BIOLOGICS FOR ATOPIC DERMATITIS

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POTENTIAL CONFLICTS OF INTEREST

- **Speaker**/received honoraria from AbbVie, Bristol-Myers Squibb, Eli Lilly and Company, Pfizer, Regeneron, and Sanofi
- **Scientific adviser**/received honoraria from AbbVie, Abcentra, Aclaris, Affibody, Aligos, Almirall, Alumis, Amgen, Anaptysbio, Arcutis, Arena, Aslan, Athenex, Bluefin Biomedicine, Boehringer Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, Dermavant, EcoR1, Eli Lilly and Company, Escient, Evelo, Evommune, Forte, Galderma, HighlightII Pharma, Incyte, Janssen, Landos, Leo, Merck, Microbion, Novartis, Pfizer, Q32 Bio, Rani, Rapt, Regeneron, Sanofi Genzyme, Spherix Global Insights, Sun Pharma, TLL Pharmaceutical, TrialSpark, UCB Pharma, Union, Vibliome, and Xencor
- **Clinical study investigator**/institution has received clinical study funds from AbbVie, Acelyrin, Aclaris, Allakos, Alumis, Amgen, Arcutis, Athenex, Boehringer Ingelheim, Bristol-Myers Squibb, Concert, Dermavant, Eli Lilly and Company, Evelo, Evommune, Galderma, Incyte, Janssen, Leo, Merck, Novartis, Pfizer, Regeneron, Sun Pharma, UCB Pharma, and Ventyx

WHEN TO USE SYSTEMIC THERAPY FOR AD: FROM THE INTERNATIONAL ECZEMA COUNCIL

- ***If topical therapy and/or phototherapy not achieving adequate control of disease***
- **Large impact on quality of life**
- **Alternate diagnoses considered, e.g., CTCL, allergic contact dermatitis**
- **Infection addressed**
- **Adequate education delivered**

REF: Simpson et al, *J Am Acad Dermatol*, 2017

KEY CURRENT AND FUTURE BIOLOGIC AND ORAL DRUG CHOICES FOR MODERATE-TO-SEVERE AD

Biologics

- **Dupilumab (blocks IL-4+IL-13)**
- **Tralokinumab (blocks IL-13)**
- **Lebrikizumab* (blocks IL-13)**
- **Nemolizumab* (blocks IL-31R)**

- **Methotrexate**
- **Cyclosporine**

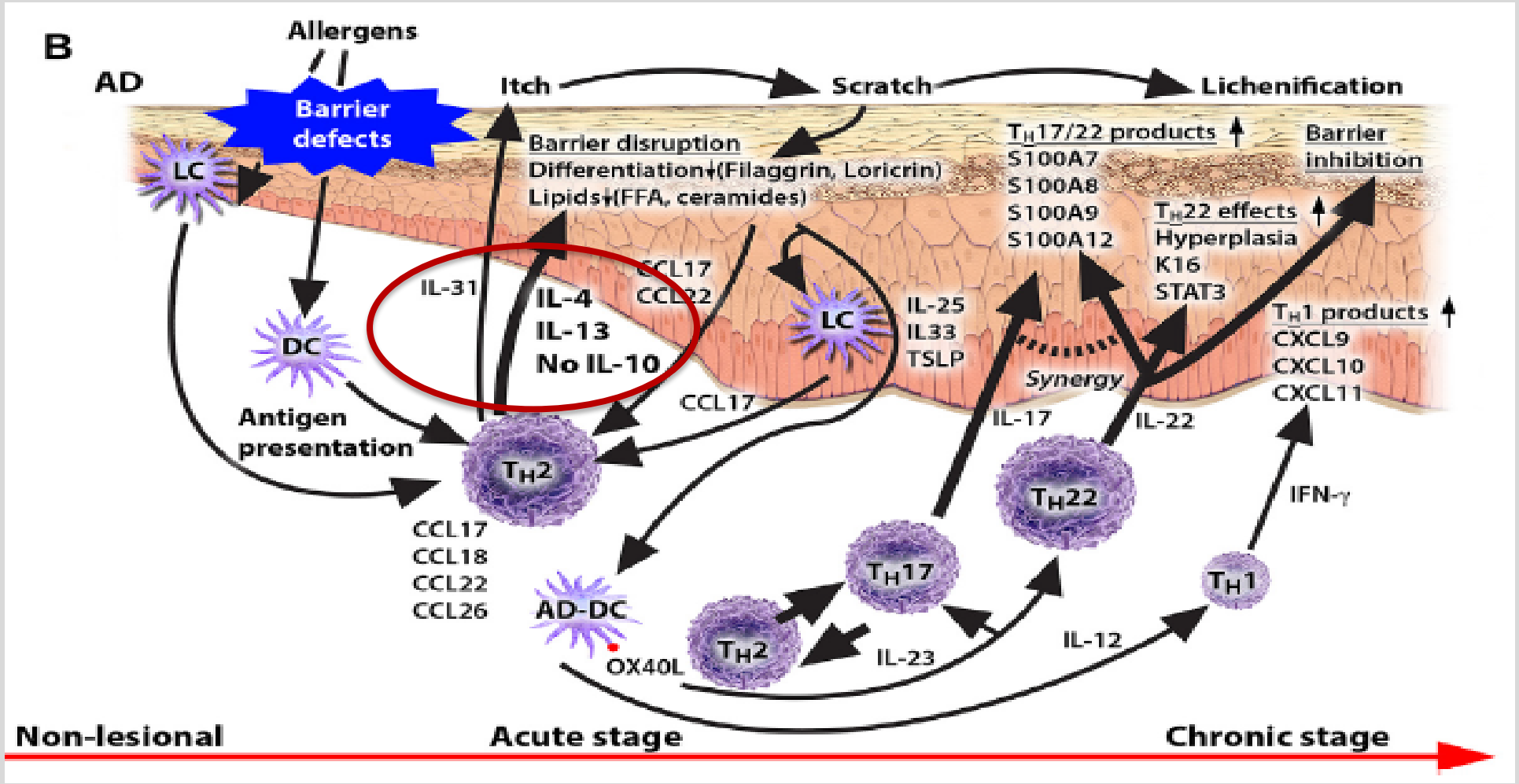
JAK inhibitors

- **Upadacitinib**
- **Abrocitinib**

***not yet FDA-approved**

The translational revolution and use of biologics in patients with inflammatory skin diseases

Shinji Noda, MD, PhD,[a] James G. Krueger, MD, PhD,[a] and Emma Guttman-Yassky, MD, PhD[a,b] *New York, NY*



REF: Noda et al, *J Allergy Clin Immunol*, 2015

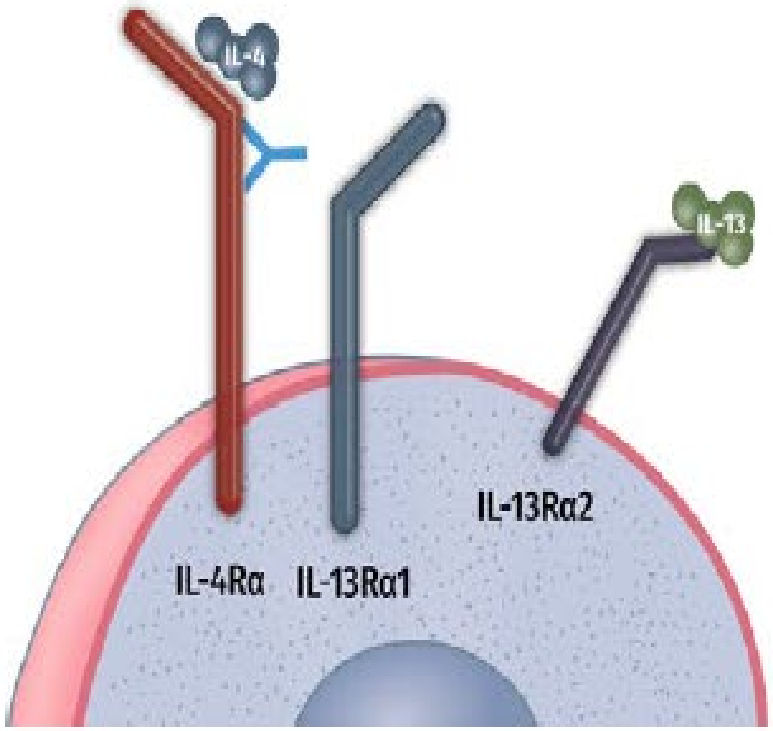
IL-4 AND IL-13

- Prototypic Th2 cytokines involved in allergy-mediated inflammation and normal control of parasitic infections
- Actions: 1) decrease filaggrin and anti-microbial peptides; 2) increase IgE; 3) mediate chronic itch
- Excess levels found in atopic dermatitis skin and asthma lungs

BLOCKING ACTIONS OF IL-4 AND IL-13

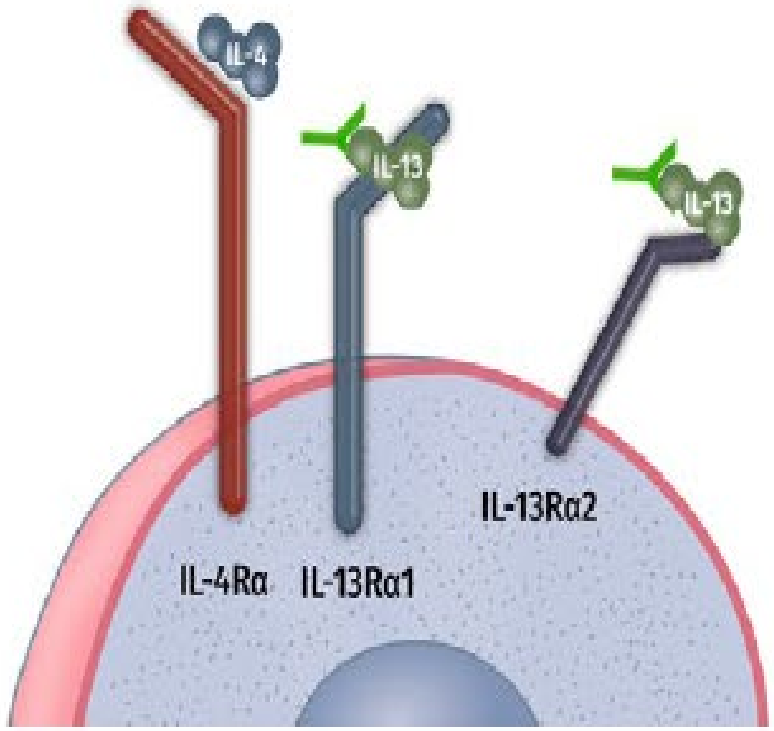
Dupilumab

Binds IL-4Rα, blocking IL-13 and IL-4 signaling



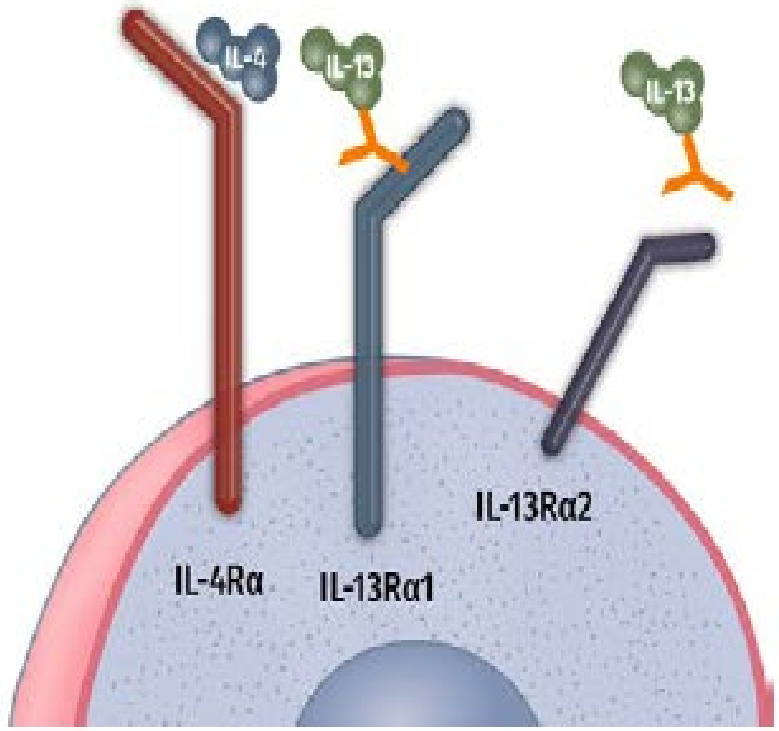
Lebrikizumab

Binds IL-13, specifically preventing formation of IL-13Rα1/IL-4Rα complex, thus blocking downstream signaling



Tralokinumab

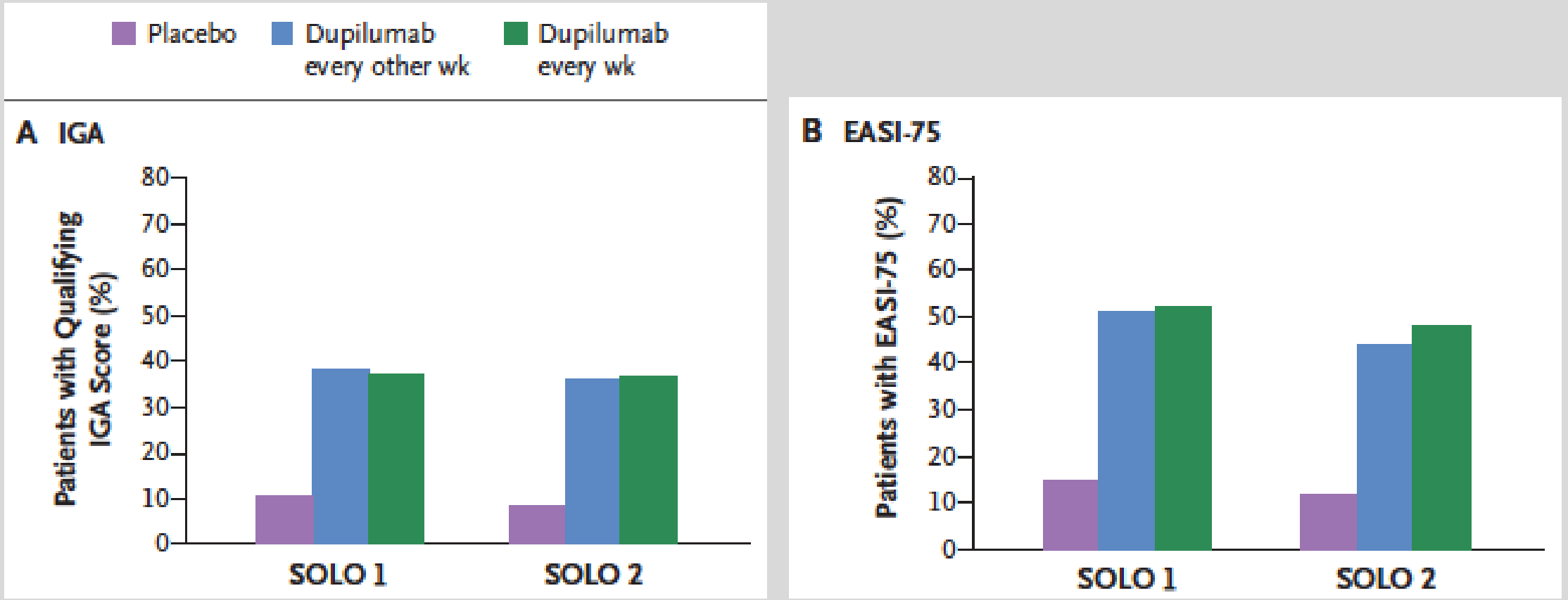
Binds IL-13, preventing IL-13 binding to IL-13Rα1 and IL-13Rα2 decoy receptor, thus blocking both IL-13 signalling and endogenous IL-13 regualtion



REF: Moyle et al, *Exp Dermatol*, 2019

Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis

E.L. Simpson, T. Bieber, E. Guttman-Yassky, L.A. Beck, A. Blauvelt, M.J. Cork, J.I. Silverberg, M. Deleuran, Y. Kataoka, J.-P. Lacour, K. Kingo, M. Worm, Y. Poulin, A. Wollenberg, Y. Soo, N.M.H. Graham, G. Pirozzi, B. Akinlade, H. Staudinger, V. Mastey, L. Eckert, A. Gadkari, N. Stahl, G.D. Yancopoulos, and M. Ardeleanu, for the SOLO 1 and SOLO 2 Investigators*

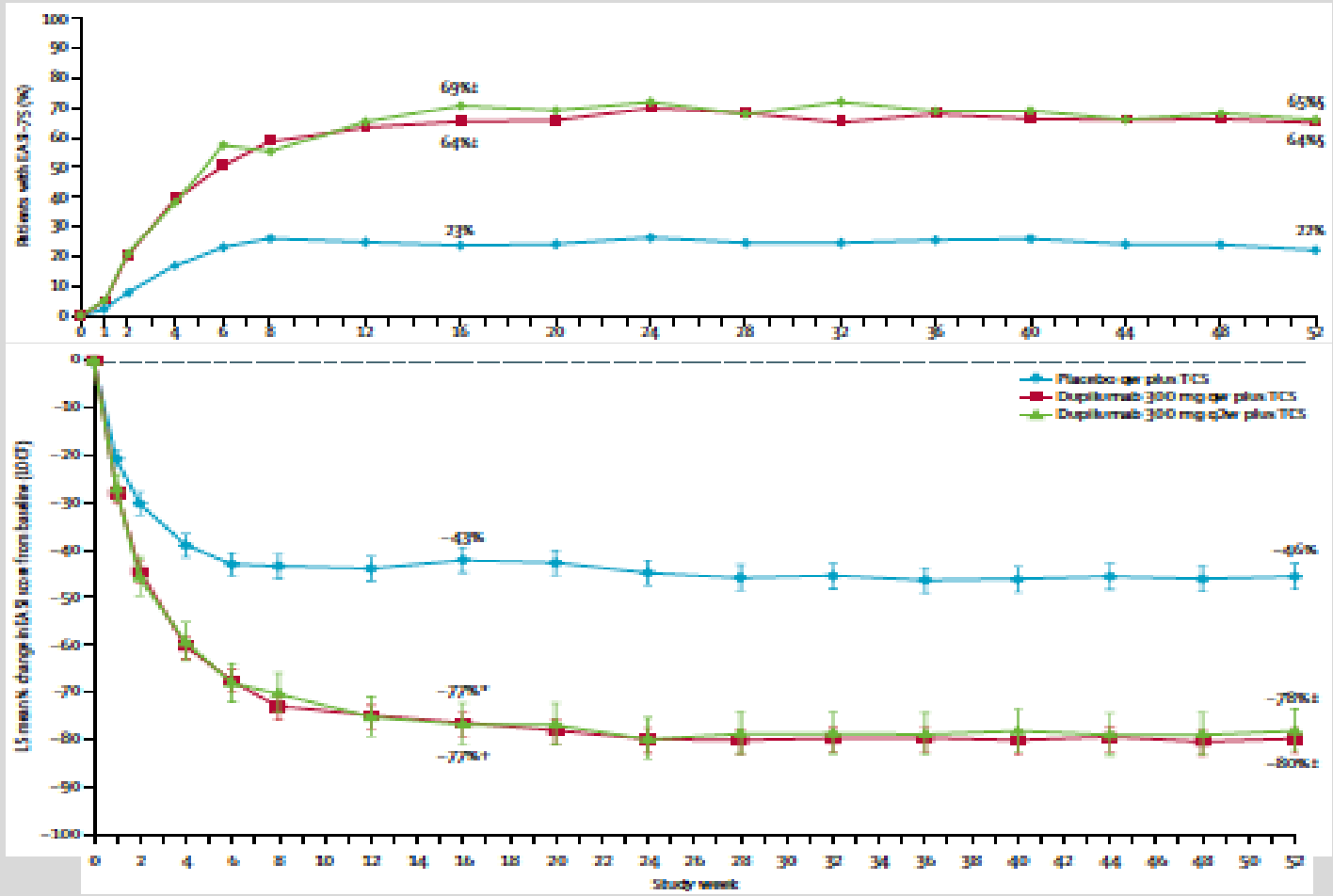


REF: Simpson et al, *N Engl J Med*, 2016

CHRONOS: EASI 75 AND MEAN IMPROVEMENT IN EASI OVER 52 WEEKS

EASI 75

MEAN IMPROVE-MENT IN EASI



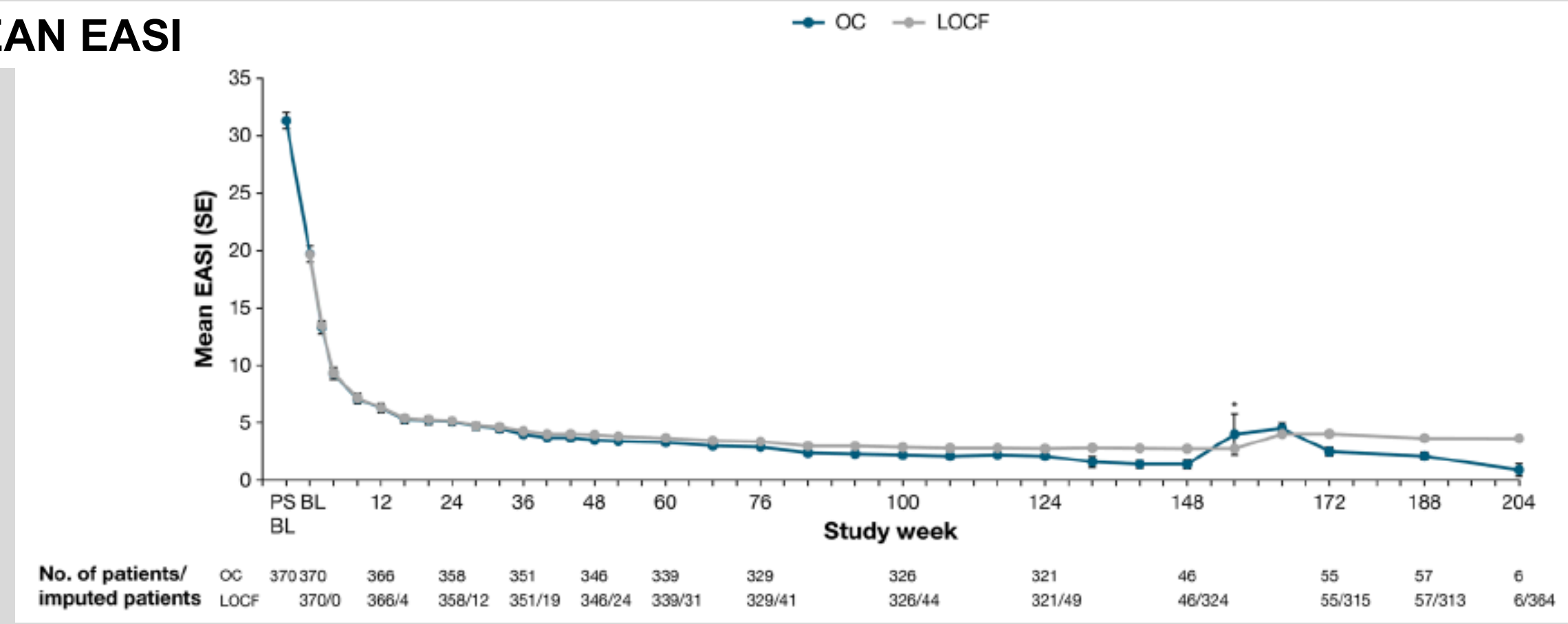
65%

80%

REF: Blauvelt et al, *Lancet*, 2017

LONG-TERM DUPILUMAB EFFICACY OVER 4 YEARS

MEAN EASI

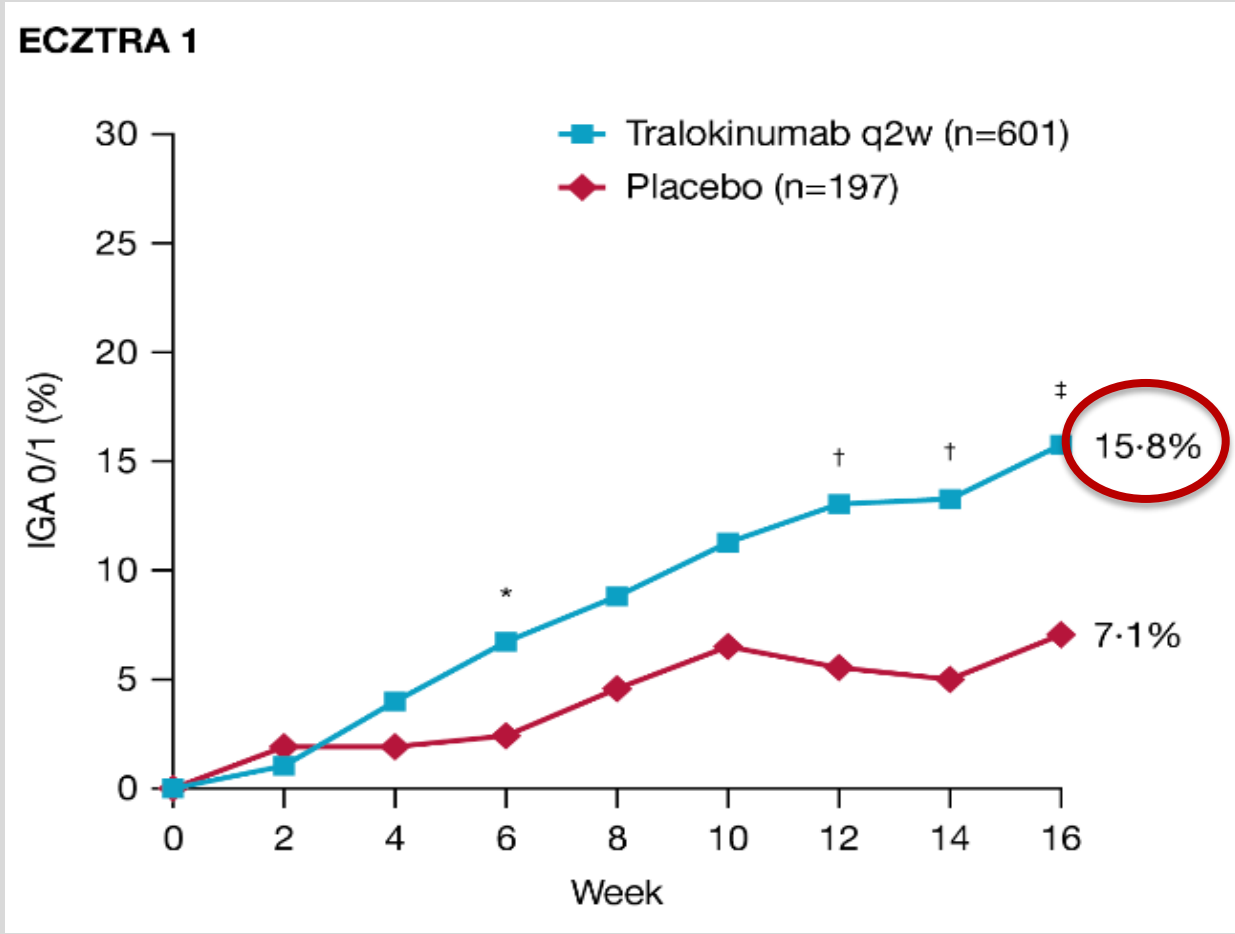


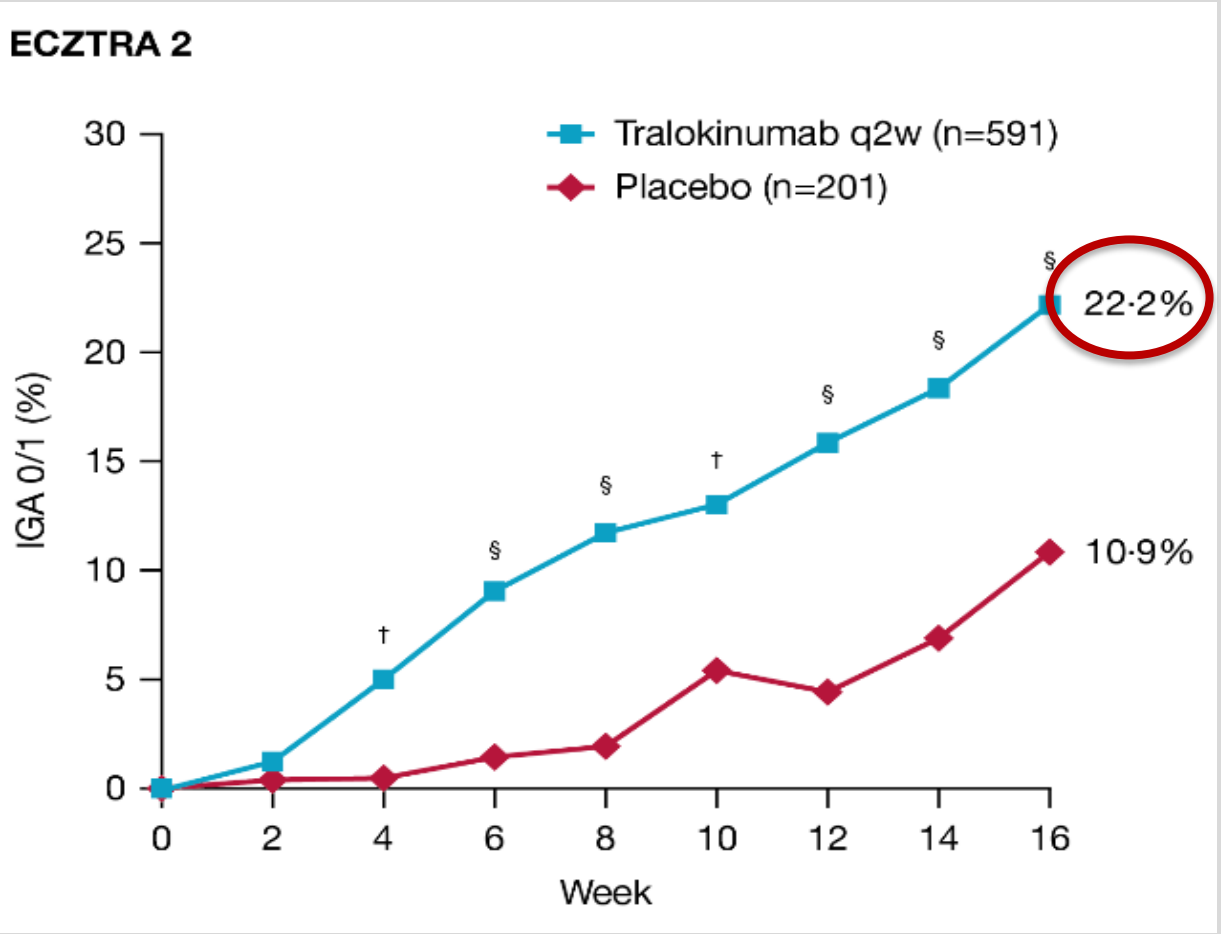
REF: Beck et al, *Am J Clin Dermatol*, 2022

DUPILUMAB: KEY POINTS FOR CLINICAL PRACTICE

- Very efficacious (long-term clinical trial and real-world evidence)
  - Most patients do well
  - Concomitant topical corticosteroids/TCI may be used
- Dose = 600 mg SC x1 (loading dose), then 300 mg SC QOW
- Conjunctivitis in 10-20%, otherwise safe (no lab testing)
  - Manage with wetting drops +/- corticosteroid drops
  - Consider ophthalmology consultation
- Approved for AD down to age 6 months
- Also indicated for asthma, chronic rhinosinusitis with nasal polyposis, eosinophilic esophagitis, and prurigo nodularis
- *AD usually recurs slowing after stopping drug, which necessitates long-term therapy for optimal disease control*

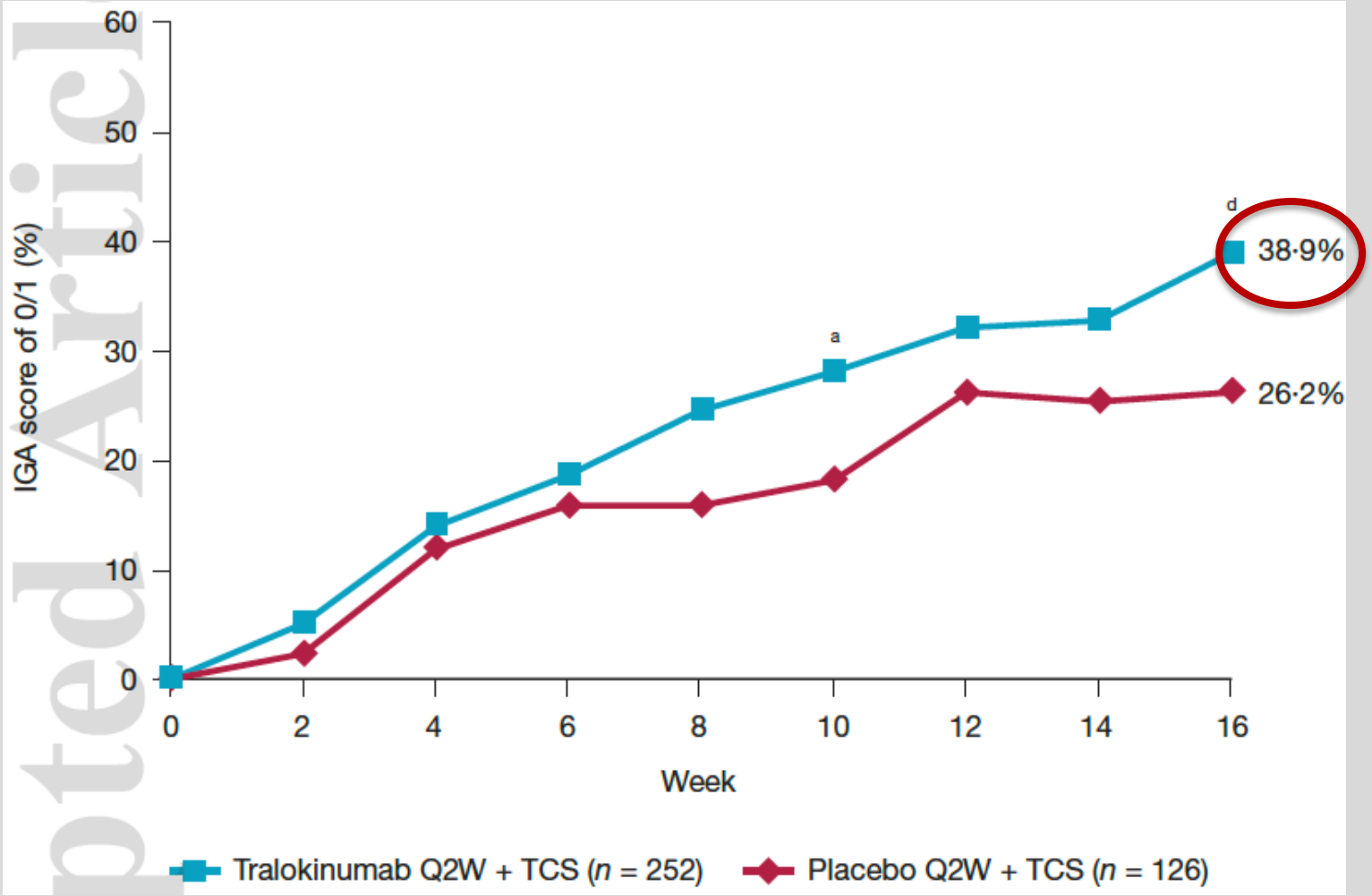
TRALOKINUMAB, AN ANTI-IL-13 mAb, IMPROVES AD (2 phase 3, no topical steroids)



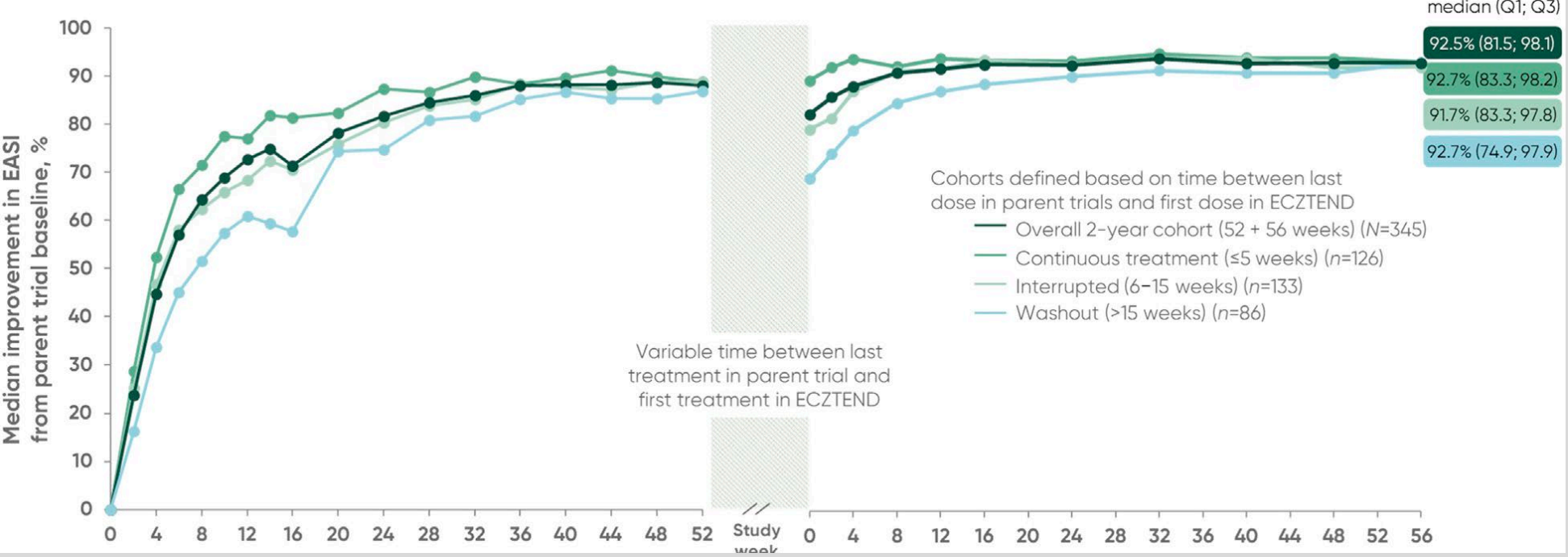


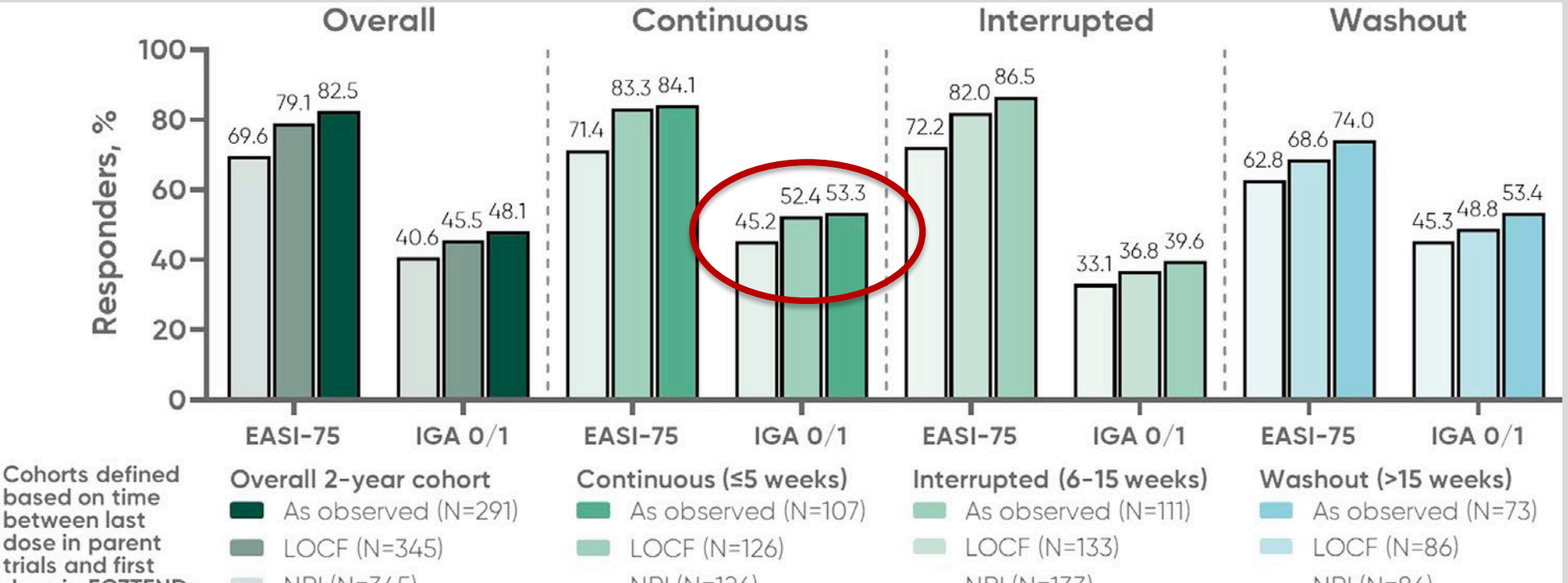
REF: Wollenberg et al, *Br J Dermatol*, 2020

TRALOKINUMAB, AN ANTI-IL-13 mAb, IMPROVES AD (phase 3, with topical steroids)



REF: Silverberg et al, *Br J Dermatol*, 2020





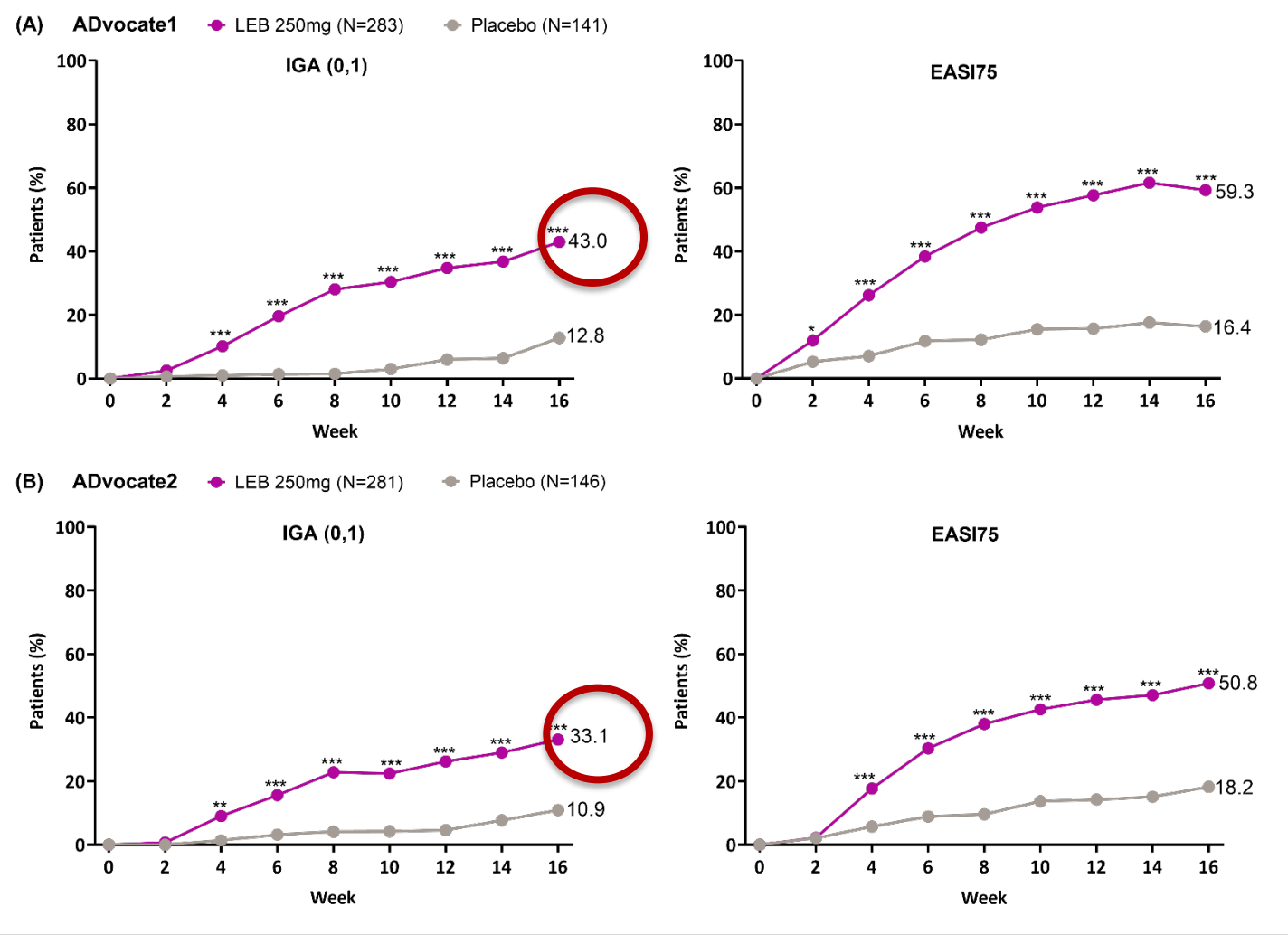
TRALOKINUMAB, AN ANTI-IL-13 mAb, IMPROVES AD OVER 2 YEARS (+/- topical steroids)

REF: Blauvelt et al, *J Am Acad Dermatol*, 2022

TRALOKINUMAB: KEY POINTS FOR CLINICAL PRACTICE

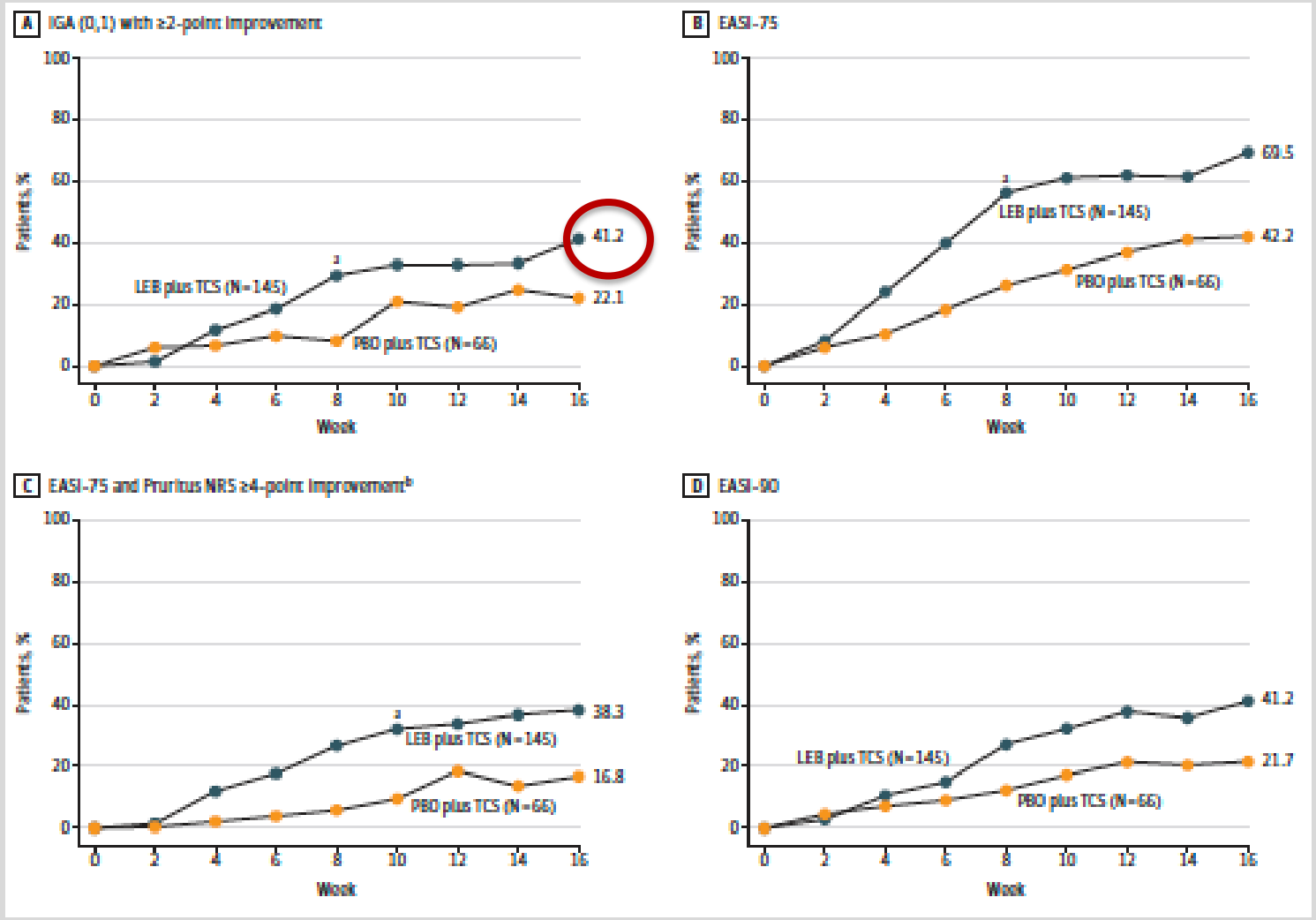
- **MOA**: anti-IL-13 mAb (**first FDA-approved selective IL-13 blocker**)
- **Rx**: 600 mg SC x1 (loading dose), then 300 mg SC every 2 weeks (**can go to every 4 weeks**)
- Approved for moderate-to-severe AD patients ages 18 and up
- **Efficacy**: good, especially over time (concomitant topical corticosteroids/TCI may be used)
- **Safety**: excellent (**conjunctivitis** less than 10%)

LEBRIKIZUMAB, AN ANTI-IL-13 mAb, IMPROVES AD (2 phase 3 studies, no topical steroids)



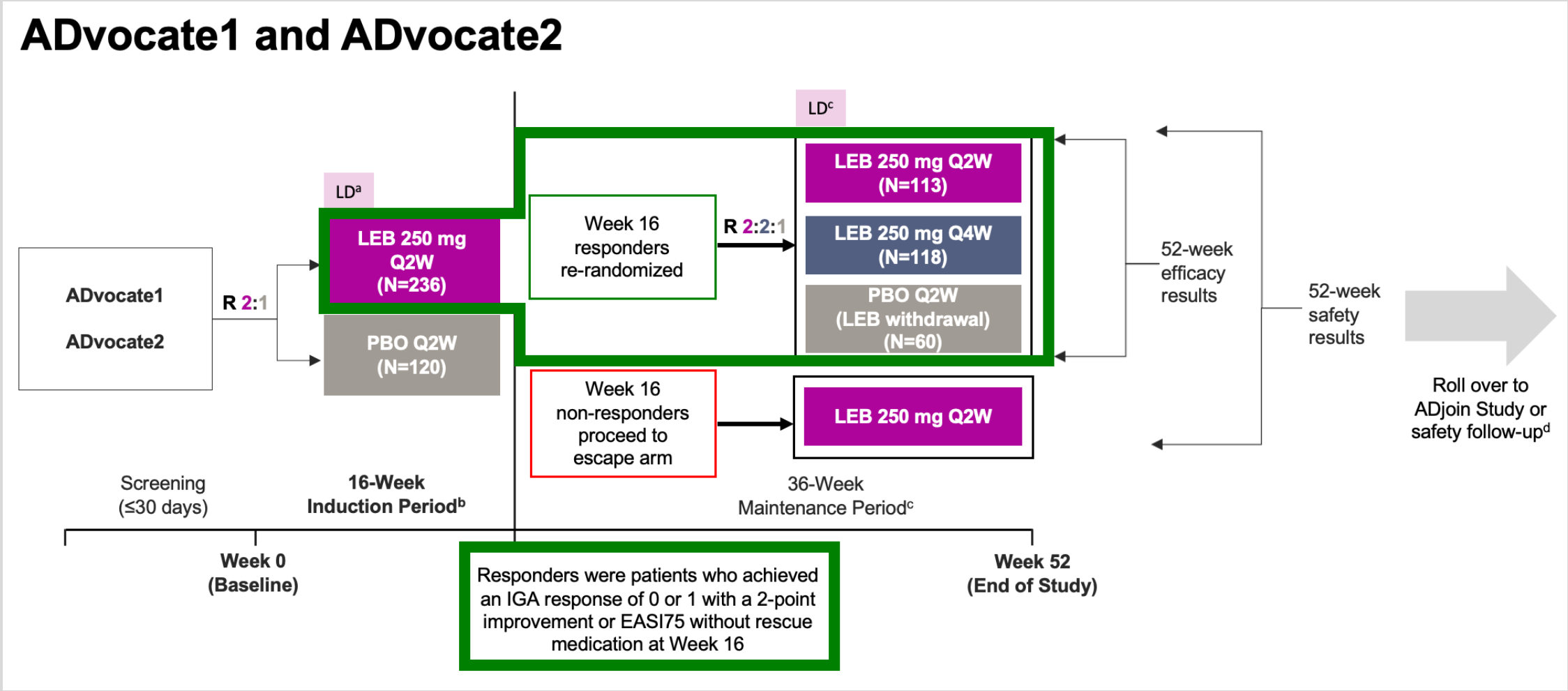
REF: Simpson et al, *AAD Annual Meeting*, 2022

LEBRIKIZUMAB, AN ANTI-IL-13 mAb, IMPROVES AD (phase 3, with topical steroids)



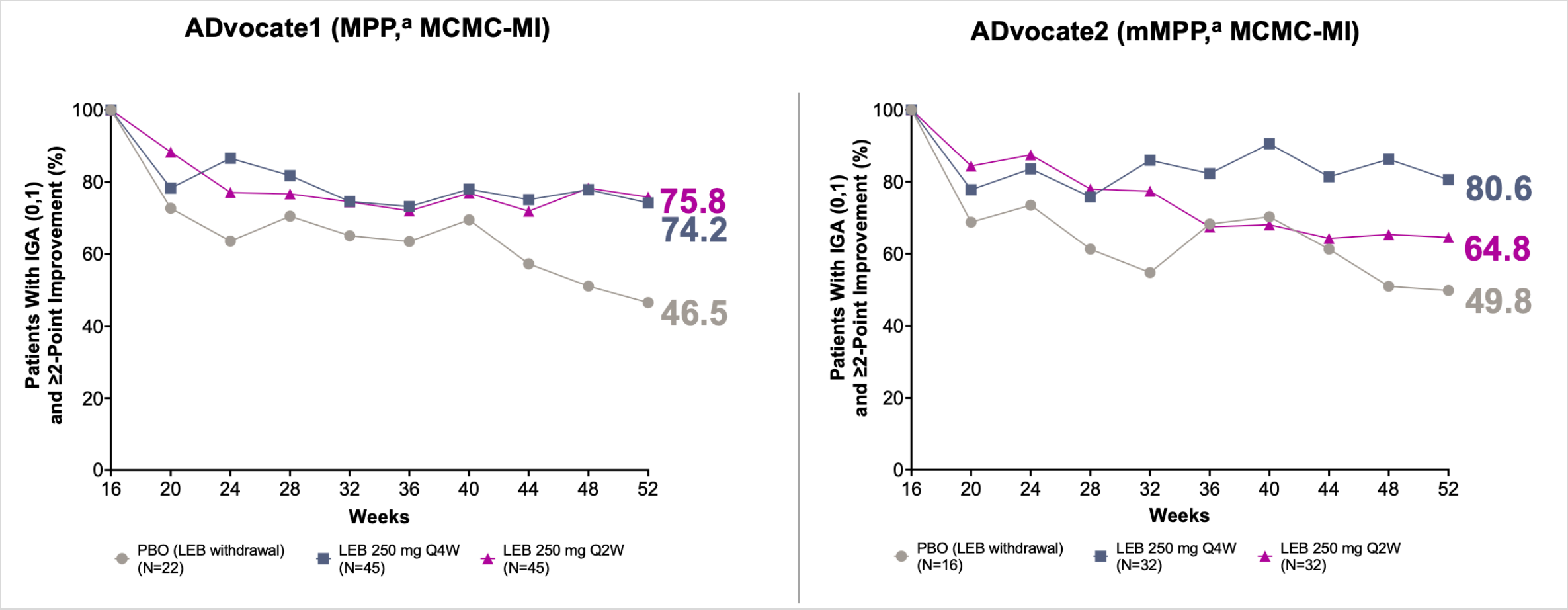
REF: Simpson et al, *JAMA Dermatol*, 2023

PHASE 3 MAINTENANCE/RANDOMIZED WITHDRAWAL STUDY DESIGN FOR LEBRIKIZUMAB



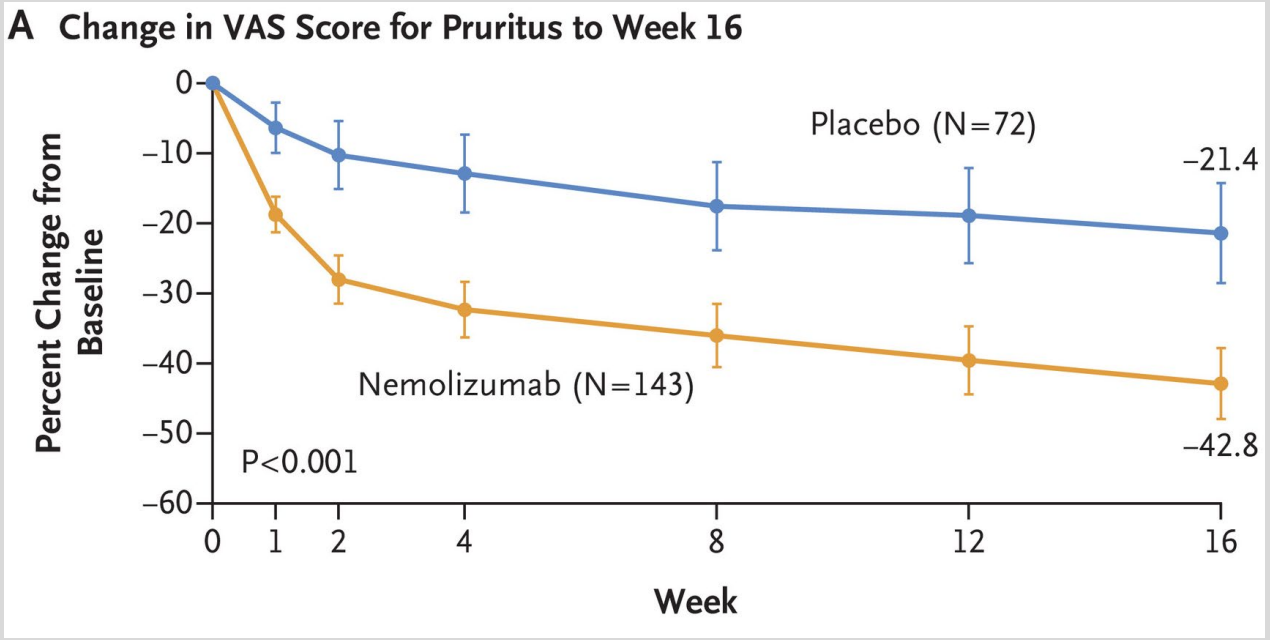
REF: Blauvelt et al, *EADV Annual Meeting*, 2022

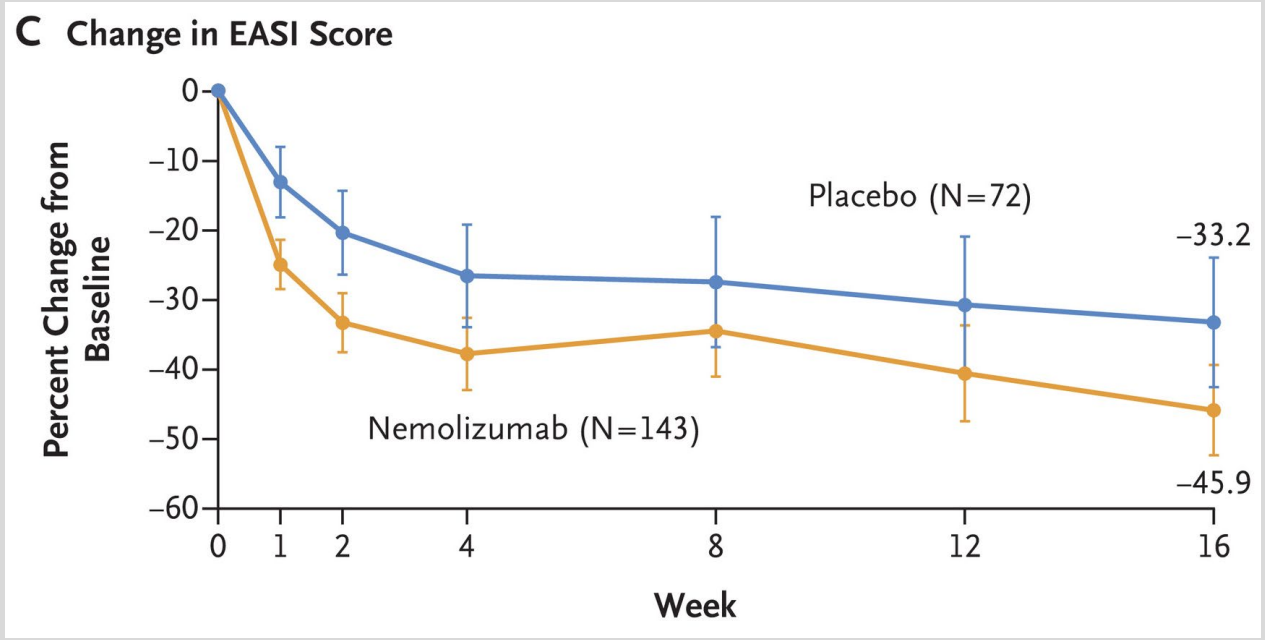
MAINTENANCE OF IGA 0/1 OVER 52 WEEKS WITH LEBRIKIZUMAB



REF: Blauvelt et al, *EADV Annual Meeting*, 2022

NEMOLIZUMAB, AN ANTI-IL-31 RECEPTOR A mAb, IMPROVES AD (phase 3, with topical steroids)



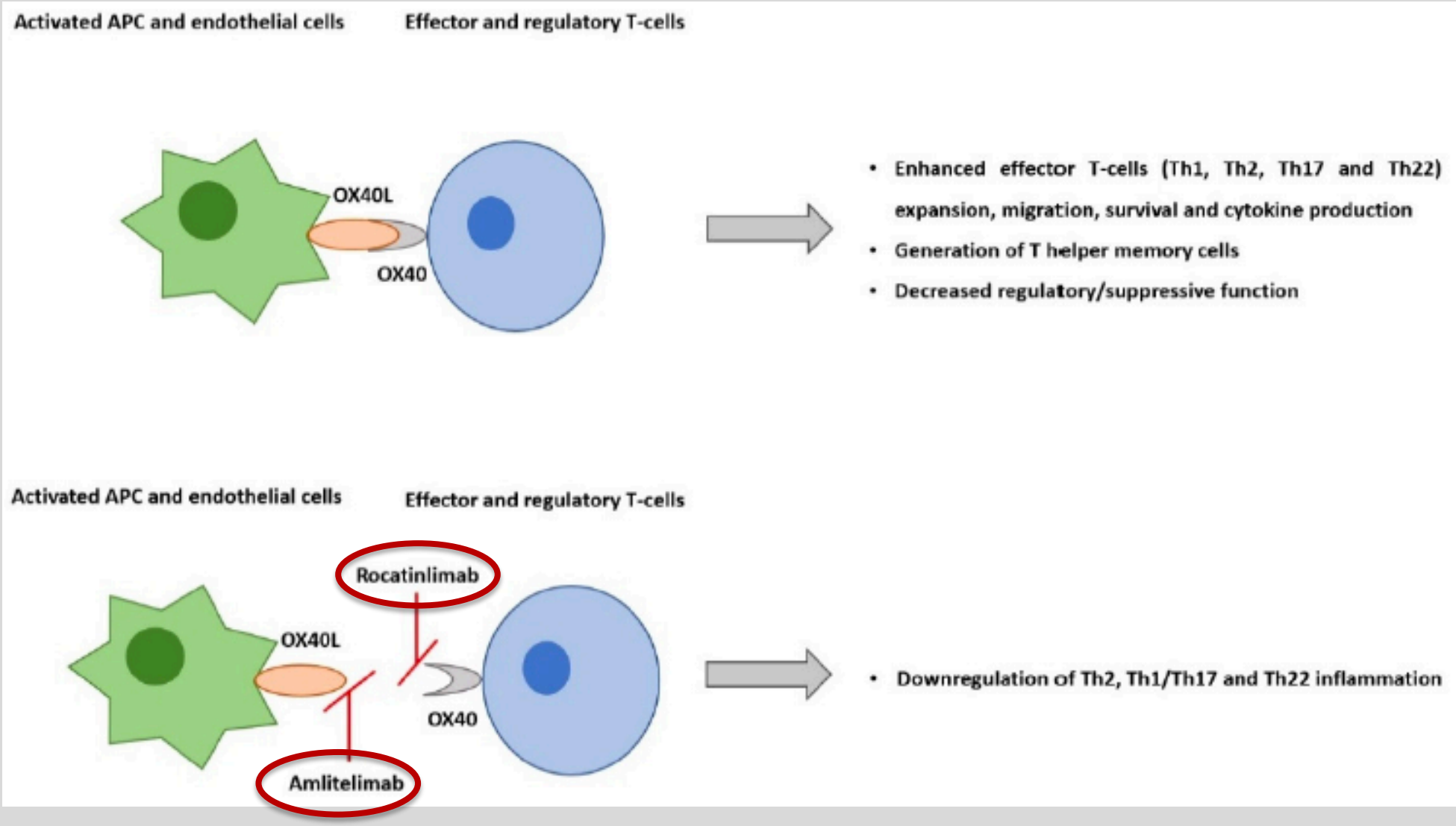


REF: Kabashima et al, *N Engl J Med*, 2020

BIOLOGICS IN THE PIPELINE FOR MODERATE-TO-SEVERE AD

- **Rocatinlimab (blocks OX40)**
- **Amlitelimab (blocks OX40L)**

OX40-OX40L Inhibition for the Treatment of Atopic Dermatitis—Focus on Rocatinlimab and Amlitelimab

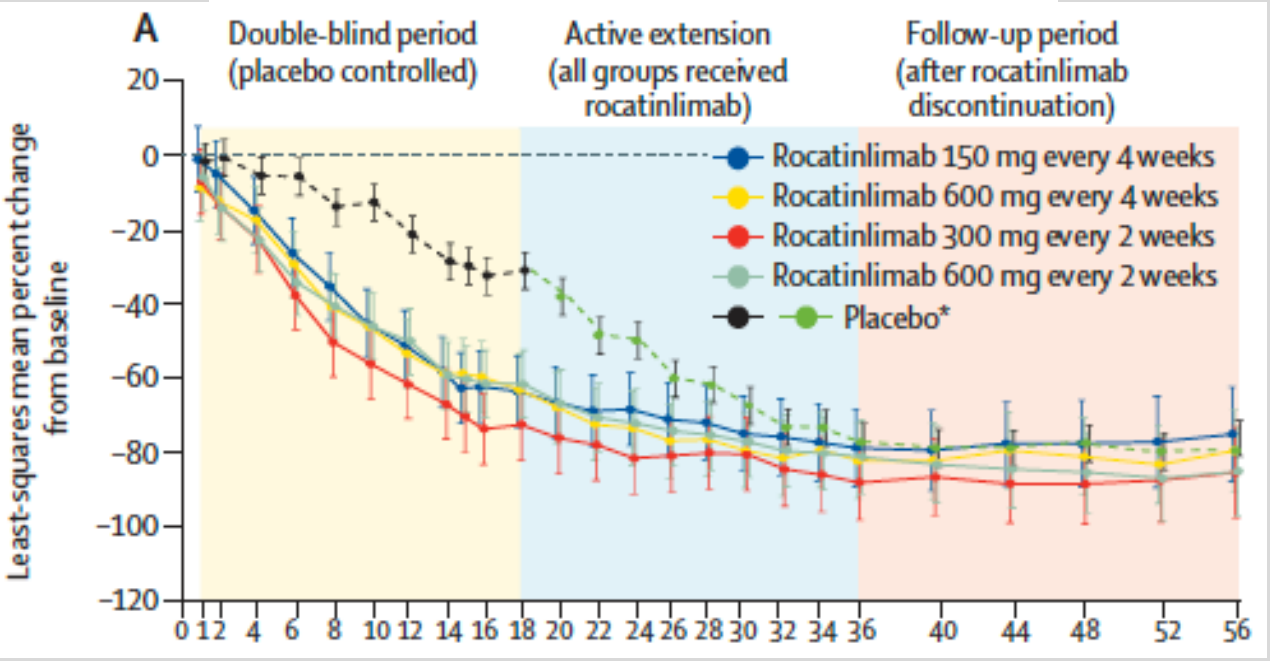


REF: Le and Torres, *Pharmaceutics*, 2022

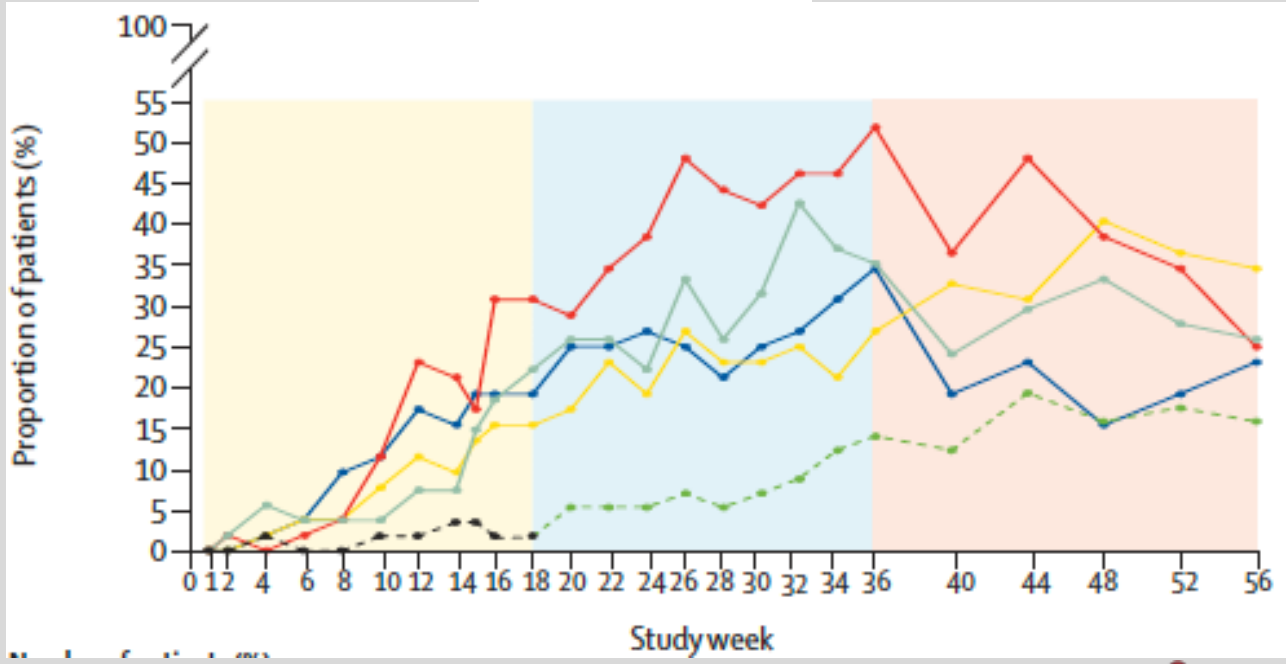
An anti-OX40 antibody to treat moderate-to-severe atopic dermatitis: a multicentre, double-blind, placebo-controlled phase 2b study

ROCATINLIMAB

% CHANGE IN EASI

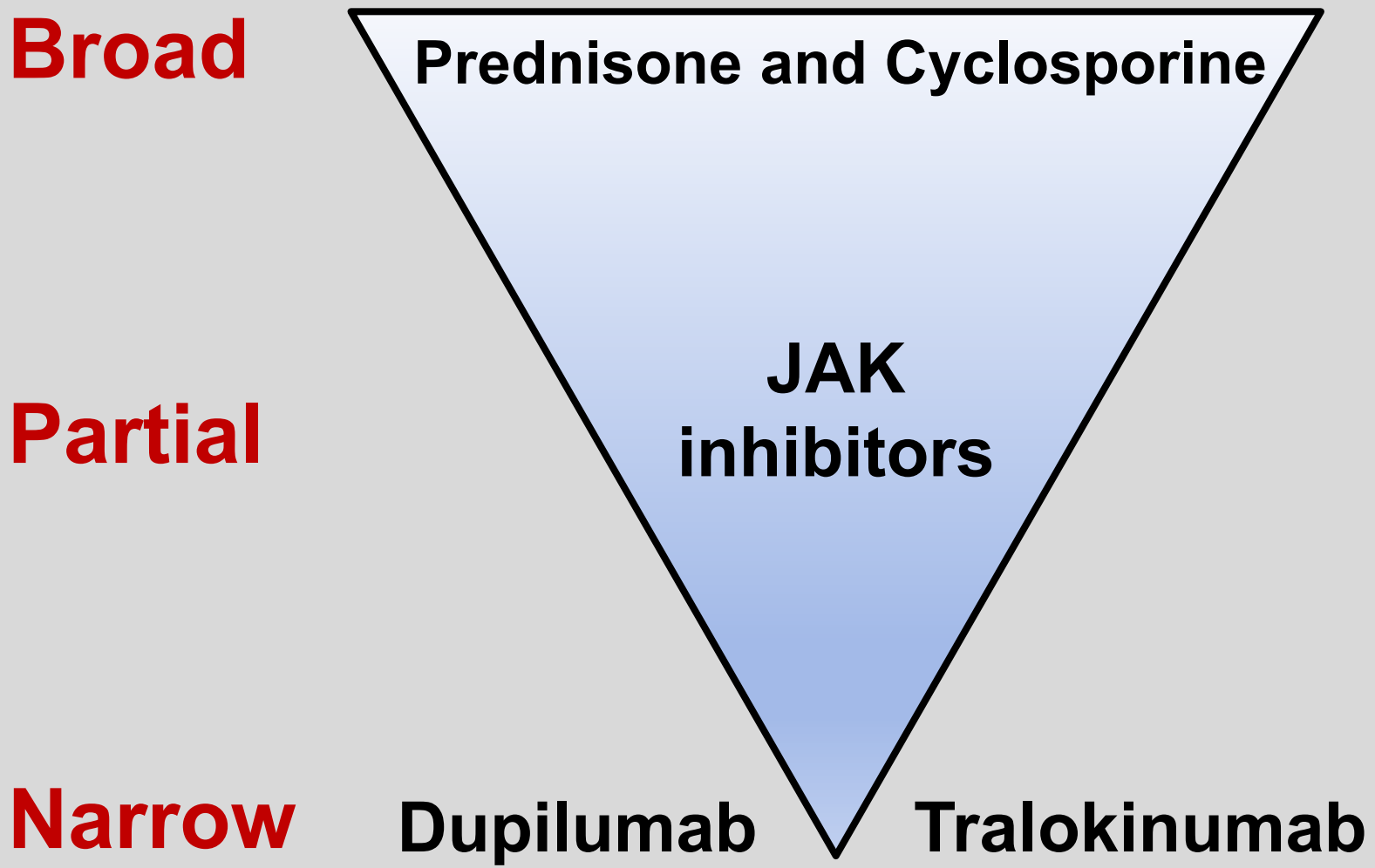


IGA 0/1



REF: Guttman-Yassky et al, *Lancet*, 2022

IMMUNOSUPPRESSION OF SYSTEMIC DRUGS FOR AD



"DUPILUMAB IS NOT AN IMMUNOSUPPRESSANT"

- FDA-approved language in the dupilumab product insert
- *No increased risk of infections*, either systemic or cutaneous
- No increased risk of cancer
- No blood test monitoring is recommended
- No cases of TB: thus, *no pre-treatment TB testing is required*

BIOLOGIC (DUPILUMAB AND TRALOKINUMAB) SAFETY ISSUES

- Injection site reactions most common side effect, but usually clinically insignificant
- Ocular surface disease (dry eye, eye pruritus, conjunctivitis, blepharitis, keratitis) also common
- "Red face" (reported mainly w/ dupilumab)
- Rare (reported w/ dupilumab)
  - Psoriasis and inflammatory arthritis ("PsA-like")
  - CTCL

OCULAR SURFACE DISEASE

- Dupilumab rates (10-20%) slightly higher than tralokinumab rates (5-10%)
- Mechanism unknown, but associated with AD (not seen in asthma)
  - Not allergic conjunctivitis (seen as baseline condition in 27% of patients in phase 3 trials)
  - Not infectious
- Risk factors: bad facial eczema, prior Hx of allergic conjunctivitis
- Does not affect vision
- Most cases mild-to-moderate and do not interfere with drug continuation
- Mainstays of treatment: lubricating eye drops and corticosteroid eye drops (as needed)

REF: Akinlade et al, *Br J Dermatol*, 2019

Facial erythema in patients with atopic dermatitis treated with Dupilumab – a descriptive study of morphology and Aetiology

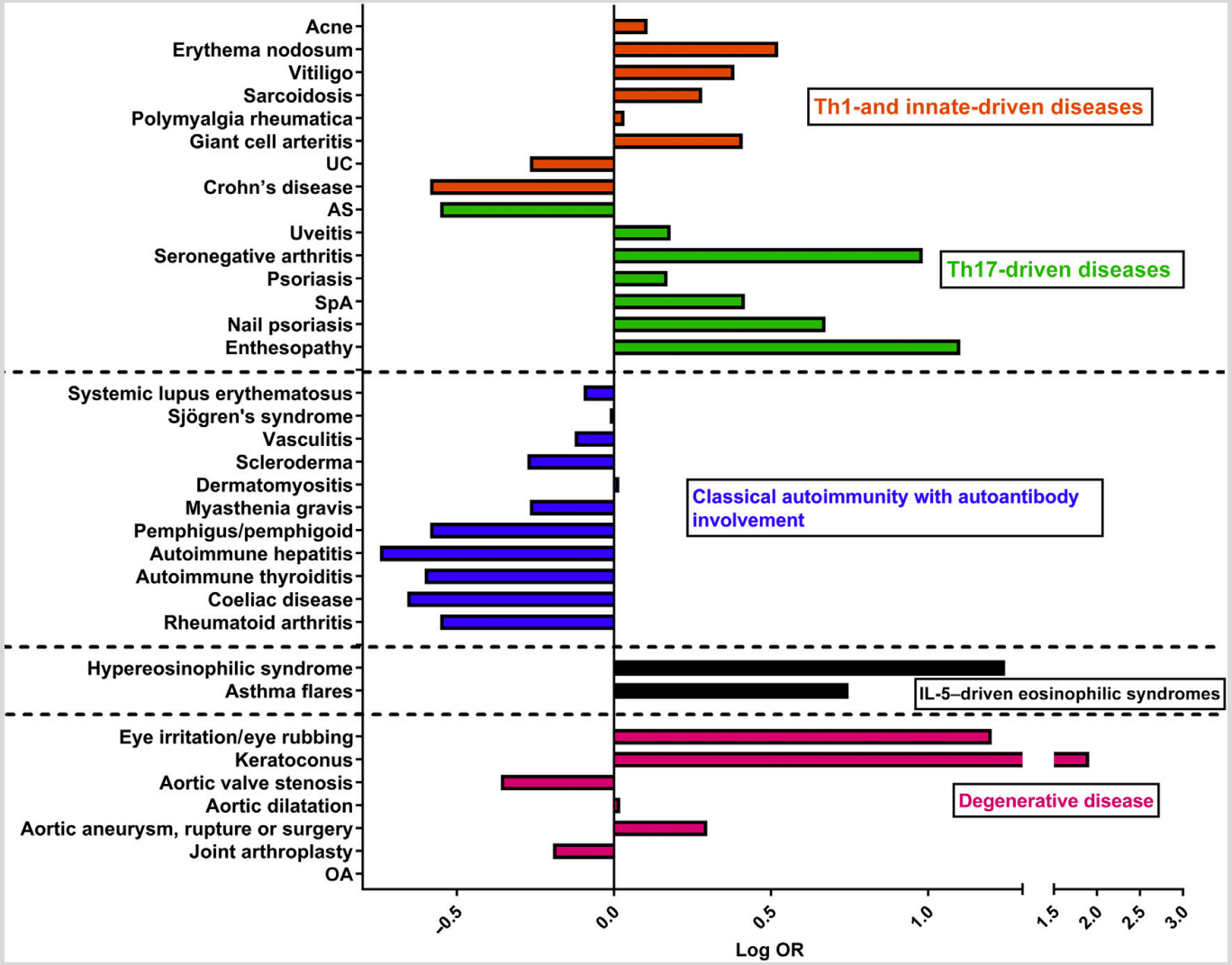
J. Ahn,[1,†] D.H. Lee,[1,†] C.H. Na,[2] D.H. Shim,[2] Y.S. Choi,[3] H.J. Jung,[1] E.L. Simpson[4,*]

Conclusions The vast majority of patients treated with dupilumab in academic institutions from Korea and the United States experienced improvement in their facial dermatitis with dupilumab therapy. A small proportion of patients had new onset and exacerbation. Although the mechanisms of this adverse event remain unclear, steroid withdrawal should be considered as a diagnosis of the erythema in some patients.

Bottom line: ***closely evaluate all patients on dupilumab who present with a "red face" for breakthrough AD and steroid withdrawal; also, consider allergic contact dermatitis, rosacea, and photosensitivity***

REF: Ahn et al, *J Eur Acad Dermatol Venereol*, 2022

DUPILUMAB CAN BE ASSOCIATED WITH RARE OCCURRENCE OF PSORIASIS/PsA



REF: Bridgewood et al, *J Invest Dermatol*, 2022

Diagnosis of mycosis fungoides or Sézary syndrome after dupilumab use: A systematic review

- **23 cases** diagnosed post-dupilumab treatment were reviewed
- Some cases may represent initial **mis-diagnosis** of CTCL as AD
- *Some cases are more worrisome, with clear long-standing AD (w/ biopsy) prior to dupilumab use*
- All cases with **Naranjo score of 3 or 4 (possible)**

*Naranjo score: total: –4 to +13; the reaction is definite: ≥9, probable: 5-8, possible:1-4, and doubtful: ≤0.

REF: Jfri et al, *J Am Acad Dermatol*, 2022

MODERATE-TO-SEVERE AD TREATMENT: BIOLOGICS vs. JAK INHIBITORS

	BIOLOGICS	JAKis
EFFICACY	very good	excellent
SAFETY	excellent (more targeted)	mostly good (more broad)
COST	expensive	expensive
CONTINUOUS vs. EPISODIC USE	continuous	continuous and episodic
ASTHMA EFFICACY	yes	?

Thank you!

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