CMEO Snack 2

Refining Treatment Targets for the Management of Psoriasis

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Today's Activity Is Eligible for ABIM MOC Credit and as a CME for MIPS Improvement Activity

Complete your post-test and evaluation at the conclusion of the activity

ABIM CME MOC ACCREDITED

Be sure to fill in your **ABIM ID number** and **DOB** (MM/DD) on the evaluation so we can submit your credit to ABIM

CME for MIPS IMPROVEMENT ACTIVITY

Over the next 90 days, actively work to incorporate improvements in your clinical practice from this presentation

- Complete the follow-up survey from CME Outfitters in approximately 3 months
- CME Outfitters will send you confirmation of your participation to submit to CMS attesting to your completion of a CME for MIPS Improvement Activity

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Learning Objective

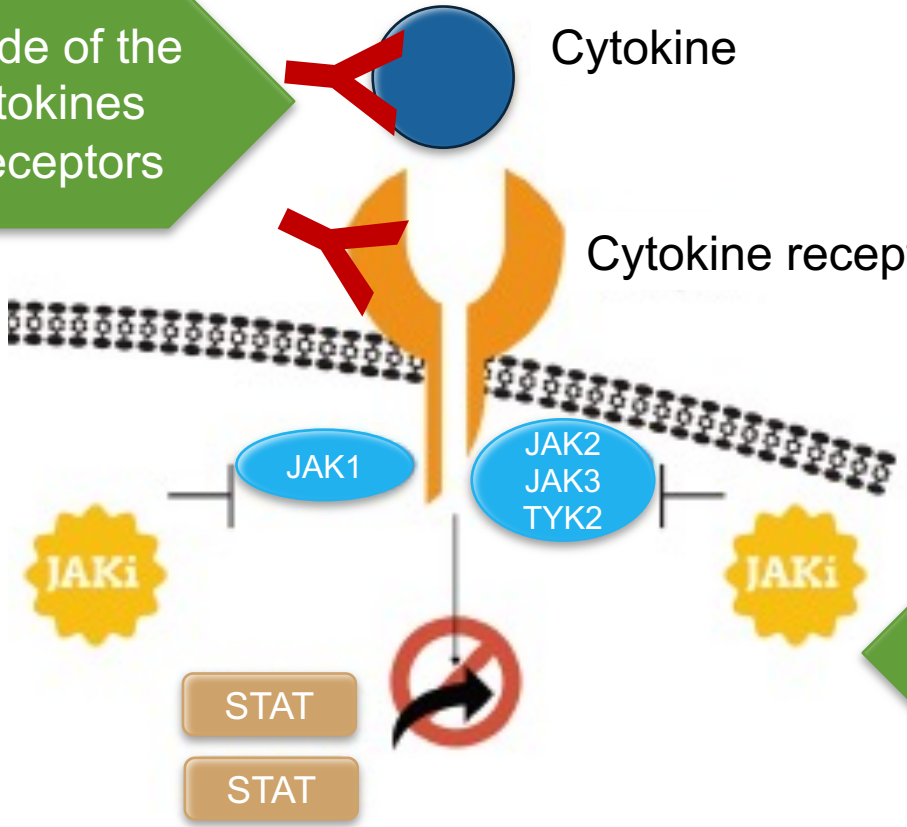
Evaluate the role of tyrosine kinase 2 (TYK2) versus Janus kinase 1 (JAK 1), JAK2, and JAK3 signaling pathways in psoriasis (PsO) and their role as emerging treatment targets.

Pathogenesis of Psoriasis

- Although complex and not fully understood, the interleukin (IL)-12 and IL-23 axis is currently considered to be the main pathogenic pathway of PsO
- Monoclonal antibodies (mAbs) target the IL-12/IL-23 axis
  - Ustekinumab
  - Secukinumab
  - Ixekizumab
  - Guselkumab
  - Risankizumab
  - Tildrakizumab
  - Brodalumab
- The need for parenteral administration, risk of immunogenicity, potential adverse events, and loss of efficacy merits continued discovery and clinical trials

Kvist-Hansen A, et al. *Dermatol Ther (Heidelb)*. 2020;10(1):29-42.

mAbs act outside of the cell to block cytokines and cytokine receptors



TYK2 and JAKi act inside of the cell to block pro-inflammatory cytokines

JAKi = Janus kinase inhibitors

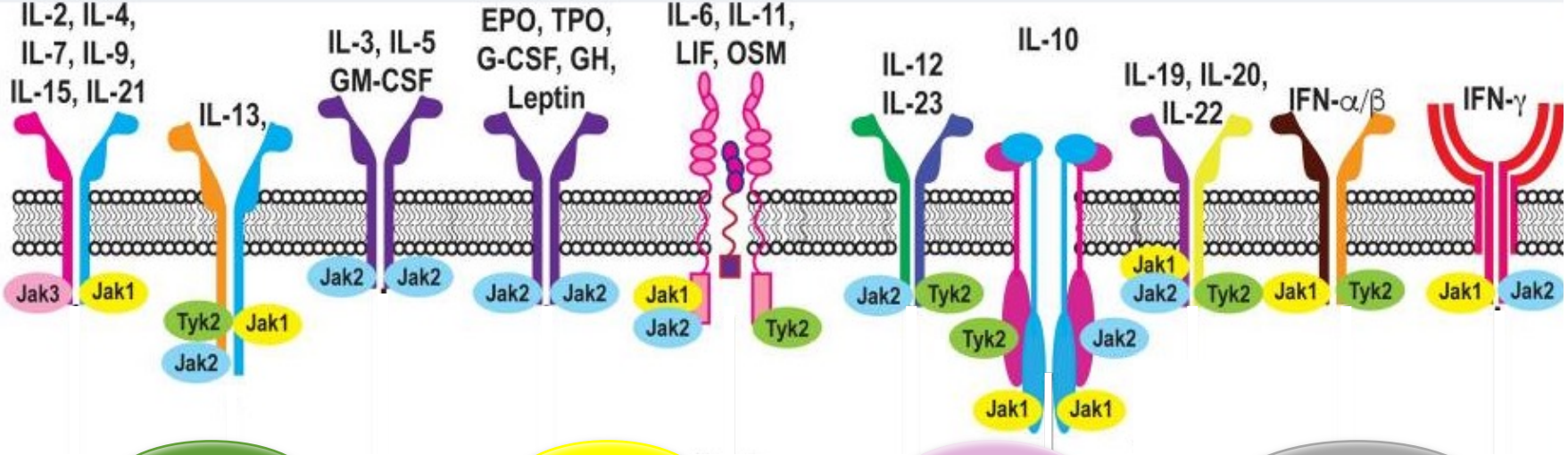
1. Nogueira M, et al. *Drugs*. 2020;80(4):341-352. 2. Schwartz DM, et al. *Nat Rev Drug Discov*. 2017;17(1):78.

JAK Inhibitors in the Pathogenesis of Psoriasis

- IL-23 receptor relies on a heterodimer of JAK2 and TYK2 for signal transduction highlighting the role of JAKs in the pathogenesis of PsO and the therapeutic potential of JAKs
- JAKi target different members of the JAK family, with some more selective than others
- First generation JAKi target 2 or 3 different JAKs resulting in a broader effect, but may also present more side effects than newer generation selective TYK2 inhibitors that target just one JAK

Kvist-Hansen A, et al. *Dermatol Ther (Heidelb)*. 2020;10(1):29-42.

Different Cytokine Receptors Associate with Different JAKs



TYK2	JAK1	JAK3	Non-selective
Deucravacitinib PF-06826647	Filgotinib Upadacitinib	Decernotinib PF-06651600	Tofacitinib Baracitinib Ruxolitinib

Schwartz DM, et al. *Nat Rev Drug Discov*. 2017;17(1):78.

PsO-Associated Cytokines and Members of JAK/STAT Families to Which They Relate

Cytokines	Main JAKs Activated	Main STATs Activated
JAK1, JAK2, JAK3 Dependent Cytokines		
IFN-γ	JAK1, JAK2	STAT1
IL-2	JAK1, JAK3	STAT5
IL-19, IL-20	JAK1, JAK2	STAT1, STAT3
IL-21	JAK1, JAK3	STAT1, STAT3, STAT5
TYK2 Dependent Cytokines		
IFN-∝	JAK2, TYK2	STAT1, STAT2
IL-12	TYK2, JAK2	STAT4
IL-22	TYK2, JAK1	STAT1, STAT3, STAT5
IL-23	TYK2, JAK2	STAT1, STAT3, STAT4
TNF-∝, IL-1, IL-8, IL-17, IL-18, IL-36	Do not directly activate JAK/STAT	

IFN = interferon; STAT = signal transducer and activator of transcription; TNF = tumor necrosis factor alpha

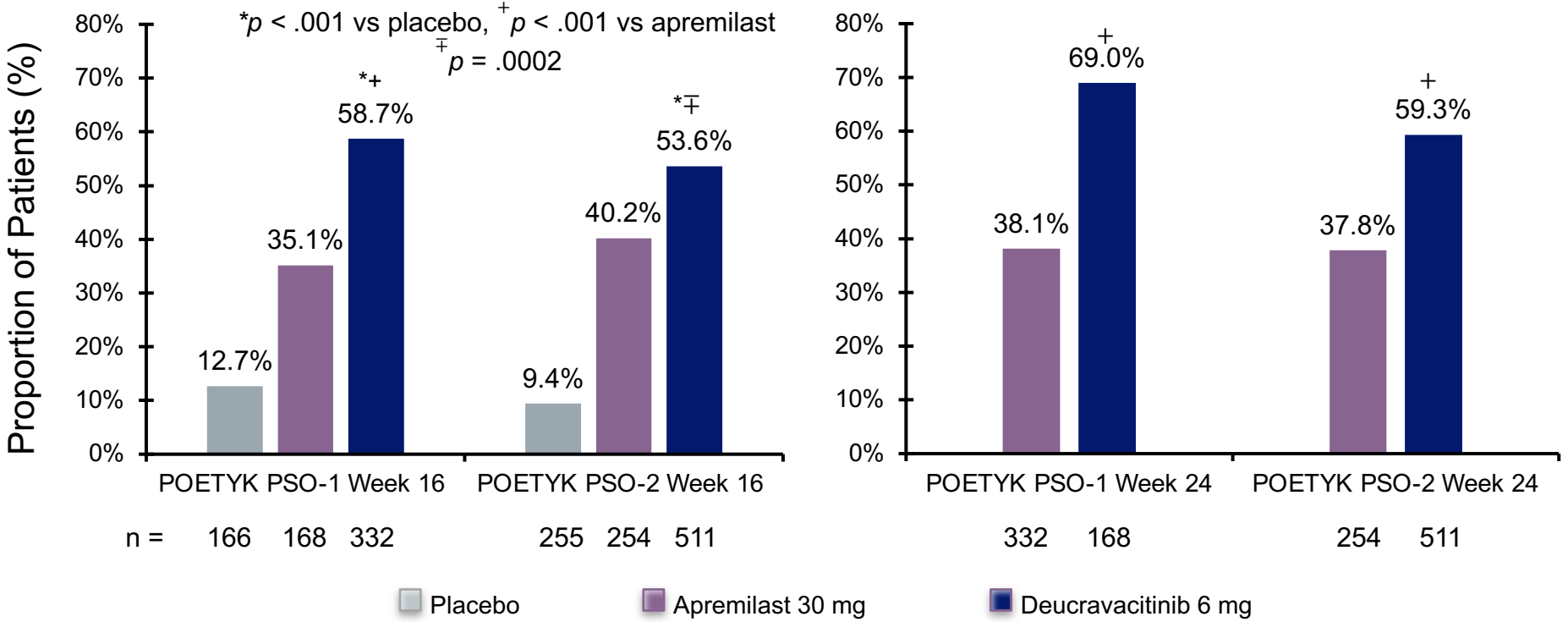
Nogueira M, et al. *Drugs*. 2020;80(4):341-352.

TYK2 Inhibitors and PsO

- Skin infiltration of various immune cells and production of pro-inflammatory cytokines IL-17 and IL-22 are impaired in the absence of TYK2[1]
- As knowledge about PsO has evolved, the focus on JAK inhibition has shifted and seems to be moving toward TYK2[2]

1. Ishizaki M, et al. *Int Immunol*. 2014;26(5):257-267. 2. Nogueira M, et al. *Drugs*. 2020;80(4):341-352.

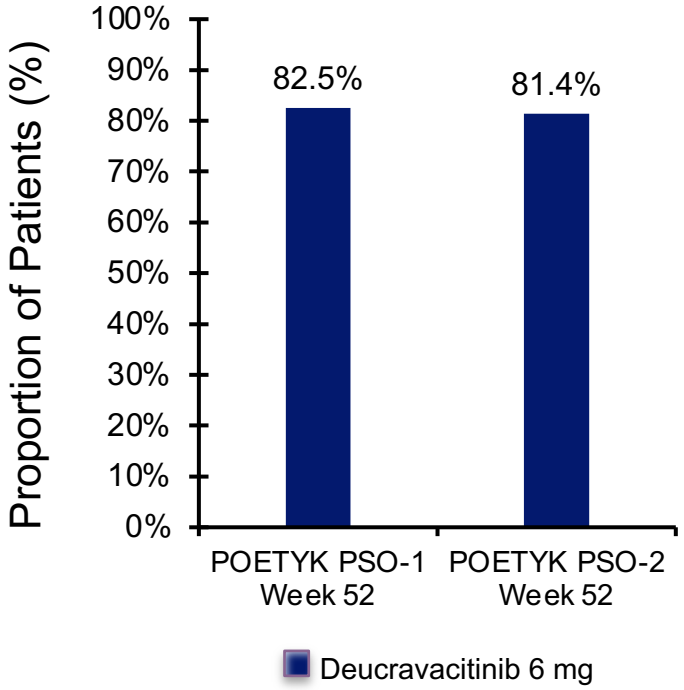
POETYK PSO-1 and POETYK PSO-2: PASI-75 Results at Week 16 and 24



Armstrong A. et al. Efficacy and safety of deucravacitinib, an oral, selective tyrosine kinase 2 (TYK2) inhibitor, compared with placebo and apremilast in moderate to severe plaque psoriasis: results from the phase 3 POETYK PSO-1 Study. AAD Virtual Meeting Experience (VMX); 2021.

POETYK PSO-1 and POETYK PSO-2: PASI-75 Response Maintained at Week 52

- Among patients who achieved PASI-75 response at Week 24 with deucravacitinib and continued treatment with deucravacitinib, PASI-75 response was maintained at 52-weeks in over 80% of patients



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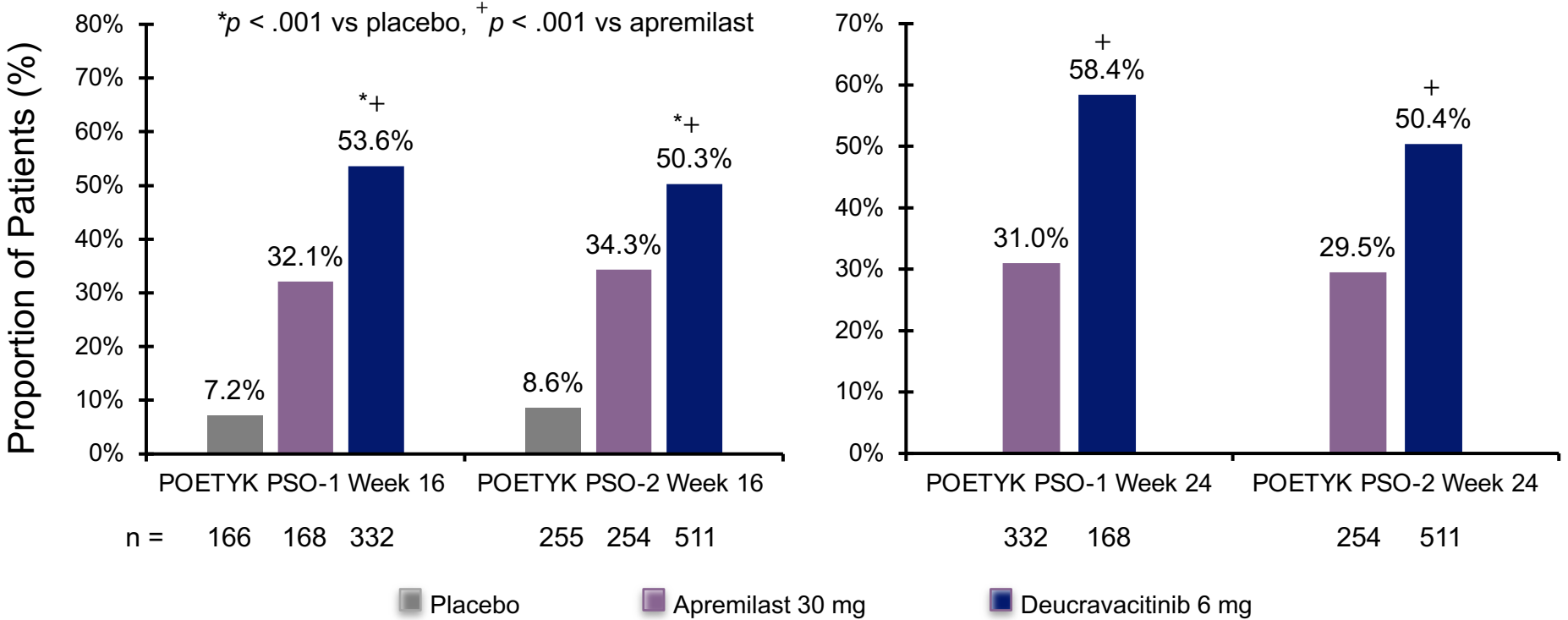
POETYK PSO-1 and POETYK PSO-2: Static Physician Global Assessment (sPGA 0/1) at Wk 16 & 24



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Adverse Events

Adverse Events Weeks 0-16	• Adverse events were similar across each arm • 55.7% with deucravacitinib, 57.6% with apremilast, 49.6% with PBO • Discontinuation rates: 2.4% with deucravacitinib, 57.6% with apremilast, 49.6% with PBO
Serious Adverse Events	• Serious adverse events: 1.8% with deucravacitinib, 1.2% with apremilast, 2.9% with PBO • Discontinuation: 2.4% with deucravacitinib, 5.2% with apremilast, 3.8% in PBO • Exposure-adjusted incidence rate for herpes zoster: 0.9 per 100 patient years with deucravacitinib
Most Common Adverse Events	• Nasopharyngitis, upper respiratory tract infection, headache, diarrhea, and nausea • One death occurred in each treatment group deemed not to be related to study drugs

PBO = placebo

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SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Understanding the pathogenesis of PsO offers insights into efficacy and safety profiles for emerging agents
- Do not paint all JAK inhibitors with a broad brush! Differences in mechanisms of action offer new and effective options for patients with PsO

CME Outfitters Snack 1

Why New Treatments are Needed for the Management of Psoriasis

CME Outfitters Snack 3

Forecasting a Bright and Clear Tomorrow for Psoriasis Treatment

www.CMEOutfitters.com/dermatology-hub