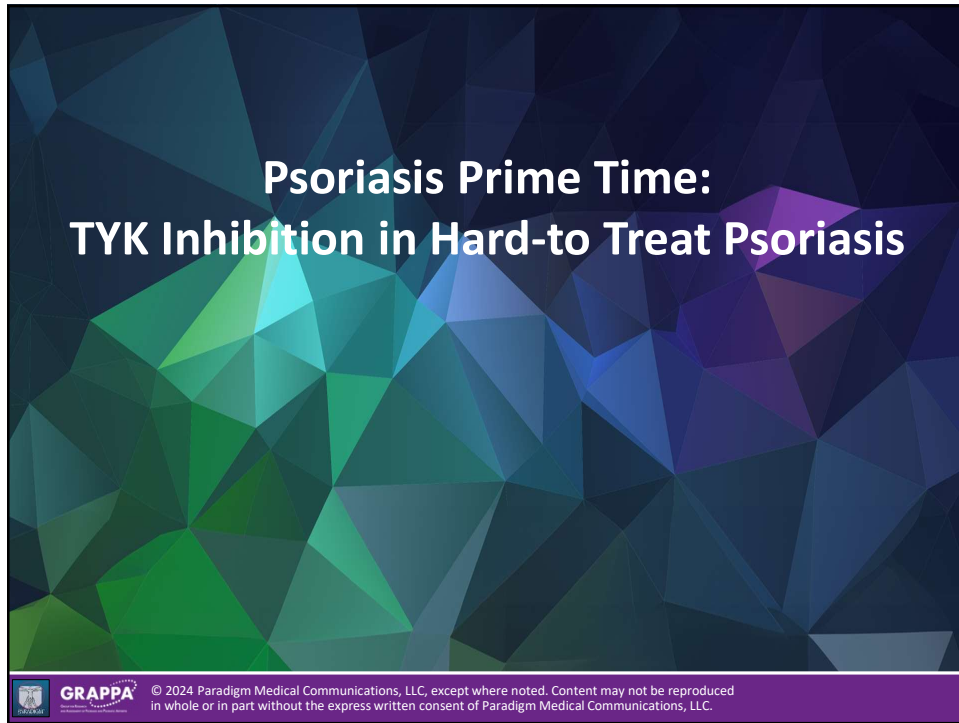
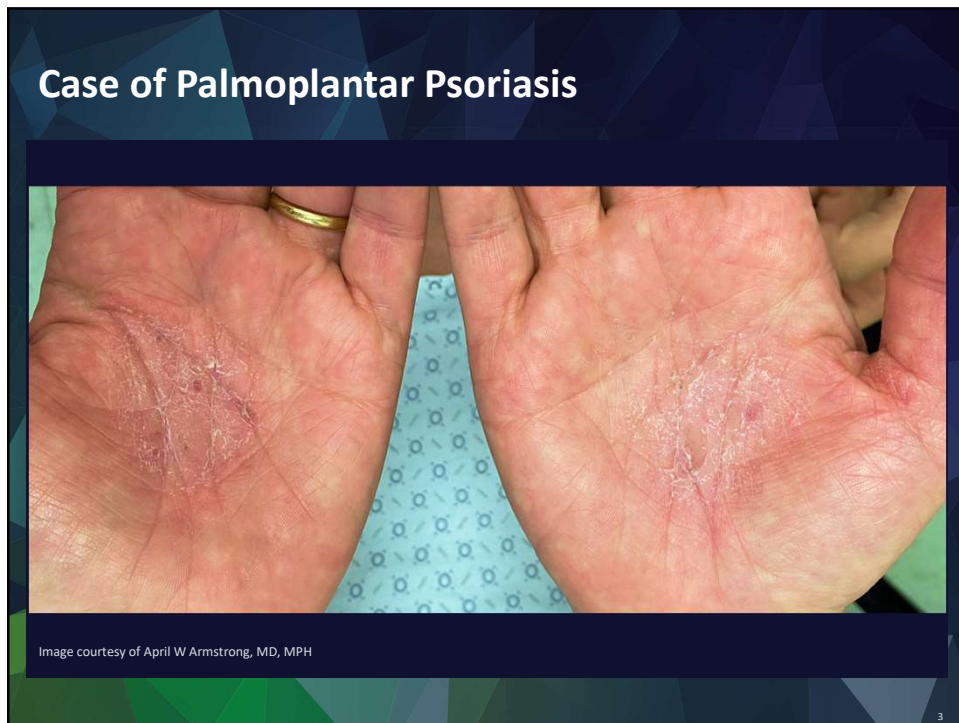


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Case of Palmoplantar Psoriasis

- Palms
- Some plantar involvement
- Elbows
- Knees
- Multiple topical agents
 - Clobetasol
- No signs of inflammatory arthritis

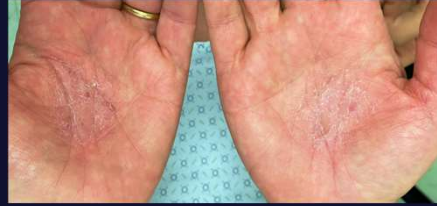
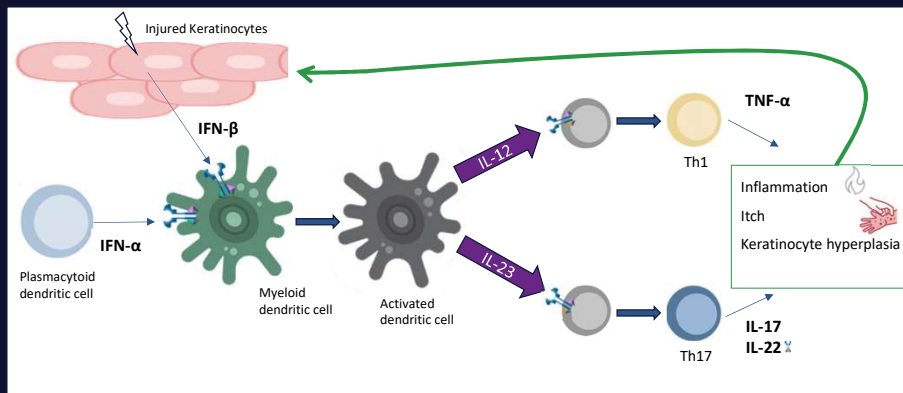


Image courtesy of April W Armstrong, MD, MPH

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IL-23/IL-17 Pathway

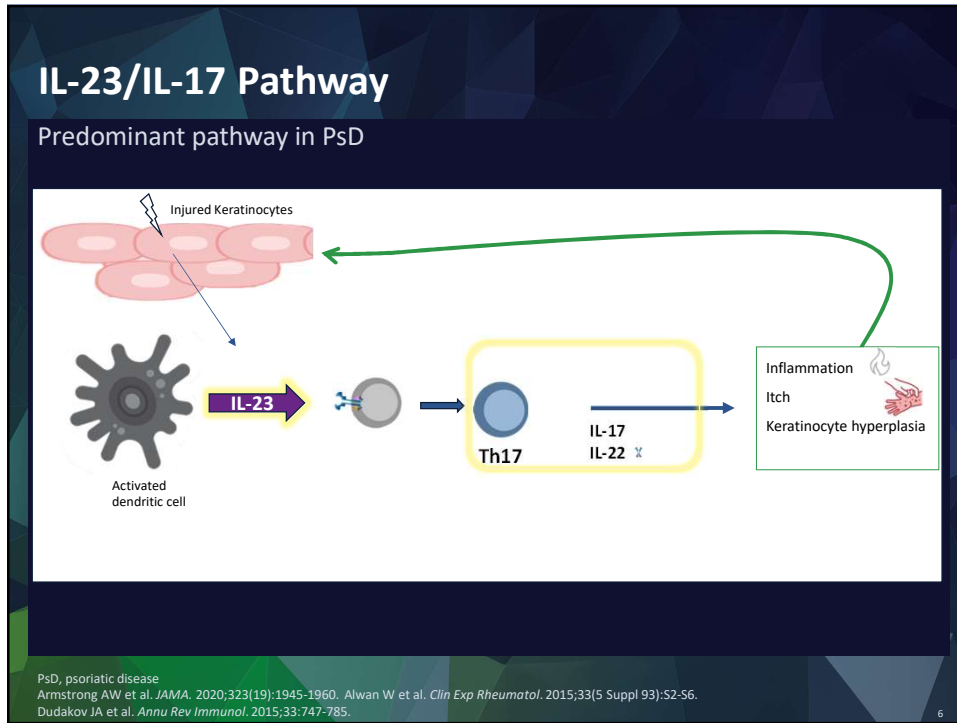


IFN, interferon; IL, interleukin; TNF, tumor necrosis factor
Armstrong AW et al. *JAMA*. 2020;323(19):1945-1960. Alwan W et al. *Clin Exp Rheumatol*. 2015;33(5 Suppl 93):S2-S6.
Dudakov JA et al. *Annu Rev Immunol*. 2015;33:747-785.

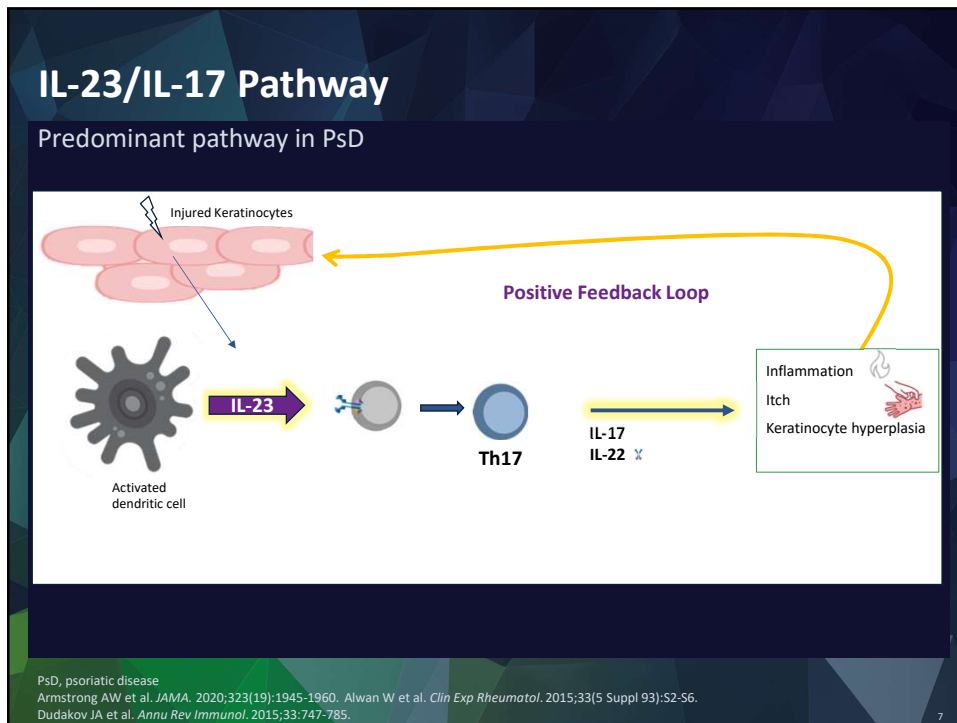
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JAK Family







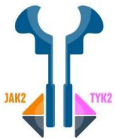

JAK, Janus kinase; TYK, tyrosine kinase
Schwartz DM et al. *Nat Rev Rheumatol*. 2016;12(1):25-36. Baker KF et al. *Ann Rheum Dis*. 2018;77(2):175-187. Choy EH. *Rheumatology (Oxford)*. 2019;58(6):953-962. Morand E et al. *Nat Rev Rheumatol*. 2024;20(4):232-240.

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JAK Selectivity

- Specific JAK pairs associate with specific cytokine receptors

yc Cytokines (IL-2, IL-4, IL-7, IL-9, IL-15, IL-21)	Type 1 IFNs, IL-10 family of cytokines	IL-6, IL-11, IL-13, IL-27, IL-31, IL-35	IFN γ	IL-12, IL-23	EPO, TPO, GM-CSF, IL-3, IL-5
					

EPO, erythropoietin; GM-CSF, granulocyte-macrophage colony-stimulating factor; TPO, thrombopoietin
Baker KF et al. *Ann Rheum Dis*. 2018;77(2):175-187. Choy EH. *Rheumatology (Oxford)*. 2019;58(6):953-962.

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JAK Selectivity

These cytokines bind to receptors	yc Cytokines (IL-2, IL-4, IL-7, IL-9, IL-15, IL-21)	Type 1 IFNs, IL-10 family of cytokines	IL-6, IL-11, IL-13, IL-27, IL-31, IL-35	IFN γ	IL-12, IL-23	EPO, TPO, GM-CSF, IL-3, IL-5
With these JAKs	JAK1, JAK3	JAK1, TYK2	JAK1, JAK2, TYK2	JAK1, JAK2	JAK2, TYK2	JAK2, JAK2
With these effects	Growth/maturation lymphoid cells Differentiation/homeostasis T cells, NK cells B cell class switching Inflammation	Antiviral Antitumor Inflammation	Naive T cell differentiation T cell homeostasis Granulopoiesis Inflammation	Antiviral Antimycobacterial Inflammation	Innate immunity Differentiation/proliferation of Th17 cells Inflammation	Erythropoiesis Myelopoiesis Megakaryocyte/ platelet production

NK, natural killer
Baker KF et al. *Ann Rheum Dis.* 2018;77(2):175-187. Choy EH. *Rheumatology (Oxford).* 2019;58(6):953-962.

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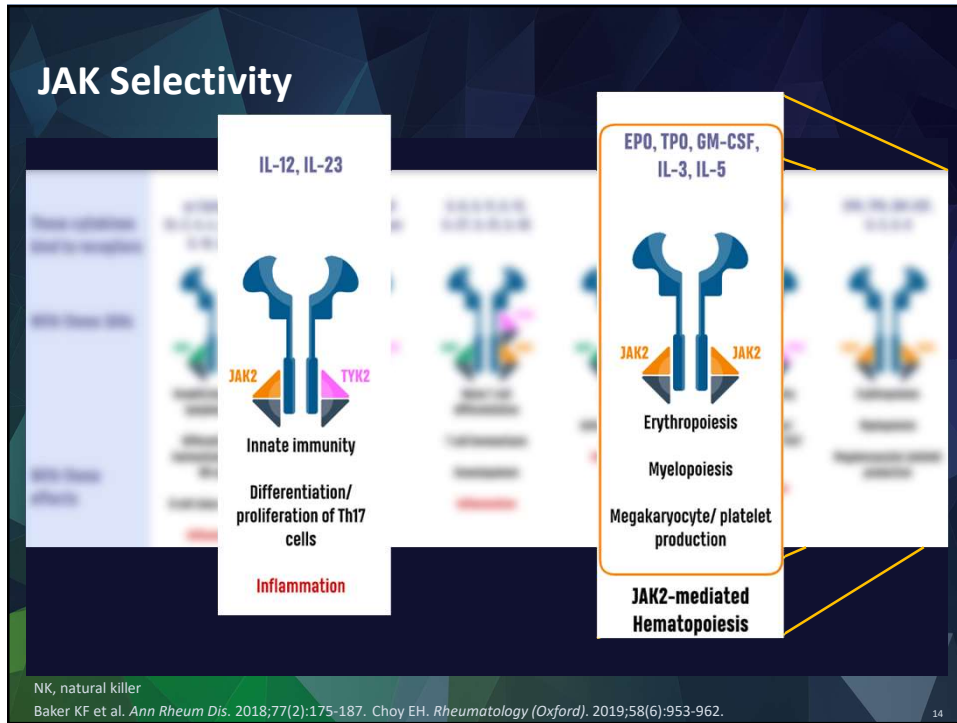
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With these JAKs	JAK1, JAK3	JAK1, TYK2	JAK1, JAK2, TYK2	JAK1, JAK2	JAK2, TYK2	JAK2, JAK2
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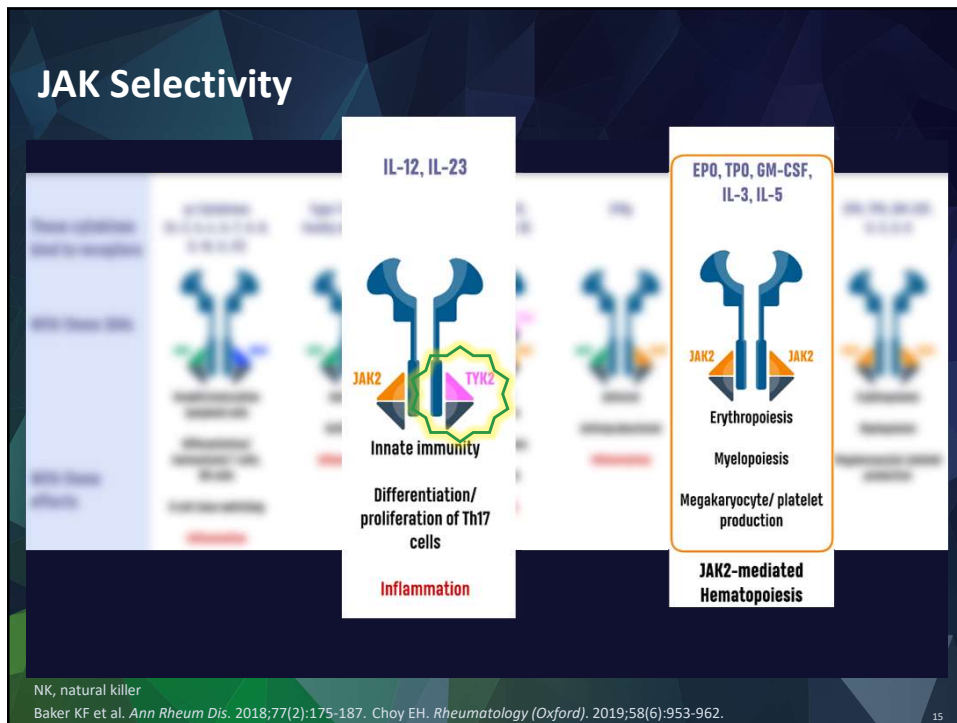
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JAK Family

A diagram showing four members of the JAK family: JAK1 (green), JAK2 (orange), JAK3 (blue), and TYK2 (pink). Each member is represented by a stylized icon of a protein structure with its name in a matching color.

Schwartz DM et al. *Nat Rev Rheumatol.* 2016;12(1):25-36. Baker KF et al. *Ann Rheum Dis.* 2018;77(2):175-187. Choy EH. *Rheumatology (Oxford).* 2019;58(6):953-962. Morand E et al. *Nat Rev Rheumatol.* 2024;20(4):232-240.

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JAK Family

A diagram showing four members of the JAK family: JAK1 (green), JAK2 (orange), JAK3 (blue), and TYK2 (pink). A bracket below the icons spans from the first to the last, with the text "Active domain (Highly conserved across the family)" centered under it.

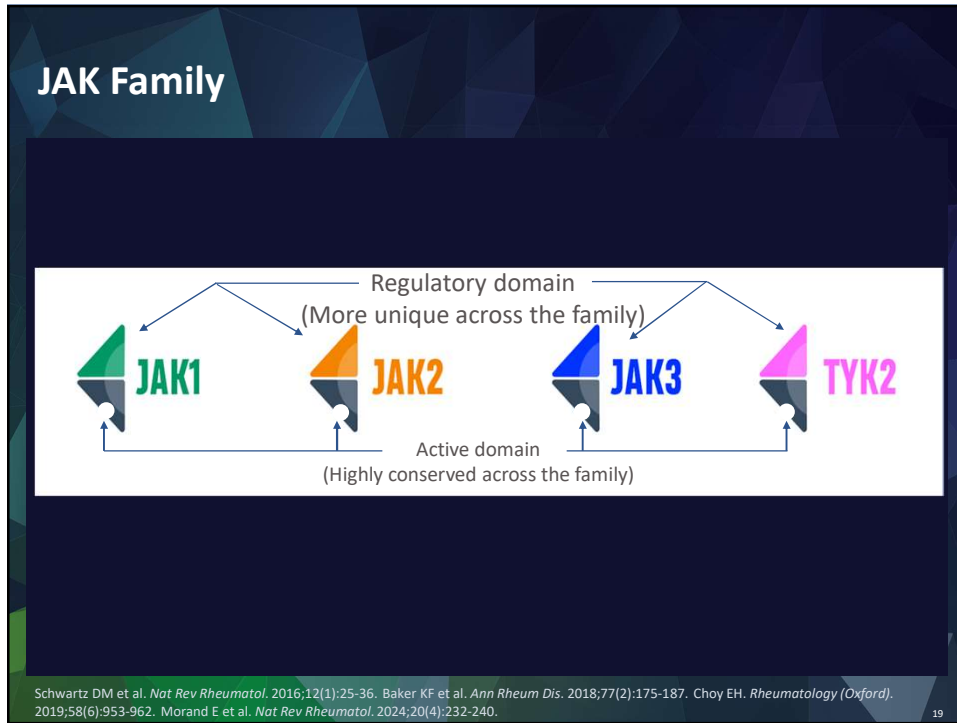
Schwartz DM et al. *Nat Rev Rheumatol.* 2016;12(1):25-36. Baker KF et al. *Ann Rheum Dis.* 2018;77(2):175-187. Choy EH. *Rheumatology (Oxford).* 2019;58(6):953-962. Morand E et al. *Nat Rev Rheumatol.* 2024;20(4):232-240.

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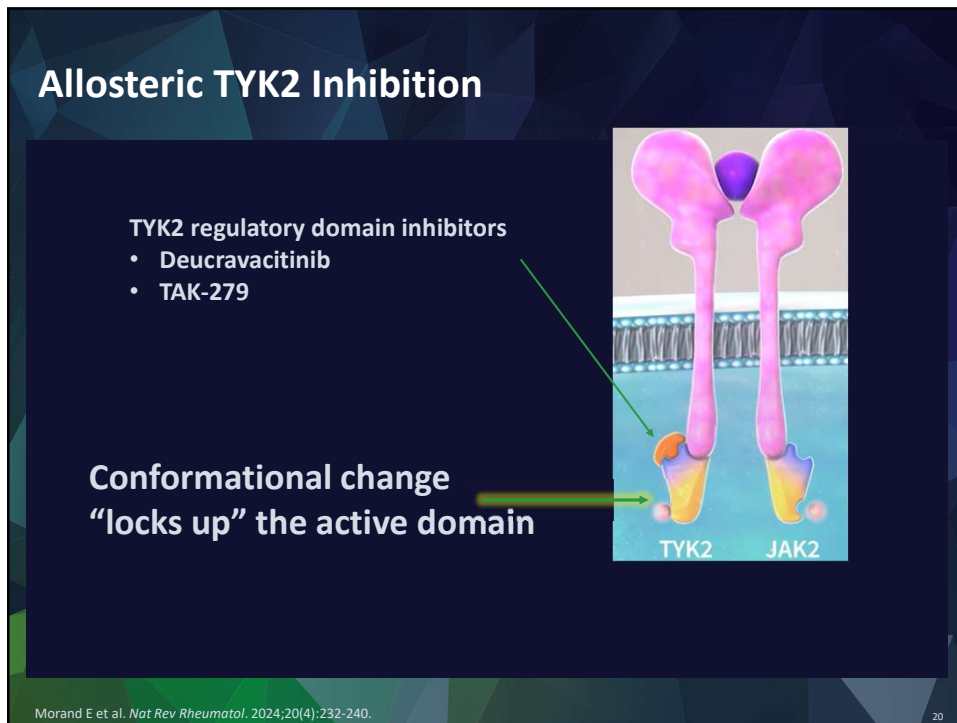
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Selectivity Profiles of JAK/TYK2 Inhibitors

IC ₅₀ (nM) ¹	JAK1	JAK2	JAK3	TYK2 Active Site (JH1)	TYK2 Regulatory (JH2)
Tofacitinib	15	77	55	489	—
Baricitinib	4	7	787	61	—
Upadacitinib	47	120	2304	4690	—
Abrocitinib	29	803	>15,000	1250	—
TYK2 Inhibitors					
Brepocitinib	17	77	6494	23	—
Ropsacitinib PF-06826647	383	74	>10,000	17	—
Deucravacitinib	>10,000	>10,000	>10,000	>10,000	0.2

Zasocitinib (TAK-279) is more selective for TYK2 than deucravacitinib; clinical relevance is unknown²

1. Wroblewski ST et al. *J Med Chem.* 2019;62(20):8973-8995. 2. Drakos A et al. *Pharmaceutics.* 2024;16(1):111.

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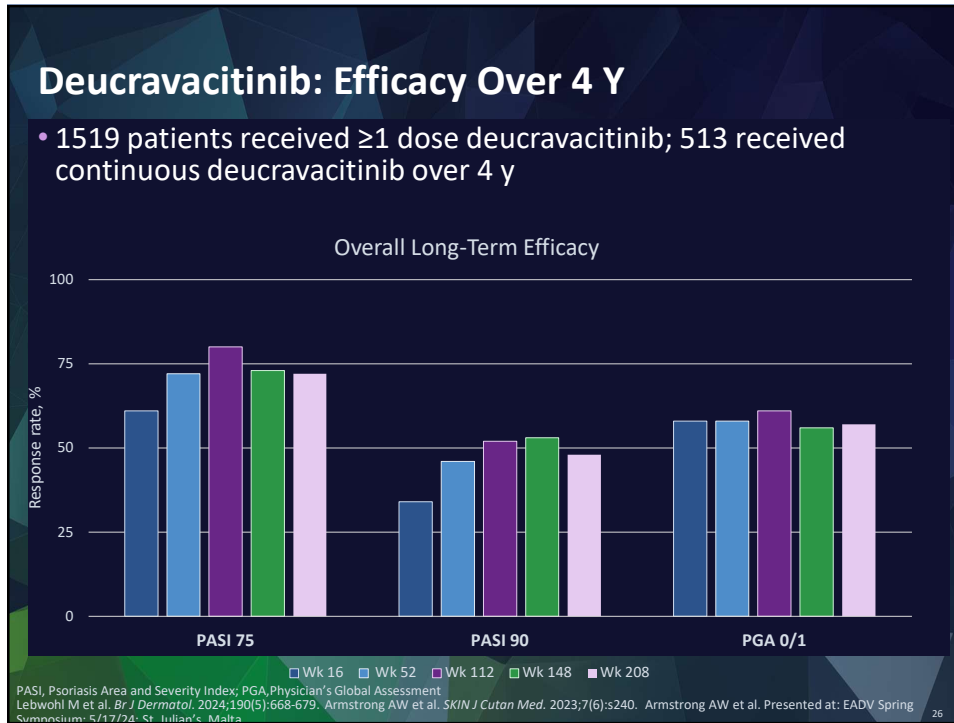
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Deucravacitinib: Long-Term Safety

AE, EAIRs/100 PY	Y1	Y2	Y3
Nasopharyngitis	26.1	12.9	11.4
URI	13.4	6.5	
COVID-19	0.2	5.1	6.5
Herpes zoster	0.9	0.7	0.6
MACE	1.2	0.4	0.3
VTE	0.2	0.1	0.1
Malignancies	1.0	0.9	0.9
Lymphoma	0.1	0.1	
Acne	2.9	1.3	
Folliculitis	2.8	1.3	

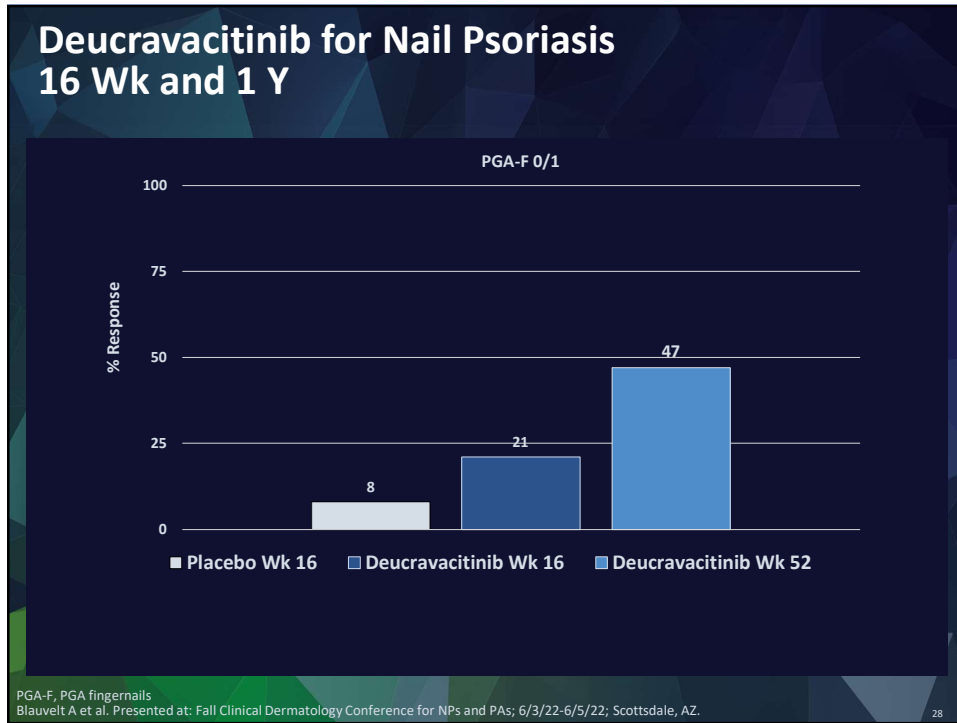
Y4 EAIRs consistent or decreased from y 1.

AE, adverse event; EAIR, exposure-adjusted incidence rate; MACE, major adverse cardiovascular events; PY, patient years; URI, upper respiratory infection; VTE, venous thromboembolism
Lebwohl M et al. *Br J Dermatol*. 2024;190(5):668-679. Armstrong AW et al. *SKIN J Cutan Med*. 2023;7(6):s240. Armstrong AW et al. Presented at:

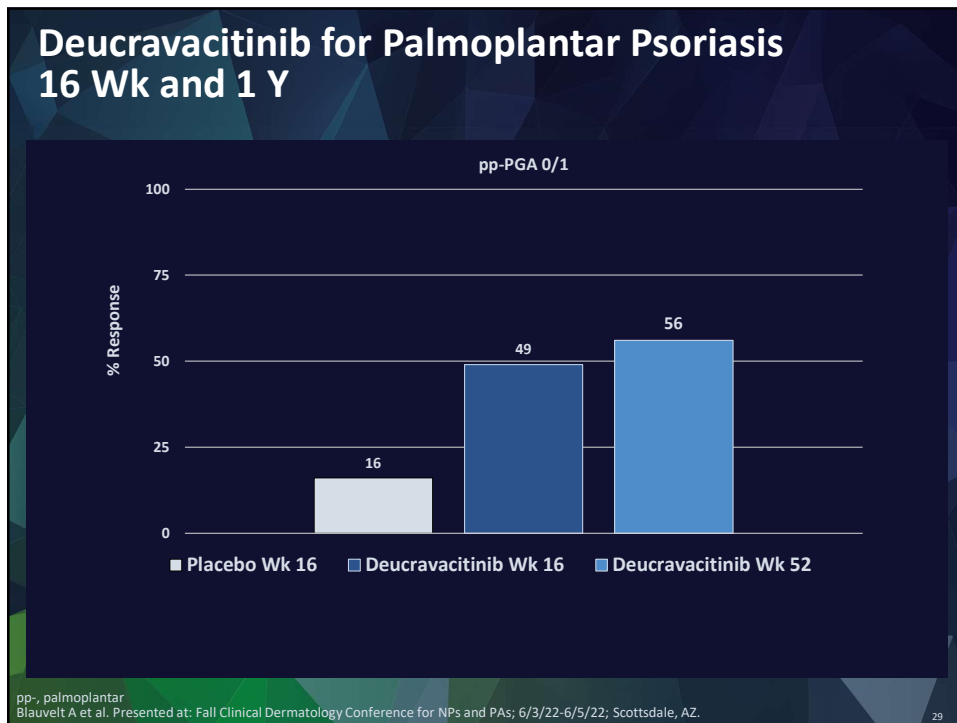
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Biologic Efficacy in Palmoplantar Psoriasis

	OR (95% CI) PGA 0,1 vs Placebo
Guselkumab	20.1 (9.24-45.3)
Bimekizumab	18.6 (3.97-108)
Adalimumab	11.1 (5.31-24.6)
Secukinumab 150 mg	8.81 (3.35-27.2)
Ustekinumab	8.66 (1.74-47.5)
Ixekizumab	7.11 (4.14-12.2)
Etanercept	3.89 (2.01-7.62)
Apremilast	2.99 (1.44-6.81)

Spencer RK et al. J Am Acad Dermatol. 2023;89(2):423-425. 30

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Treating Psoriasis Reduces Risk of PsA

- 41% of patients with psoriasis have undiagnosed PsA
- A review of records (869,000) of patients with PsO without PsA who received biologics

Targeting IL23 or IL-12/23 reduced risk of PsA vs TNF inhibitors and IL-17i

vs TNFi	IL-12/23, %	IL-23, %	vs IL-17	IL-23, %
1 st Line 5 y	-37	-39	1 st Line 5 y	-47
2 nd Line 3 y	-32	-31	2 nd Line 3 y	-47

PsO, psoriasis
Joven-Ibáñez B et al. Ann Rheum Dis. 2024;83(suppl 1):168. 33

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Screening for PsA

- Physical exam
 - ▶ Psoriasis linked to PsA: Scalp, flexural skin, nails
 - ▶ Joint exam
 - ▶ Achilles insertion

1. Ogdie A et al. *J Am Acad Dermatol.* 2022;87(6):1303-1311. 2. Ogdie A, Gelfand JM. *Curr Rheumatol Rep.* 2015;17(10):64. 3. Green A et al. *Br J Dermatol.* 2020;182(3):714-720. 4. Mease PJ et al. *J Eur Acad Dermatol Venereol.* 2019;33(5):886-892.

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Screening for PsA: PEST

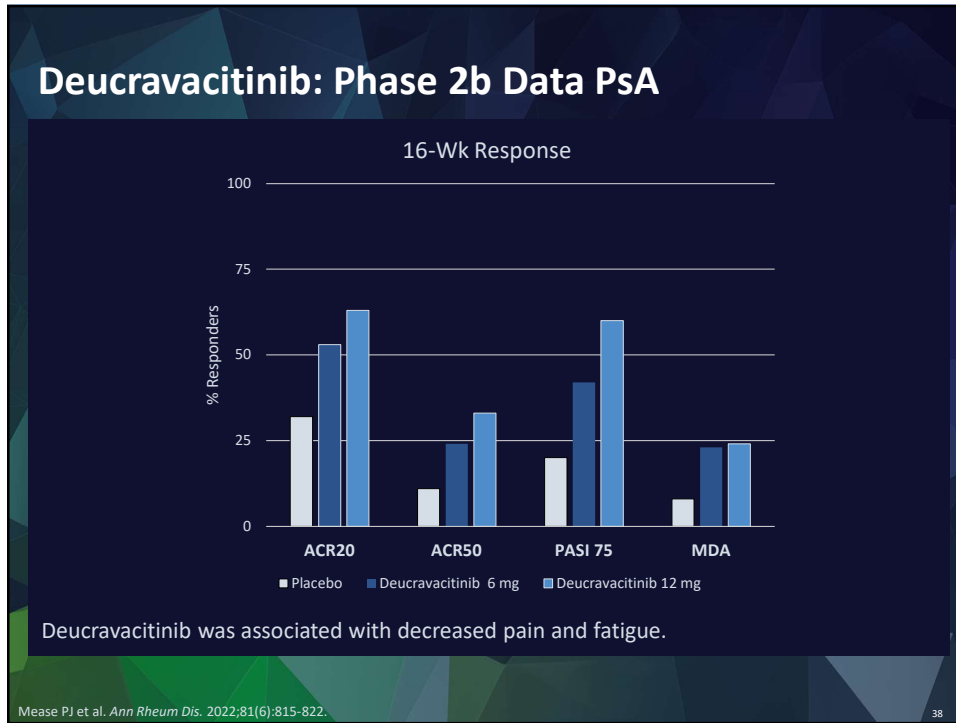
- PEST: Psoriasis Epidemiology Screening Tool
- Score ≥ 3 increased risk of PsA diagnosis
 - ▶ Swollen joints
 - ▶ Diagnosed arthritis
 - ▶ Nail pitting
 - ▶ Heel pain
 - ▶ Swollen finger or toe

Mease PJ et al. *J Eur Acad Dermatol Venereol.* 2019;33(5):886-892.

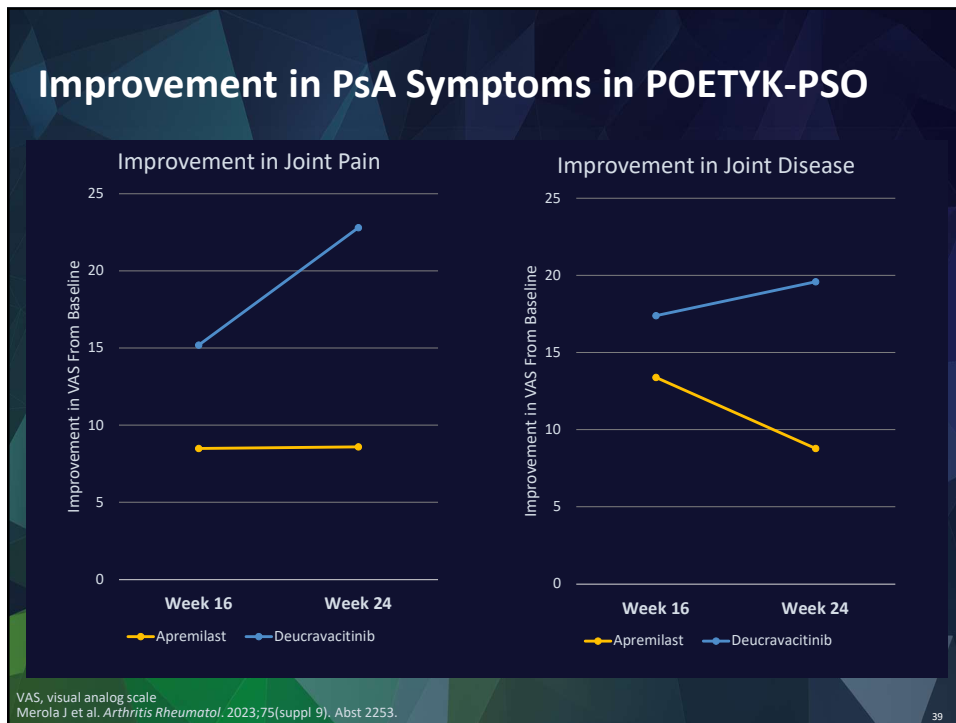
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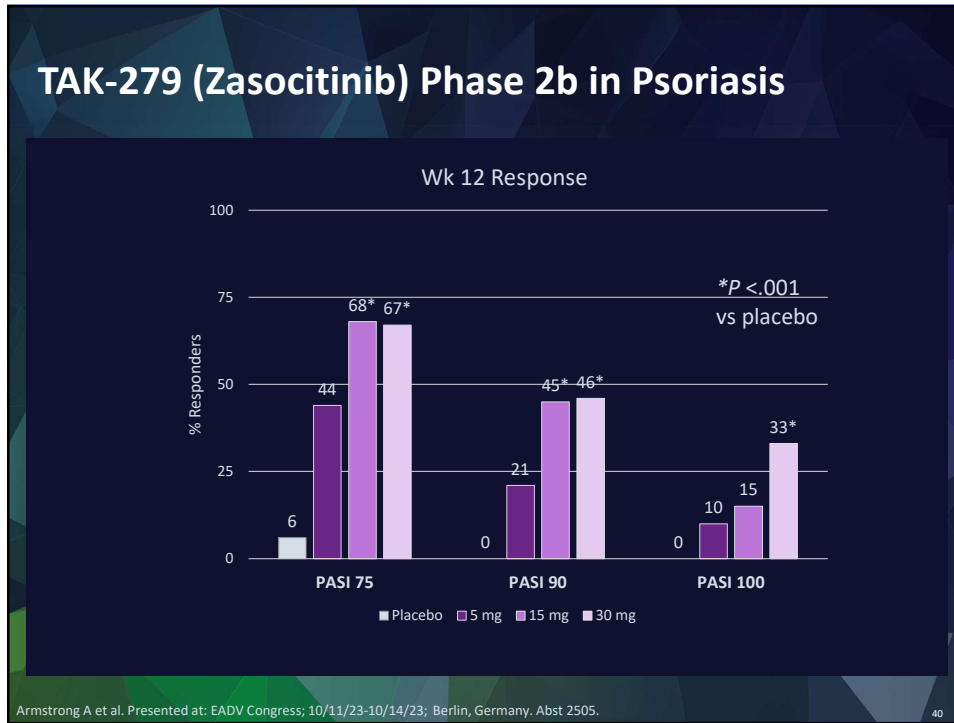


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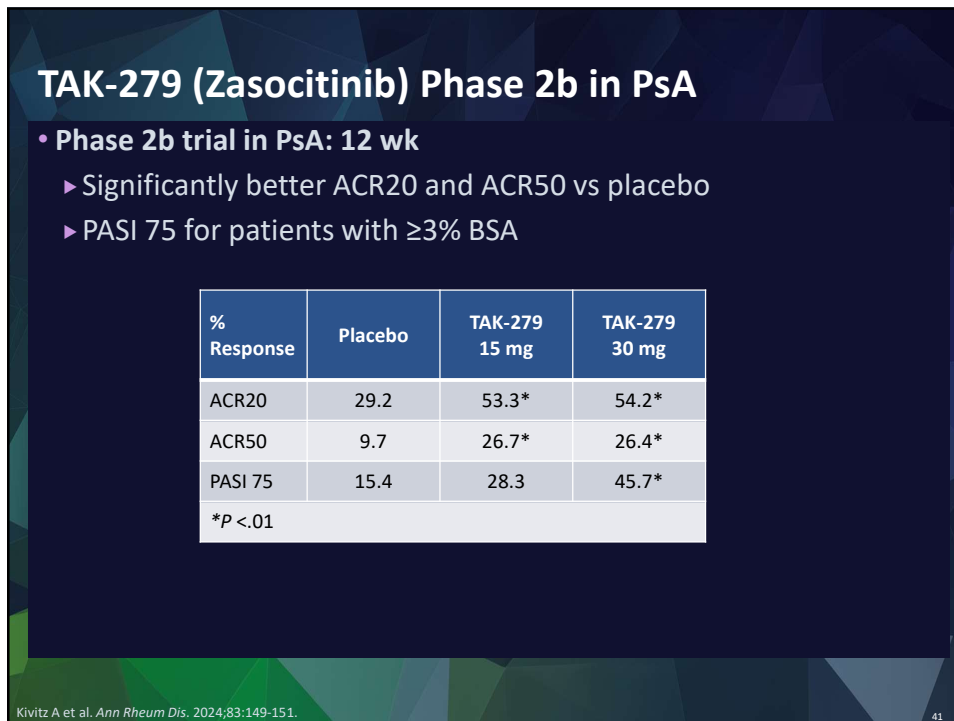


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Summary Wrap-Up

- The IL-23/Th17 pathway is active in psoriasis, making IL-23 and IL-17 attractive treatment targets
- Allosteric inhibition of the TYK2 regulatory site is selective for TYK2 and reduces the effects of TYK2-mediated cytokines
- Clinical data for deucravacitinib show superiority compared with placebo and apremilast, with good safety and tolerability
 - ▶ Efficacy in palmoplantar and nail psoriasis and PsA
- Phase 2 data for zasocitinib demonstrate efficacy for psoriasis and PsA compared with placebo, with good tolerability

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Thank you!

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