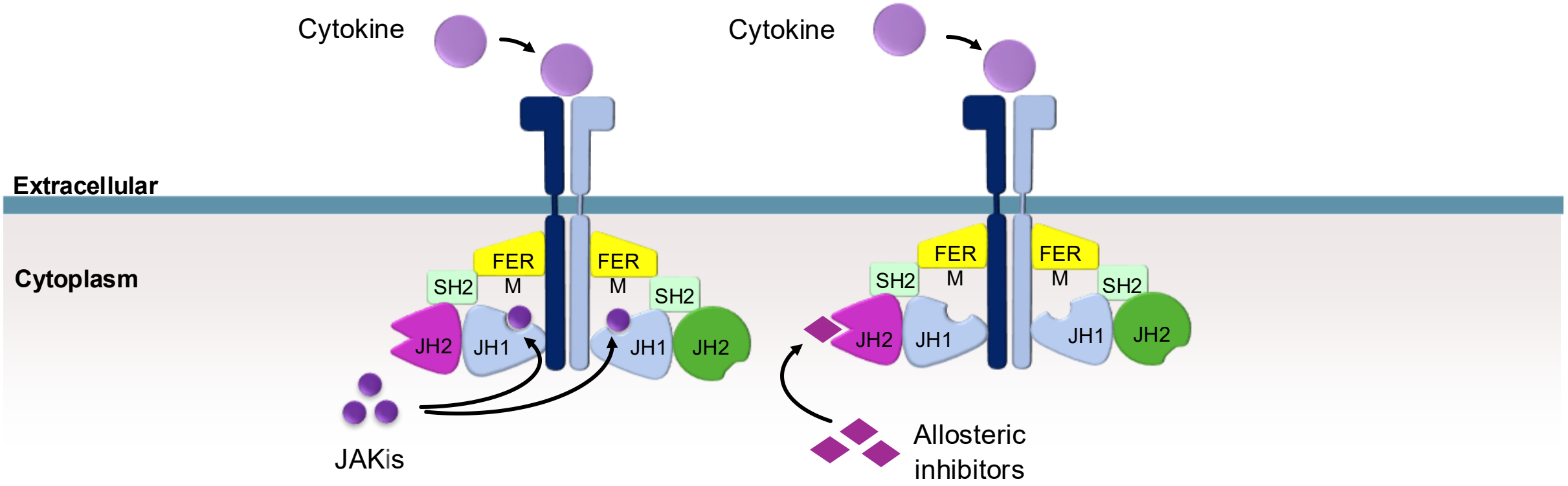
Regulatory domain: **Structurally different** across family members



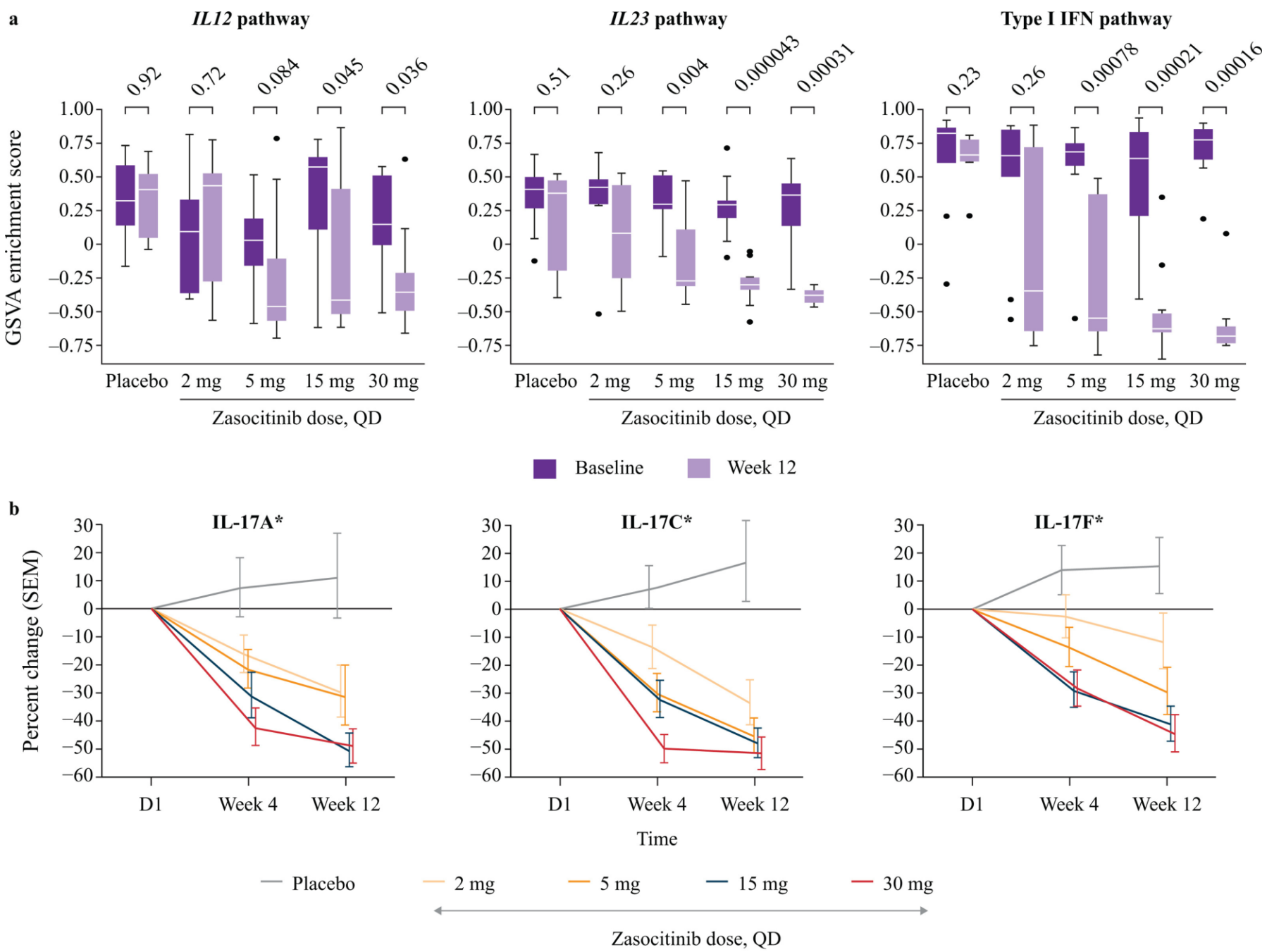
Active domain: **Structurally similar** across family members

1. Banerjee S, et al. *Drugs*. 2017;77(5):521-546. 2. Tokarski JS, et al. *J Biol Chem*. 2015;290(17):11061-11074.

Allosteric Inhibition by Deucravacitinib Locks TYK2 in the Inactive State, Preventing Downstream Cytokine Signaling[1,2]

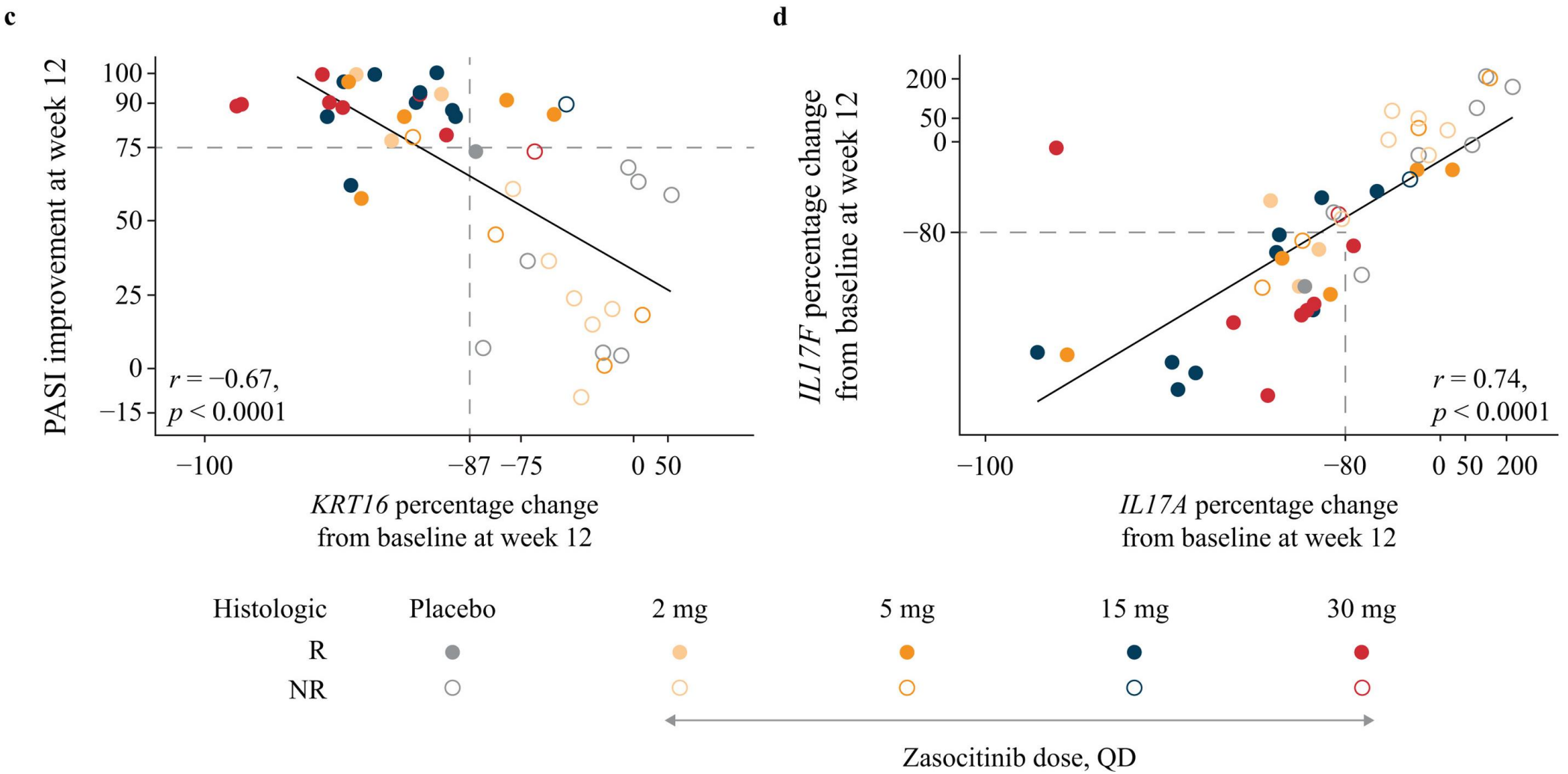


Adapted with permission from Rusiñol and Puig. *Int J Mol Sci.* 2023.[1]
JAKi = JAK inhibitor.
1. Rusiñol L, Puig L. Int J Mol Sci. 2023;24(4):3391. 2. Tokarski JS, et al. *J Biol Chem*. 2015;290(17):11061-11074.



GSVA = gene set variation analysis; SEM = standard error of the mean; D = day.

Choudhury A, et al. *J Invest Dermatol*. December 10, 2025:S0022-202X(25)03625-5 [Epub ahead of print].

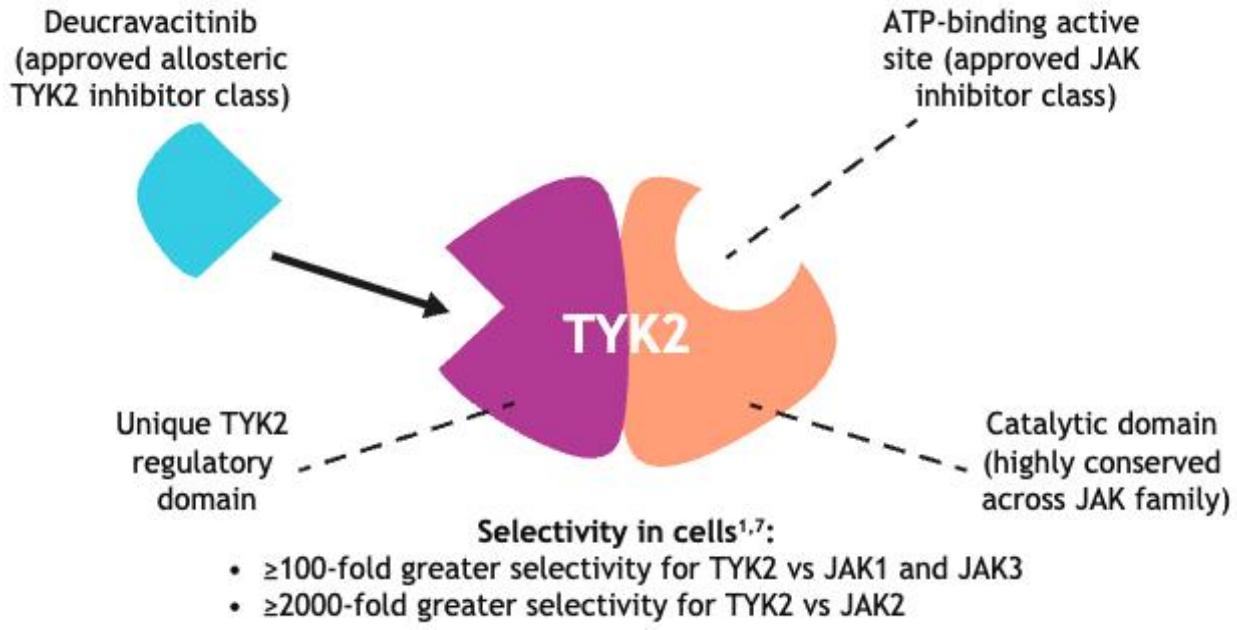


PASI = Psoriasis Area and Severity Index; R = reached; NR = not reached.

Choudhury A, et al. *J Invest Dermatol.* December 10, 2025:S0022-202X(25)03625-5 [Epub ahead of print].

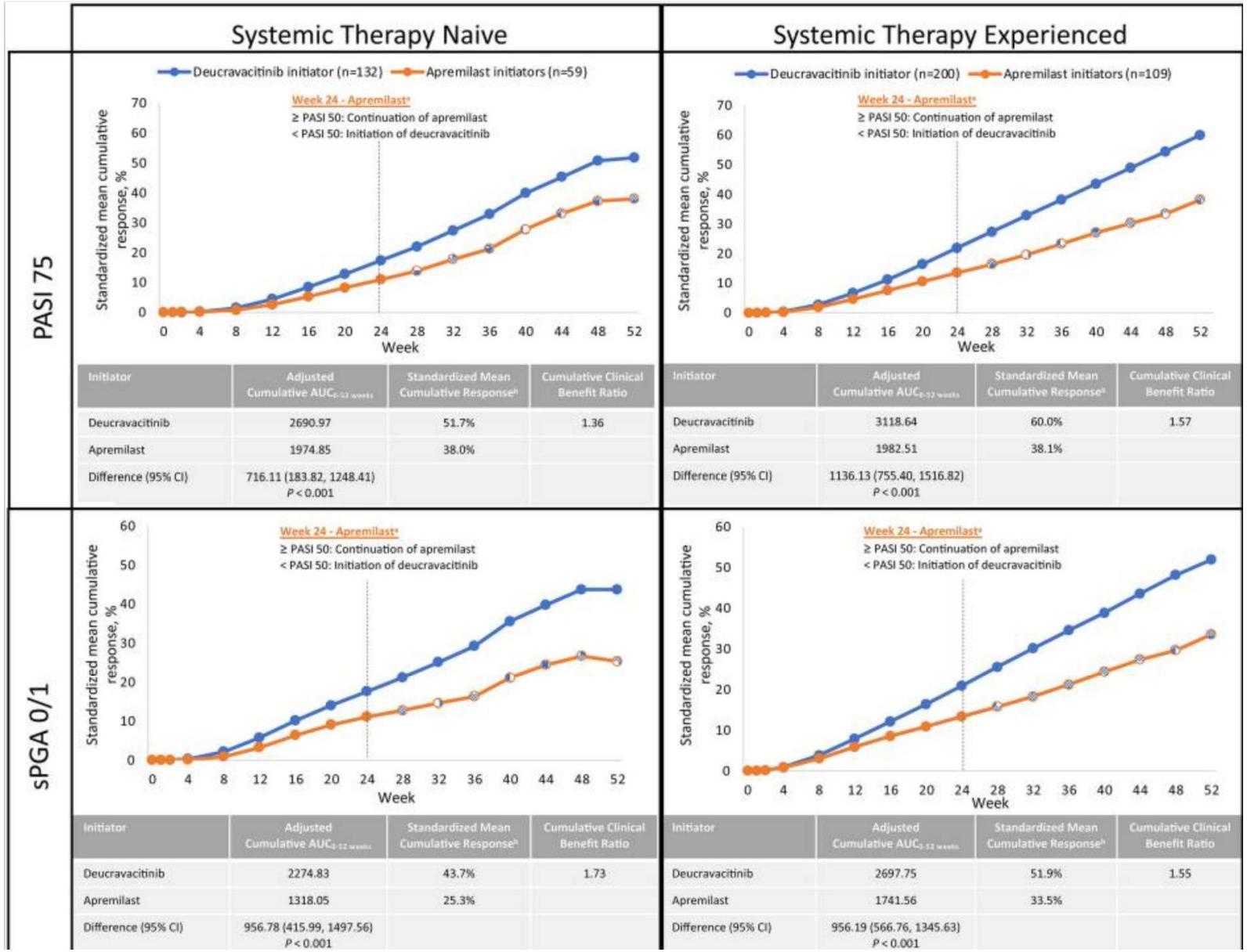
Differentiating between JAK Inhibition and TYK2 Inhibition

- Distinct inhibitory profiles with allosteric TYK2 inhibitors having very little impact on JAK signaling
- This allows for fewer off-target adverse events
  - JAK inhibitors for inflammatory skin disease (eg, atopic dermatitis) have black box warning; TYK2 inhibitor does not
- Dyslipidemia, thromboembolic events, severe infections observed with JAK inhibitors not seen with TYK2 inhibitors



Martin G. *Dermatol Ther (Heidelb).* 2023;13(2):417-435. Rusiñol L, Puig L. *Int J Mol Sci*. 2023;24(4):3391. Merola JF, et al. *SKIN: J Cutan Med*. 2024;8(6):s428. Mehrotra S, et al. *J Invest Dermatol*. 2026;146(1):214-222.e7. Gossec L, et al. Presented at: American College of Rheumatology (ACR) Convergence; 2021. Abstract 0750.

Deucravacitinib (POETYK PSO-1)



Initiator	Adjusted Cumulative AUC	Standardized Mean Cumulative Response[b]	Cumulative Clinical Benefit Ratio
Deucravacitinib	2690.97	51.7%	1.36
Apremilast	1974.85	38.0%	
Difference (95% CI)	716.11 (183.82, 1248.41) $P < 0.001$		

Initiator	Adjusted Cumulative AUC	Standardized Mean Cumulative Response[b]	Cumulative Clinical Benefit Ratio
Deucravacitinib	3118.64	60.0%	1.57
Apremilast	1982.51	38.1%	
Difference (95% CI)	1136.13 (755.40, 1516.82) $P < 0.001$		

Initiator	Adjusted Cumulative AUC	Standardized Mean Cumulative Response[b]	Cumulative Clinical Benefit Ratio
Deucravacitinib	2274.83	43.7%	1.73
Apremilast	1318.05	25.3%	
Difference (95% CI)	956.78 (415.99, 1497.56) $P < 0.001$		

Initiator	Adjusted Cumulative AUC	Standardized Mean Cumulative Response[b]	Cumulative Clinical Benefit Ratio
Deucravacitinib	2697.75	51.9%	1.55
Apremilast	1741.56	33.5%	
Difference (95% CI)	956.19 (566.76, 1345.63) $P < 0.001$		

In a post hoc analysis of data from the POETYK PSO-1 trial, treatment with deucravacitinib exhibited a higher standardized mean cumulative PASI75 response at 52 weeks.

Armstrong AW, et al. *Dermatol Ther (Heidelb).* 2024;14(7):1891-1899.

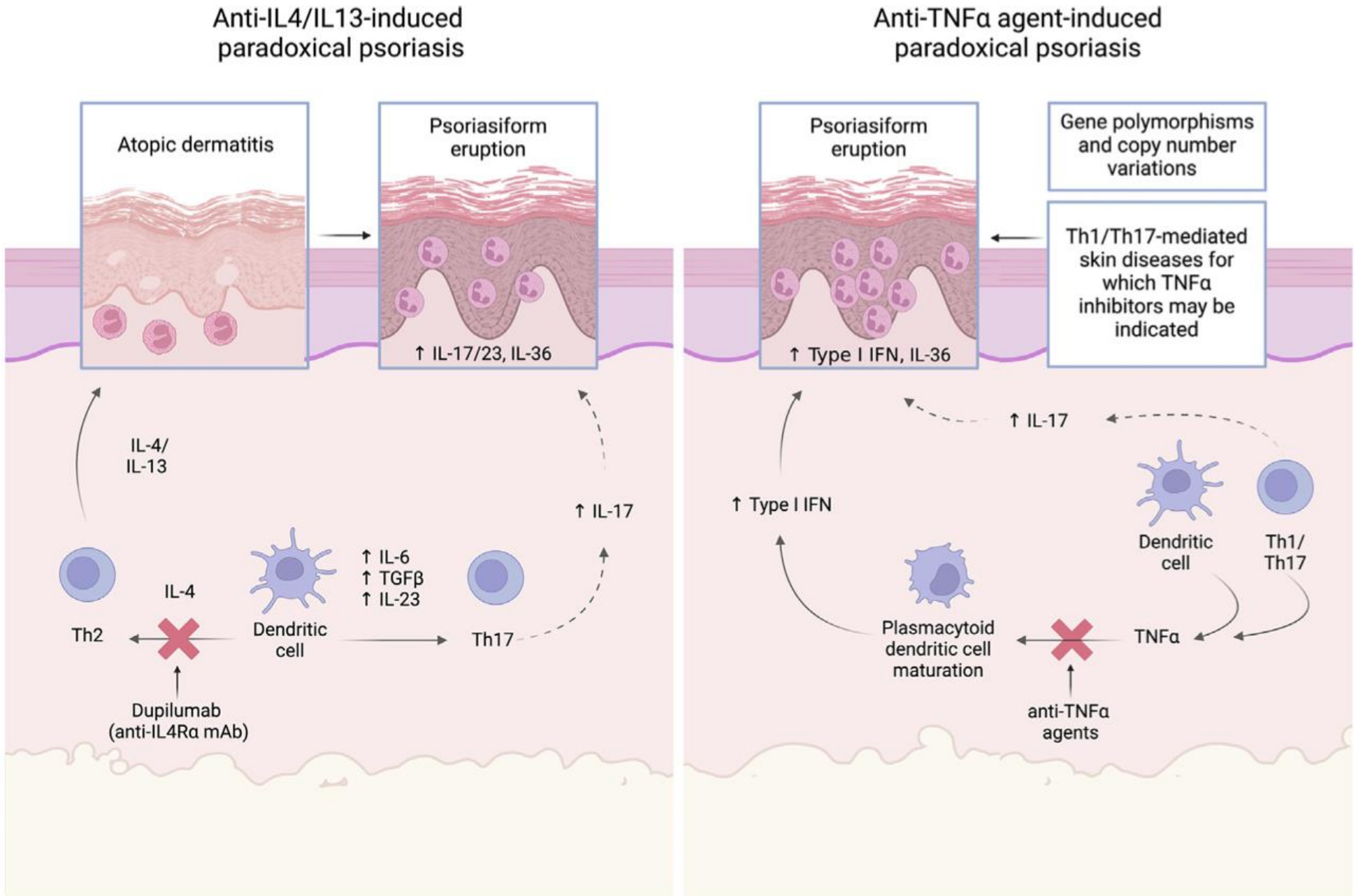
Key Learning Points

- Psoriasis is a common inflammatory skin disease
- Systemic therapy has revolutionized treatment of psoriasis
- JAK/STAT signaling directly involves TYK2, contributing to pathogenesis of psoriasis
- TYK2 inhibitors prevent downstream signaling of the IL-23 inflammatory pathway, preventing activation of TH17 cells
- Allosteric inhibition of TYK2 is highly effective at blocking TYK2 signaling with little impact on JAK 1/2/3 signaling
- TYK2 inhibition represents a new treatment target for psoriasis with emerging agents for psoriatic disease

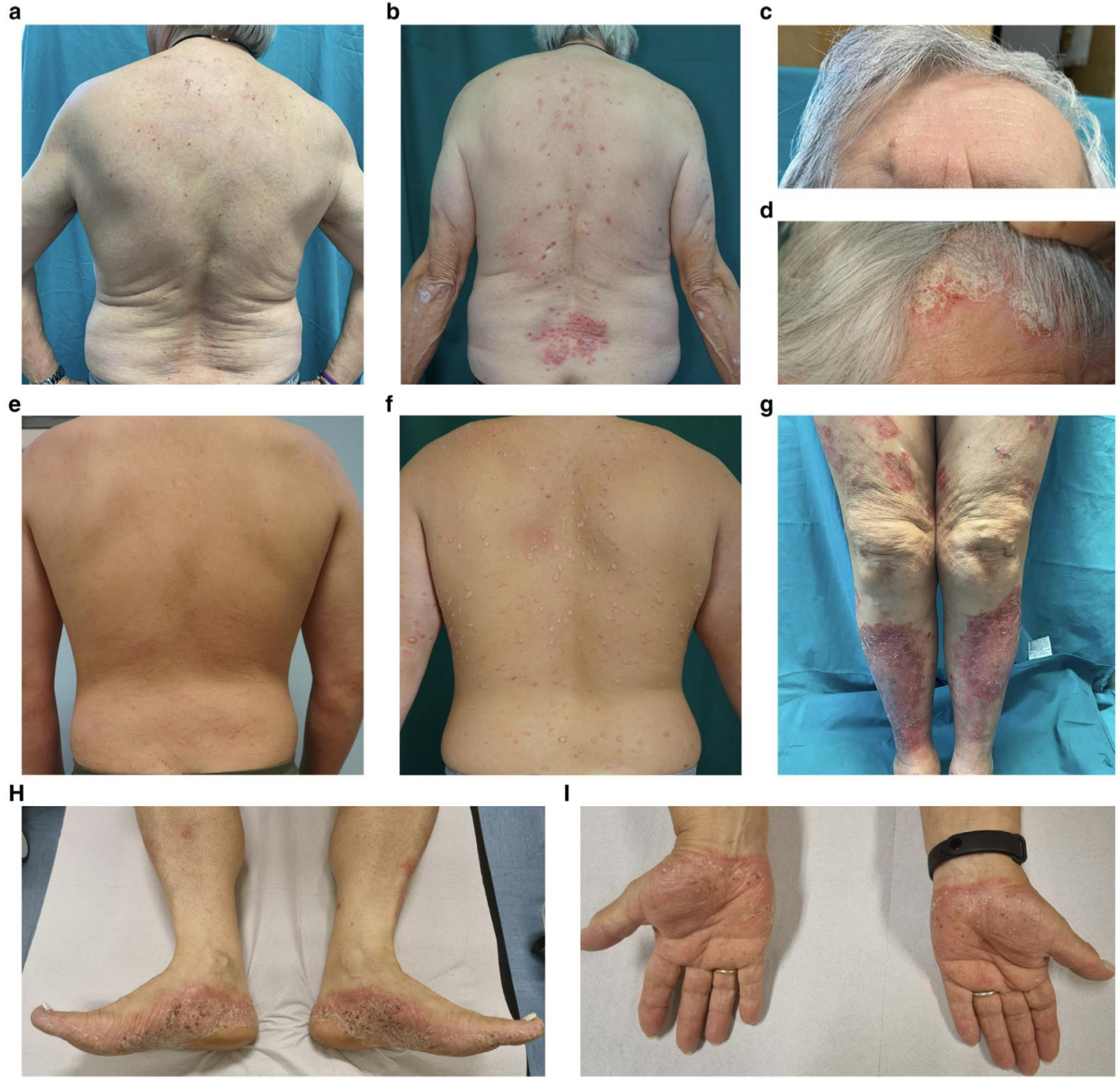
Paradoxical Psoriasis: An Updated Review of Clinical Features, Pathogenesis, and Treatment Options

Carlo Alberto Maronese[1,2,6], Mario Valenti[3,4,6], Chiara Moltrasio[1], Maurizio Romagnuolo[1], Silvia Mariel Ferrucci[1], Michel Gilliet[5], Antonio Costanzo[3,4] and Angelo Valerio Marzano[1,2]

Maronese CA, et al. *J Invest Dermatol*. 2024;144(11):2364-2376.



Maronese CA, et al. *J Invest Dermatol*. 2024;144(11):2364-2376.



Maronese CA, et al. *J Invest Dermatol*. 2024;144(11):2364-2376.

Paradoxical Psoriasis

- Most often seen with TNF inhibition in psoriasis or IBD, but also seen with IL-17 inhibitors less commonly or other drugs
- Increasing cases in atopic dermatitis treated with Th2 inhibitors
- Sometimes managed by change of therapeutic class or, in case of atopic dermatitis, by addition of IL-17 blocker
- In cases of TNF blockade, innate interferon increases thought to be pathogenic, so a TYK2 inhibitor would be a logical first drug to try

IBD = inflammatory bowel disease.

masterclasses in dermatology annual meeting

PRESENTED BY THE dermatologist

Emerging Oral Therapies

Brad P. Glick, DO, MPH

Program Director, Dermatology Residency
Larkin Health System - Palm Springs Campus
Assistant Clinical Professor of Dermatology
Herbert Wertheim College of Medicine
Miami, Florida

Janus Kinase 1 (JAK-1) Inhibitor: Upadacitinib

Selective JAK-1i: blocks intracellular signaling of pro-inflammatory cytokines (eg, IL-6, interferons)

SELECT-PsA 1 and 2: ACR20/50/70 and PASI75/90/100 reductions vs placebo in csDMARD-IR and bDMARD-IR populations

SELECT-PsA 1—demonstrated similar or superior ACR and MDA responses versus adalimumab through 104 weeks and maintained inhibition of radiographic progression

Safety: Class-consistent JAKnib risks including serious infections, herpes zoster, potential malignancy, and cardiovascular risk; 15 mg dose favored for optimal benefit-risk balance

FDA-approved for adults with active PsA after inadequate response or intolerance to DMARDs or TNF inhibitors

ACR = American College of Rheumatology; csDMARD-IR = incomplete response to conventional synthetic disease-modifying antirheumatic drugs; bDMARD-IR = incomplete response to biologic DMARD; MDA = minimal disease activity; PsA = psoriatic arthritis; FDA = US Food and Drug Administration.

Mease, P et al. *Clin Exp Rheumatol.* 2023;41(11):2286-2297.

ORIGINAL ARTICLE

Pharmacological Characterization of Zasocitinib (TAK-279): An Oral, Highly Selective, and Potent Allosteric TYK2 Inhibitor

Shailly Mehrotra[1], Yasuyo Sano[2], Petro Halkowycz[2], Elizabeth Wilson[2], Chandra Durairaj[1], Kok-Fai Kong[2], Guliang Xia[2], Faith Dunbar[3], Taylor Spector[4], Graham A. Heap[5], Christopher G. Bunick[6,7] and Iain B. McInnes[8]

Journal of Investigative Dermatology (2026) **146,** 214–222; doi:10.1016/j.jid.2025.05.014

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Mehrotra S, et al. *J Invest Dermatol*. 2026;146(1):214-222.e7.

Zasocitinib

Table 1. Zasocitinib Demonstrated >1 Millionfold Biochemical Selectivity for the TYK2 JH2 Domain over the Jak1 JH2 Domain

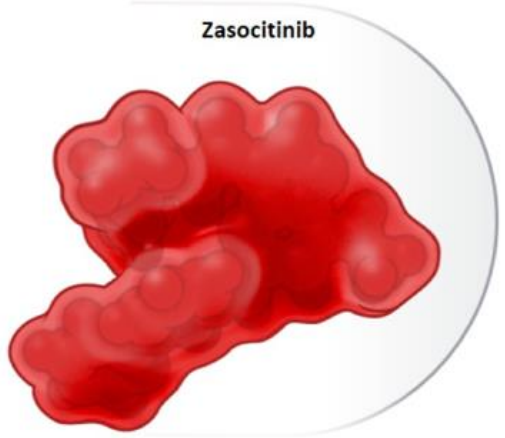
	Binding Affinity (K_i)[1]	
Domain	**Zasocitinib**	**Deucravacitinib**
Jak1 JH2, nM[2]	>15,000	1
TYK2 JH2, nM[3]	0.0087	0.0115
Biochemical selectivity, fold	$>1.7 \times 10^6$	87

Abbreviations: JH, Janus homology; K_D, dissociation constant; K_i, inhibitory constant.

[1]Determined using a homogeneous time-resolved fluorescence assay.

[2]Geometric mean of 3 samples: z-score ≥ 0.9, Jak1 JH2 (tracer) = 1 nM (K_D), and Jak1 JH2 = 0.3 nM for both inhibitors.

[3]Geometric mean of 3 samples: z-score ≥ 0.8, TYK2 (tracer) = 225 nM (50 × K_D), and TYK2 = 0.2 nM for both inhibitors.



Mehrotra S, et al. *J Invest Dermatol*. 2026;146(1):214-222.e7. Armstrong AW, et al. *JAMA Dermatol*. 2024;160(10):1066-1074. ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated December 17, 2025. Accessed September 17, 2025. https://clinicaltrials.gov/study/NCT06973291.

Research

JAMA Dermatology | Original Investigation

Tyrosine Kinase 2 Inhibition With Zasocitinib (TAK-279) in Psoriasis
A Randomized Clinical Trial

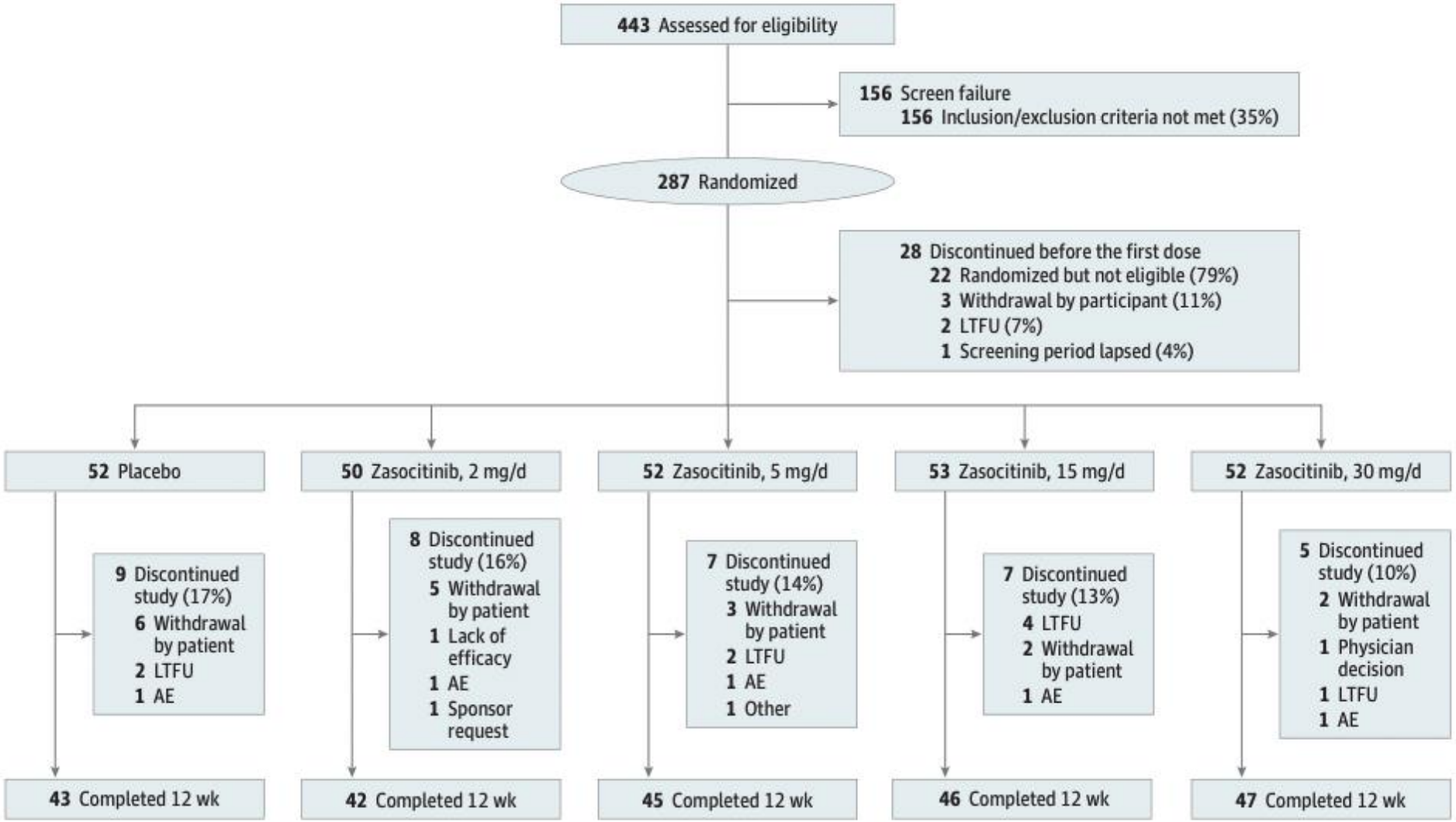
April W. Armstrong, MD, MPH; Melinda Gooderham, MD; Charles Lynde, MD; Catherine Maari, MD; Seth Forman, MD; Lawrence Green, MD; Vivian Laquer, MD; Xinyan Zhang, PhD; Nathalie Franchimont, MD, PhD; Esha A. Gangolli, PhD; Jessamyn Blau, MD; Yiwei Zhao, MD, PhD; Wenwen Zhang, PhD; Bhaskar Srivastava, MD, PhD; Graham Heap, MBBS, PhD; Kim Papp, MD, PhD

Armstrong AW, et al. *JAMA Dermatol*. 2024;160(10):1066-1074.

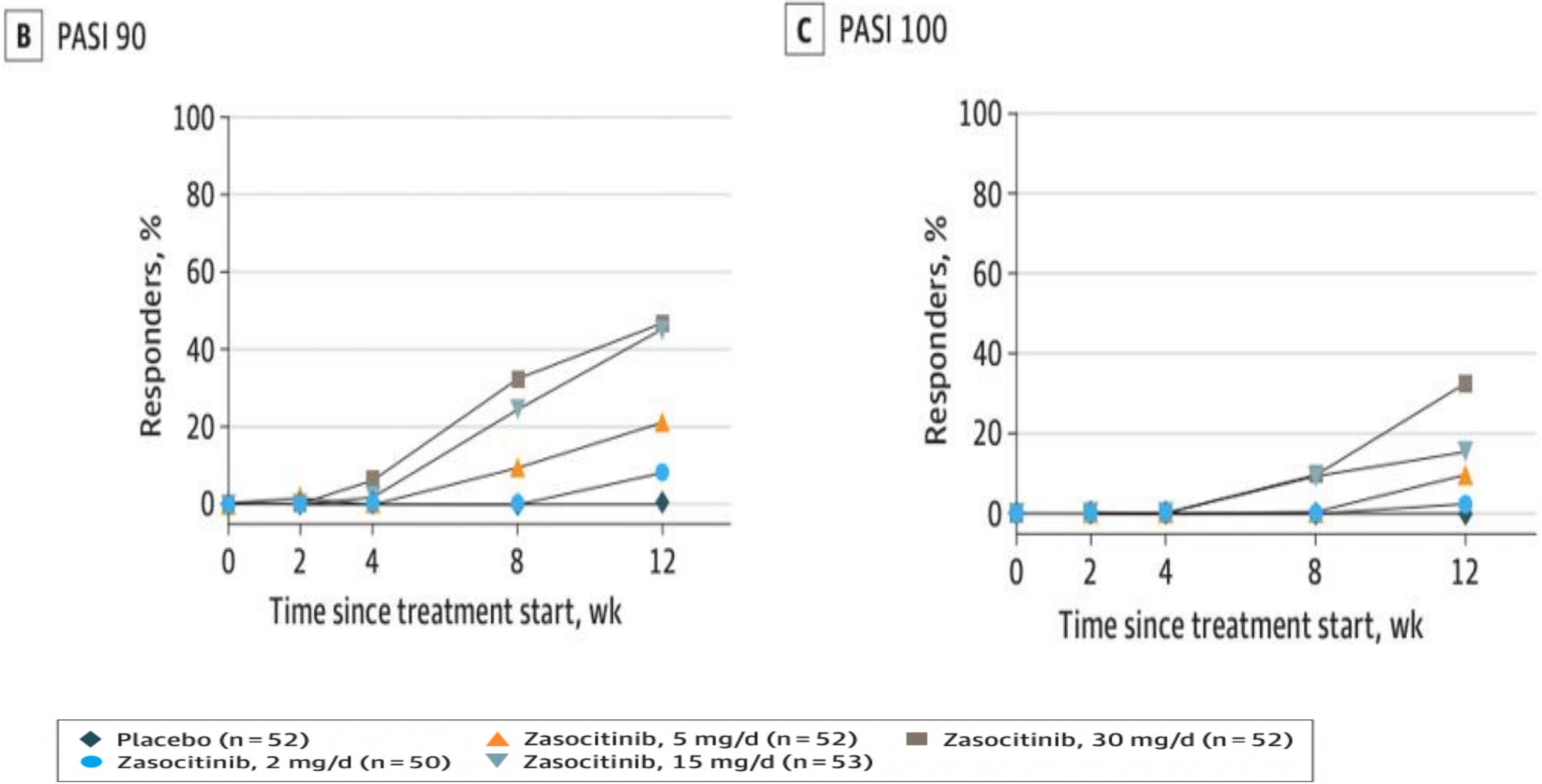
Zasocitinib

- Phase 2b placebo-controlled RCT

- Four doses
  - 2 mg/d
  - 5 mg/d
  - 15 mg/d
  - 30 mg/d



RCT = randomized controlled trial; LTFU = lost to follow-up; AE = adverse event.
Armstrong AW, et al. *JAMA Dermatol*. 2024;160(10):1066-1074.



Armstrong AW, et al. *JAMA Dermatol*. 2024;160(10):1066-1074.

Zasocitinib Safety

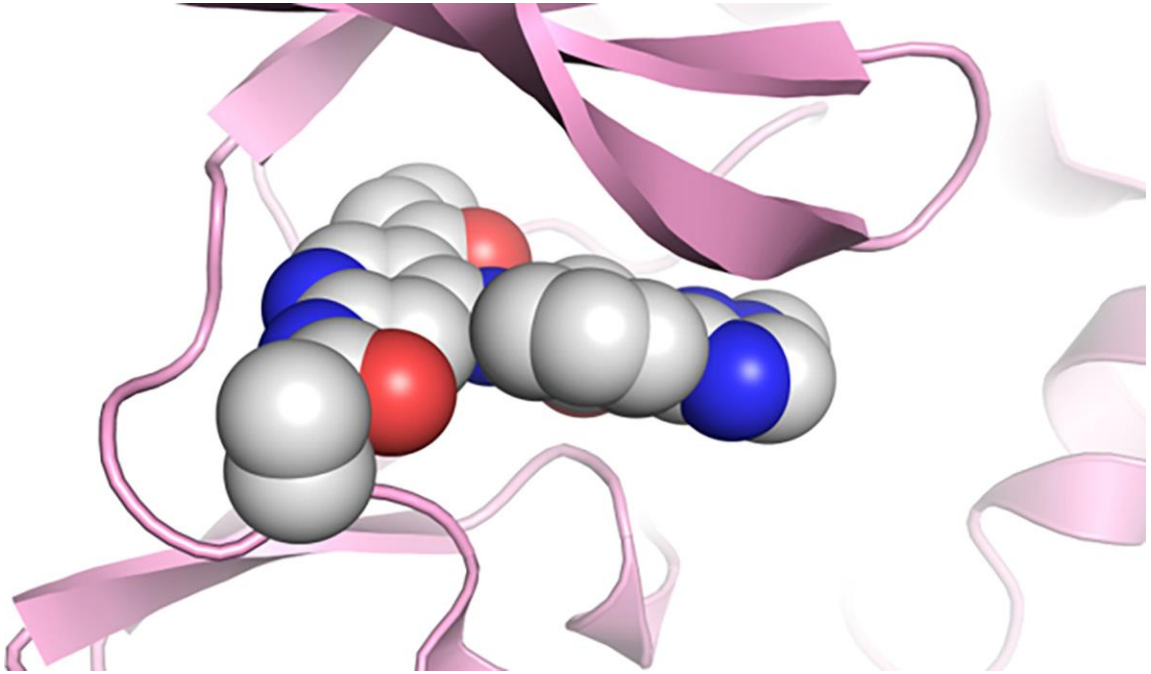
Table 3. Summary of Harms in Patients With Moderate to Severe Psoriasis in a Phase 2b Study for Zasocitinib

	No. (%)				
		Zasocitinib, once daily			
Adverse Event	Placebo (n = 52)	2 mg (n = 50)	5 mg (n = 52)	15 mg (n = 53)	30 mg (n = 52)
Deaths	0	0	0	0	0
SAEs	0	0	0	1 (2)	0
TEAEs	23 (44)	31 (62)	28 (54)	28 (53)	31 (60)
TEAEs leading to study treatment discontinuation[a]	1 (2)	1 (2)	1 (2)	1 (2)	2 (4)
Most frequent TEAEs[b]					
COVID-19[c]	1 (2)	6 (12)	4 (8)	6 (11)	7 (14)
Acne[c]	0	0	1 (2)	3 (6)	2 (4)
Acneiform dermatitis[c]	0	0	1 (2)	1 (2)	3 (6)
Diarrhea[c]	1 (2)	3 (6)	1 (2)	1 (2)	0

SAE = serious AE; TEAE = treatment-emergent AE.
Armstrong AW, et al. *JAMA Dermatol*. 2024;160(10):1066-1074.

ESK-001—Envudeucitinib

- Investigative oral highly selective allosteric TYK2 inhibitor
- Has been investigated in phase 2 program (STRIDE trial)
- Ongoing phase 3 study (ONWARD trial)
- Maximal target inhibition over 24 hours
- No clinically meaningful inhibition of other kinases



Ucpinar S, et al. *Clin Transl Sci*. 2024;17(12):e70094.

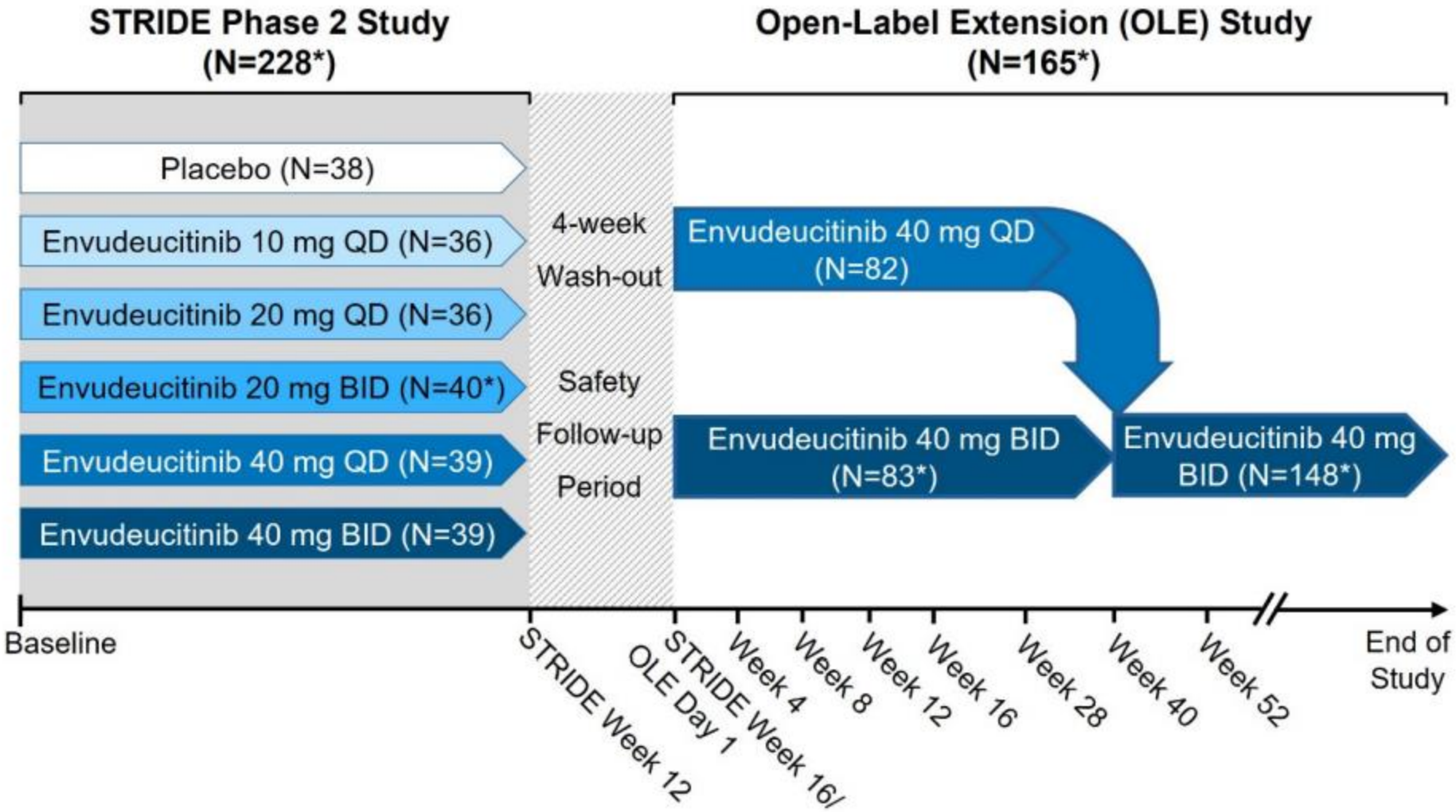
Safety and efficacy of envudeucitinib, a highly selective, oral allosteric TYK2 inhibitor, in patients with moderate-to-severe plaque psoriasis: Results from the 52-week open-label extension period of the phase 2 STRIDE study

Kim A. Papp, MD, PhD,[a] Shahram Jacobs, MD,[b] Howard Sofen, MD,[c] Michael Bukhalo, MD,[d] Elisa Muscianisi, MD,[e] Grace Ma, MS,[e] Gabriel Lau, MSc,[e] Michelle Bettinger, MPH,[e] Roman G. Rubio, MD,[e] Elena Hitraya, MD, PhD,[e] and Andrew Blauvelt, MD, PhD,[f] on behalf of the Open-Label Extension study team

Papp KA, et al. *J Am Acad Dermatol*. 2026;94(1):187-195.

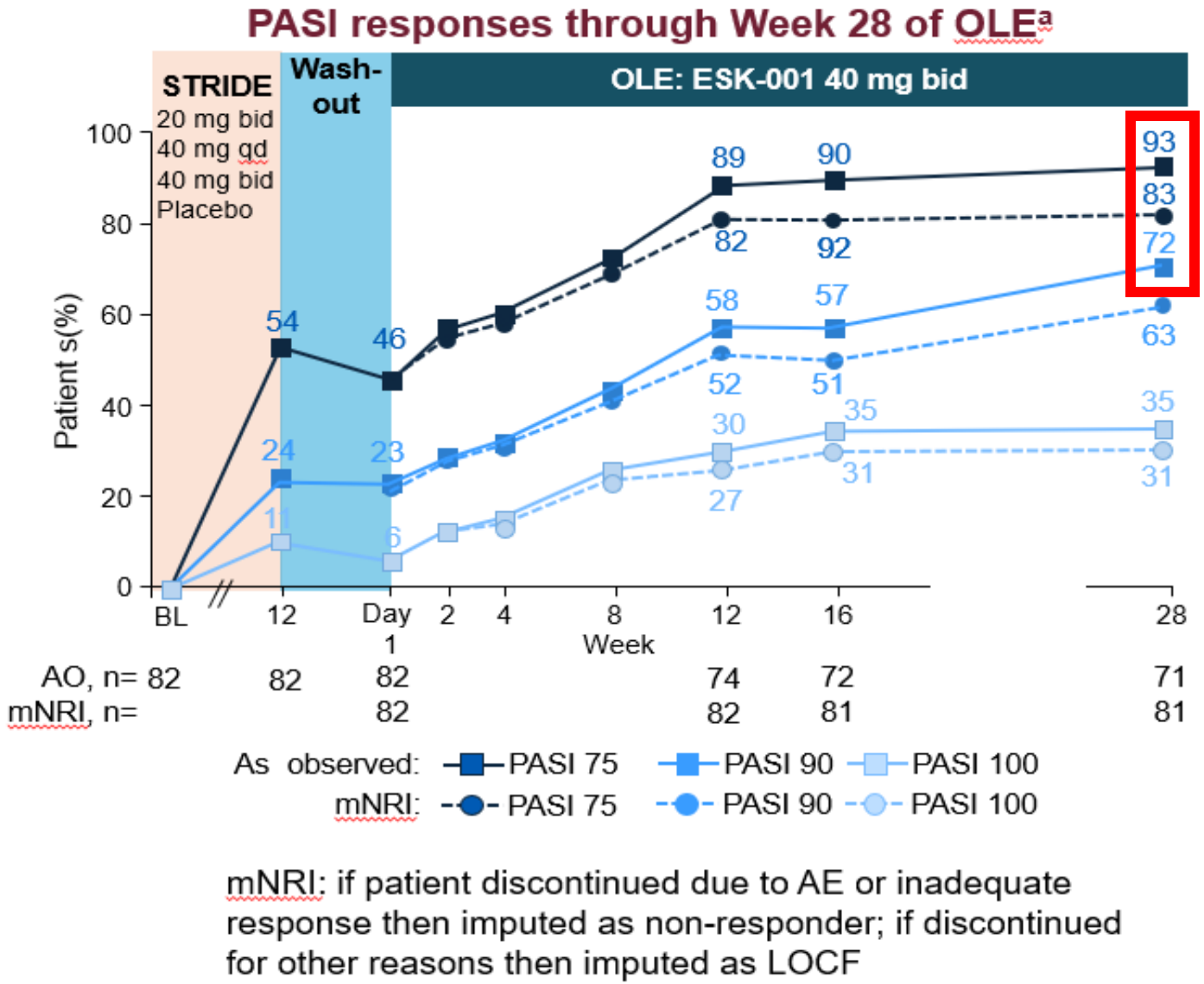
ESK-001 STRIDE

SUPPLEMENTARY FIGURES



Blauvelt A, et al. Presented at: AAD Annual Meeting; 2025. AB266. Blauvelt A, et al. *J Am Acad Dermatol*. 2026;94(1):57-65. Papp KA, et al. *J Am Acad Dermatol*. 2026;94(1):187-195.

STRIDE: Efficacy of Oral TYK2 Inhibitor ESK-001 at OLE Week 28

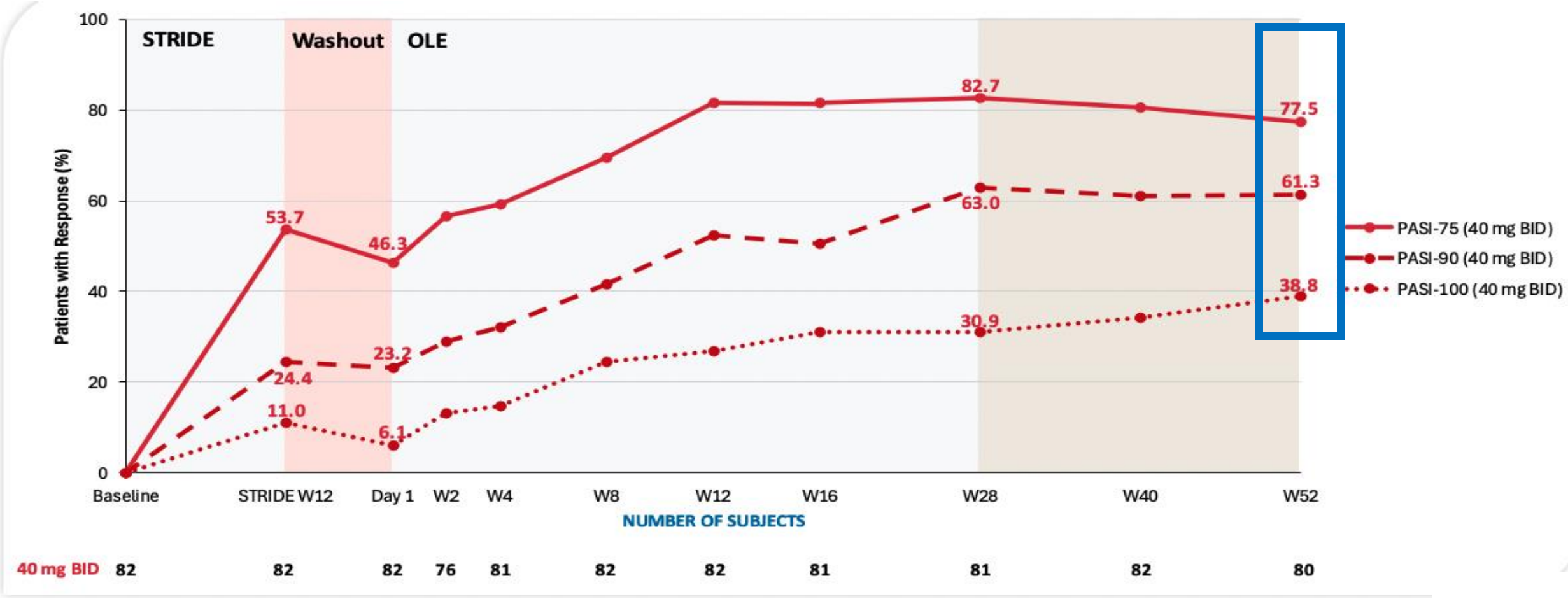


mNRI: if patient discontinued due to AE or inadequate response then imputed as non-responder; if discontinued for other reasons then imputed as LOCF

AO = as observed; BL = baseline; mNRI = modified NRI; LOCF = last observation carried forward.

Papp KA, et al. Presented at: AAD Annual Meeting; 2024. Blauvelt A, et al. Presented at: EADV Congress; 2024. D3T01.3D. Papp KA, et al. *J Am Acad Dermatol*. 2026;94(1):187-195. Blauvelt A, et al. *J Am Acad Dermatol*. 2026;94(1):57-65.

ESK-001: STRIDE OLE



Blauvelt A, et al. Presented at: AAD Annual Meeting; 2025. AB266. Blauvelt A, et al. *J Am Acad Dermatol*. 2026;94(1):57-65.

ESK-001: STRIDE Trial

Table III. Summary of TEAEs in STRIDE study (safety analysis set)

		ESK-001					
	Placebo (*N* = 38)	10 mg QD (*N* = 36)	20 mg QD (*N* = 36)	20 mg BID (*N* = 39)	40 mg QD (*N* = 39)	40 mg BID (*N* = 39)	ESK-001 pooled (*N* = 189)
TEAEs, *n* (%)	15 (39.5)	19 (52.8)	14 (38.9)	18 (46.2)	19 (48.7)	25 (64.1)	95 (50.3)
TEAEs leading to treatment discontinuation, *n* (%)*	0 (0.0)	0 (0.0)	2 (5.6)	0 (0.0)	2 (5.1)	1 (2.6)	5 (2.6)
TEAEs ≥ grade 3, *n* (%)	0 (0.0)	3 (8.3)	1 (2.8)	3 (7.7)	3 (7.7)	0 (0.0)	10 (5.3)
TEAEs related to study drug, *n* (%)	5 (13.2)	3 (8.3)	3 (8.3)	5 (12.8)	7 (17.9)	9 (23.1)	27 (14.3)
Most frequent TEAEs, *n* (%)†							
Headache‡	2 (5.3)	0 (0.0)	2 (5.6)	3 (7.7)	4 (10.3)	3 (7.7)	12 (6.3)
Upper respiratory tract infection§	0 (0.0)	2 (5.6)	2 (5.6)	1 (2.6)	2 (5.1)	3 (7.7)	10 (5.3)
Nasopharyngitis§	3 (7.9)	2 (5.6)	0 (0.0)	1 (2.6)	1 (2.6)	3 (7.7)	7 (3.7)
SAEs, *n* (%)‖	0 (0.0)	1 (2.8)	0 (0.0)	3 (7.7)	1 (2.6)	0 (0.0)	5 (2.6)
Deaths, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	

Blauvelt A, et al. *J Am Acad Dermatol*. 2026;94(1):57-65.

Preliminary Topline RCT Data—ONWARD1/2

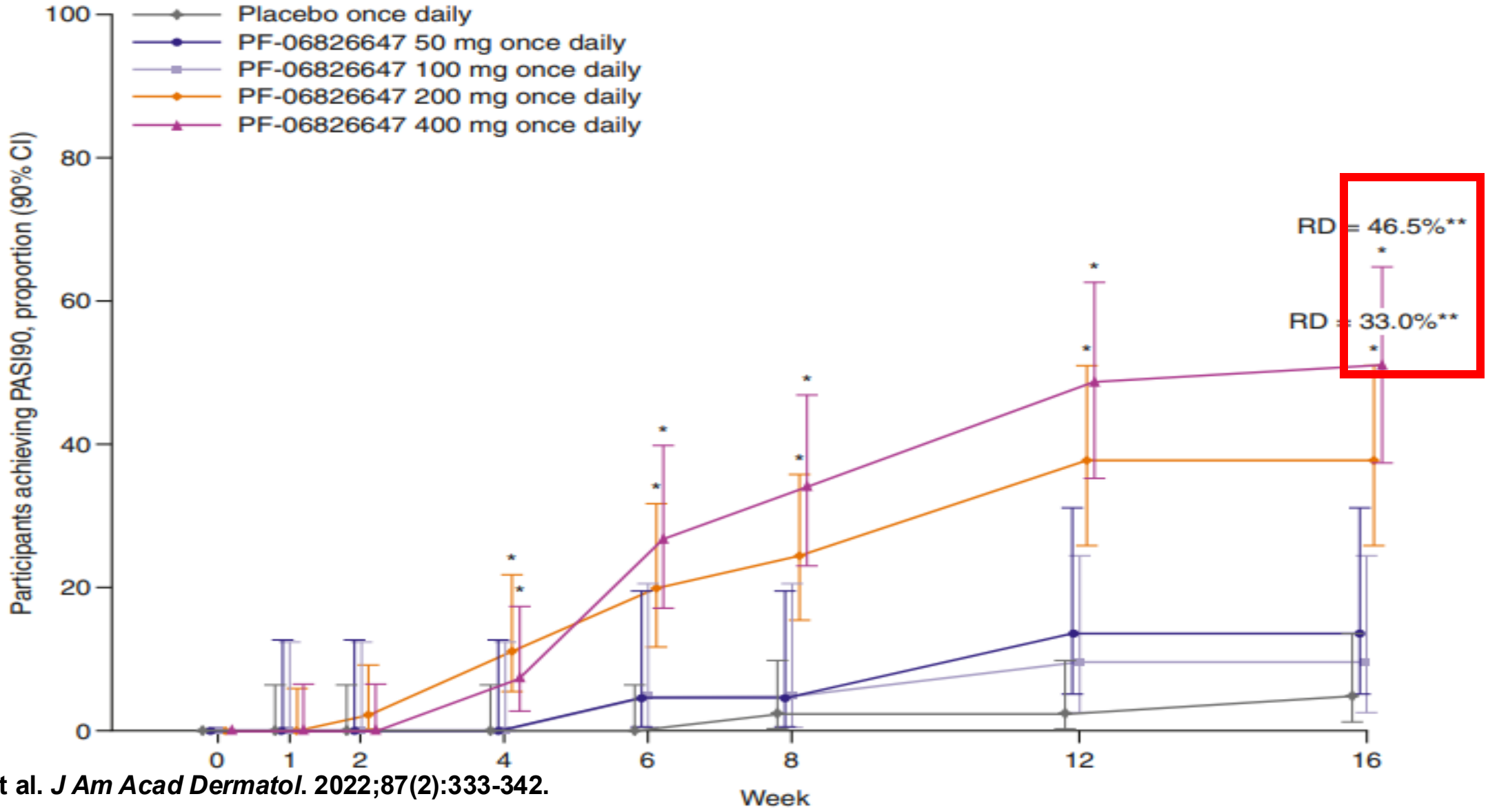
News | Articles | January 6, 2026

Phase 3 Data Support Oral TYK2 Inhibitor Envudeucitinib for Psoriasis

Author(s) *Maddi Hebebrand, MC, Associate Editor*

Hebebrand M [www.dermatologytimes.com]. Last updated January 6, 2026. Accessed February 17, 2026. https://www.dermatologytimes.com/view/phase-3-data-support-oral-tyk2-inhibitor-envudeucitinib-for-psoriasis.

PF-06826647 (Ropsacitinib)—Oral TYK2 Inhibitor



Tehlirian C, et al. *J Am Acad Dermatol*. 2022;87(2):333-342.

CC-99677—MK2 Inhibitor

- **Mechanism:** Oral, irreversible MAPK-activated protein kinase 2 (MK2) inhibitor; suppresses TNF, IL-17A/F production
- **Pre-clinical**
  - **In vitro:** Sustained TNF inhibition; suppressed IL-17A/F in PsA patient cells
  - **In vivo murine model:** Dose-dependent reduction in combined skin/joint severity score (PASI)
- **Clinical status**
  - No published phase 2/3 trials in human psoriasis or PsA yet
  - Development is preclinical, with clinical PsA trials “planned”
  - Safety and tolerability still undetermined


RESEARCH Open Access

CC-99677, a novel, oral, selective covalent MK2 inhibitor, sustainably reduces pro-inflammatory cytokine production

Rajula Gaur[1†], Kofi A. Mensah[1†], Jason Stricker[1], Mary Adams[1], Anastasia Parton[1], Dorota Cedzik[1], Jamie Connarn[1], Michael Thomas[1], Gerald Horan[1], Peter Schafer[1], Stuart Mair[2], Maria Palmisano[1] and Francisco Ramírez-Valle[1*]

Check for updates

Gaur R, et al. *Arthritis Res Ther*. 2022;24(1):199.

Key Learning Points

- TYK2 is a novel target for the treatment of psoriasis
- Inhibiting TYK2 prevents signaling from IL-12 and IL-23 (which activates T_H17 cells—central to psoriasis)
- Oral TYK2 inhibitors have been evaluated for psoriasis. Deucravacitinib is the only FDA-approved TYK2 inhibitor for PSO.
- Emerging data for zasocitinib and ESK-001
- These newer TYK2 inhibitors may have higher binding affinity for TYK2 and may be more effective
- It is likely that additional TYK2 inhibitors will be approved for psoriasis in the coming years

JNJ-77242113: Oral Peptide IL-23R Antagonist

ORIGINAL ARTICLE

I-co-tro-kin-ra

Oral Icotrokinra for Plaque Psoriasis in Adults and Adolescents

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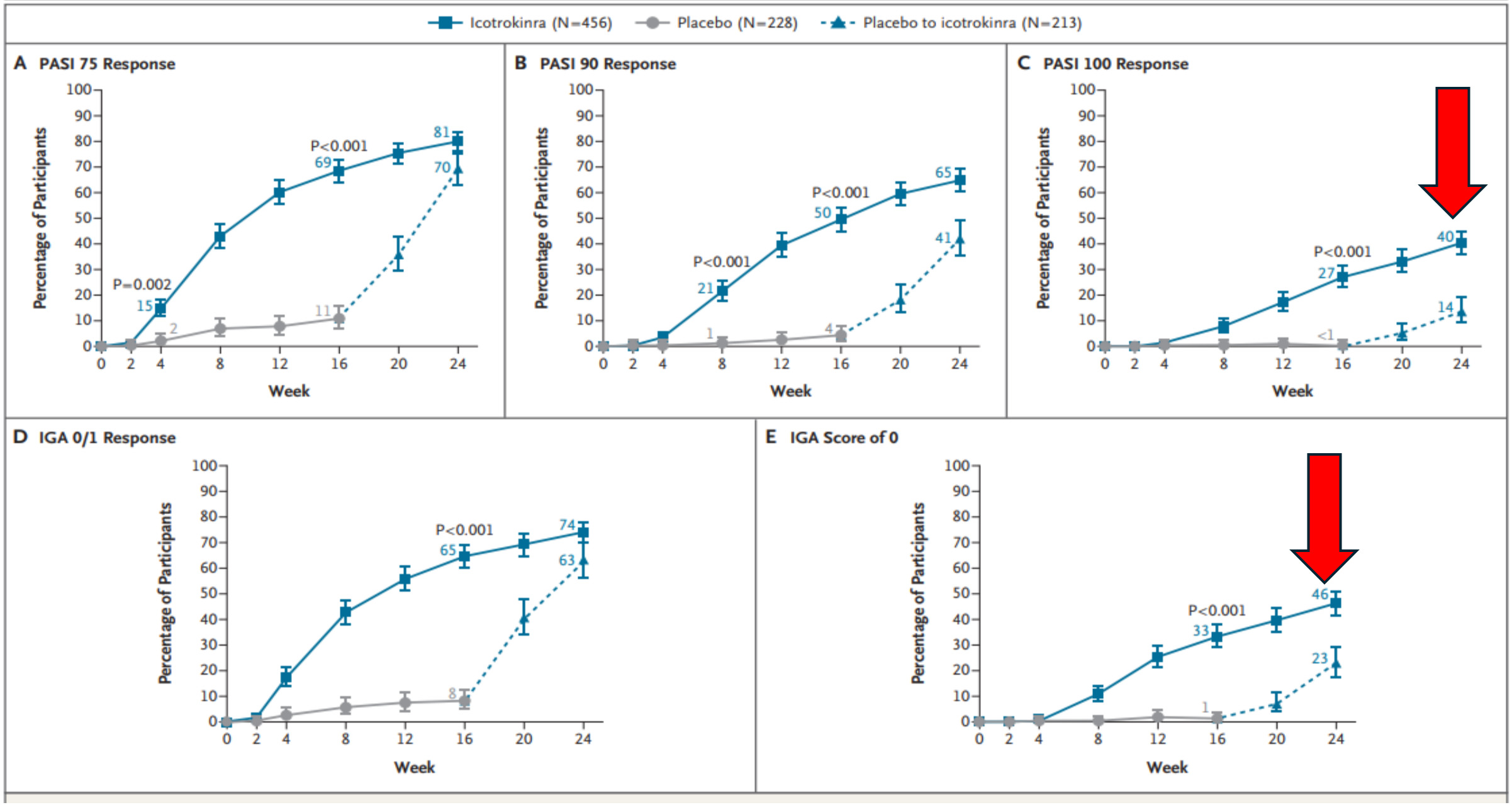
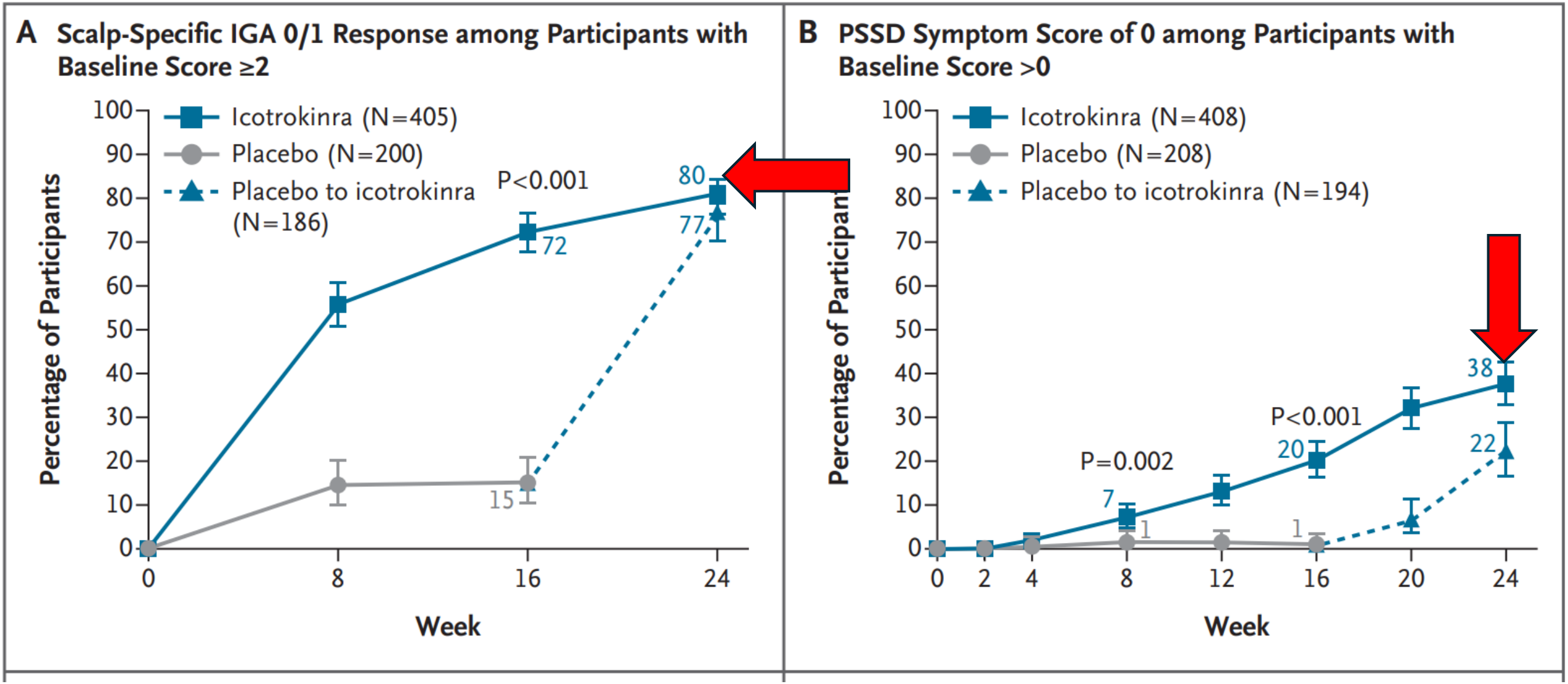
Bissonnette R, et al. *N Engl J Med.* 2025;393(18):1784-1795.



Bissonnette R, et al. *N Engl J Med.* 2025;393(18):1784-1795.



Bissonnette R, et al. *N Engl J Med*. 2025;393(18):1784-1795.

Safety

Table 3. Summary of Safety Assessments in Adult and Adolescent Participants through Week 16 and Week 24.

Variable	Icotrokinra, Weeks 0–16 (N=456)	Placebo, Weeks 0–16 (N=228)	Placebo to Icotrokinra, Weeks 16–24 (N=213)*	Icotrokinra, Weeks 0–24 (N=456)
Mean duration of follow-up — wk	15.9	15.8	8.2	23.6
Total participant-yr of follow-up	139.2	68.9	33.3	206.3
At least 1 adverse event — no. (%)†	225 (49)	112 (49)	53 (25)	253 (55)
No. per 100 participant-yr (95% CI)‡	234.5 (203.9–265.2)	239.8 (195.4–284.3)	182.4 (133.3–231.6)	199.1 (174.6–223.6)
Most common adverse events (≥5%) — no. (%)				
Nasopharyngitis	31 (7)	15 (7)	5 (2)	37 (8)
Upper respiratory tract infection	30 (7)	16 (7)	6 (3)	34 (7)
Headache	19 (4)	2 (<1)	0	21 (5)
Adverse event leading to discontinuation — no. (%)	6 (1)	1 (<1)	1 (<1)	6 (1)
No. per 100 participant-yr (95% CI)‡	4.3 (1.6–9.4)	1.5 (0.0–8.1)	3.0 (0.1–16.8)	2.9 (1.1–6.4)
Serious adverse event — no. (%)	6 (1)§	6 (3)§	1 (<1)¶	11 (2)¶
No. per 100 participant-yr (95% CI)‡	4.3 (1.6–9.4)	8.8 (3.2–19.2)	3.0 (0.1–16.8)	5.4 (2.7–9.6)
Gastrointestinal adverse event — no. (%)	26 (6)	13 (6)	1 (<1)	34 (7)
No. per 100 participant-yr (95% CI)‡	19.4 (12.7–28.5)	19.6 (10.5–33.6)	3.0 (0.1–16.8)	17.3 (12.0–24.2)
Infection — no. (%)†	107 (23)	51 (22)	21 (10)	131 (29)
No. per 100 participant-yr (95% CI)‡	89.2 (72.3–106.2)	85.5 (62.0–109.0)	66.3 (38.0–94.7)	77.6 (64.3–90.9)
Serious infection — no. (%)	1 (<1)	0	0	1 (<1)
No. per 100 participant-yr (95% CI)‡	0.7 (0.0–4.0)	0.0 (0.0–4.4)	0.0 (0.0–9.0)	0.5 (0.0–2.7)
Cancer — no. (%)	2 (<1)‖	0	0	2 (<1)‖
No. per 100 participant-yr (95% CI)‡	1.4 (0.2–5.2)	0.0 (0.0–4.4)	0.0 (0.0–9.0)	1.0 (0.1–3.5)
Active tuberculosis — no. (%)	0	0	0	0

Bissonnette R, et al. *N Engl J Med*. 2025;393(18):1784-1795.

Summary and Key Learning Points

- Psoriasis is a systemic inflammatory disease with significant unmet needs
- JAK/STAT and TYK2 pathways are central to disease pathogenesis
- Selective TYK2 inhibition offers a new balance of efficacy and safety and is effective in high-impact areas and paradoxical PSO
- New and emerging oral systemic therapies offer biologic-like efficacy and safety for patients with PSD
- Individualized, patient-centered therapeutic selection inclusive of shared decision-making is essential in the management of psoriatic disease

PSD = psoriatic disease.

Thank You