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How to use biologics in Psoriasis

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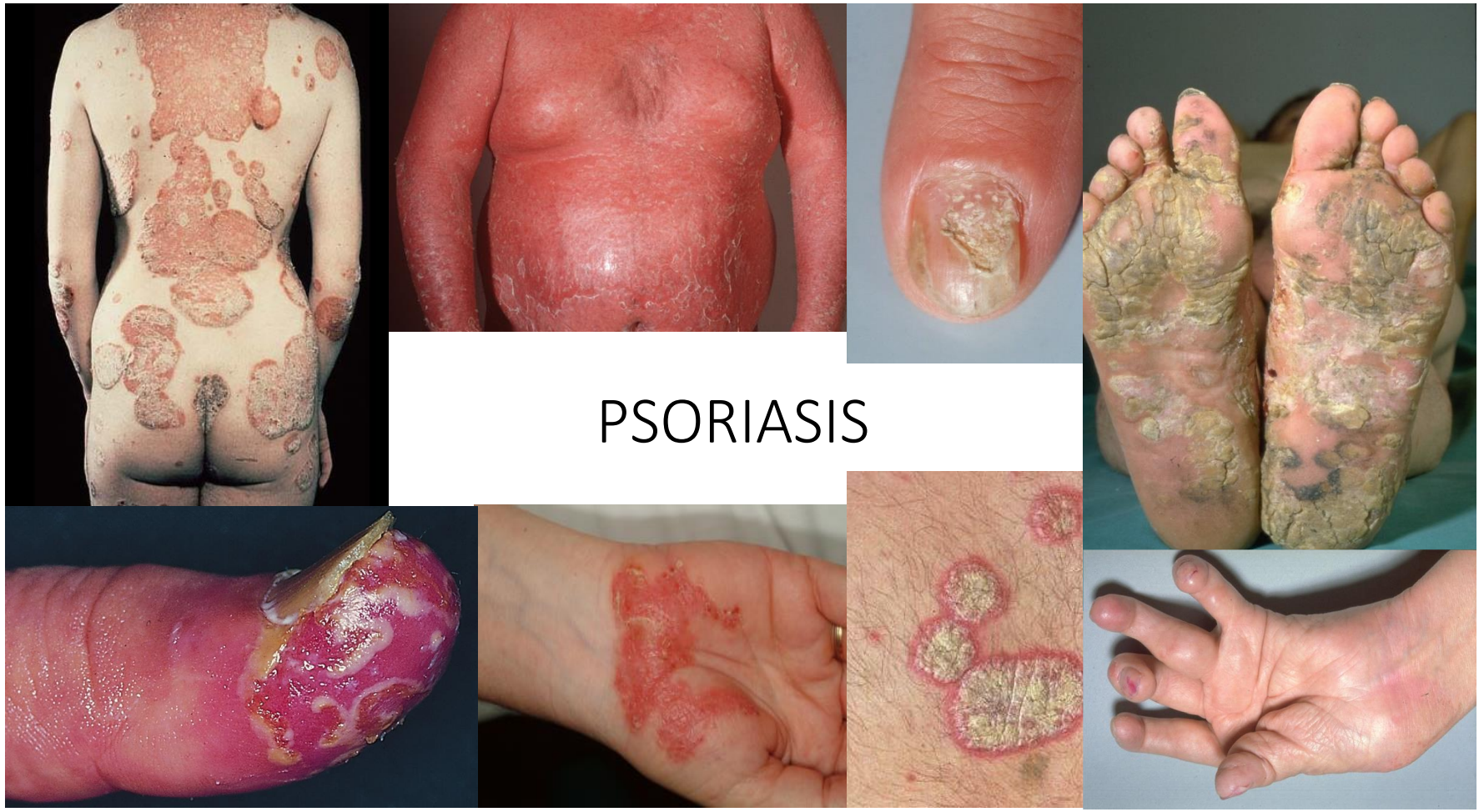
Disclosure

Rsearch support/P.I.	Celgene, Janssen, Leo Pharma, Novartis, Lilly
Employee	None
Consultant	None
Major stockholder	None
Speaker bureau	None
Honoraria	Sanofi, Janssen, Abbvie, Pfizer, Novartis, Celgene, Lilly
Scientific Advisory Board	Sanofi, Janssen, Abbvie, Pfizer, Novartis, Celgene, Lilly

Presentation might include discussion of the off-label use of a drug or drugs

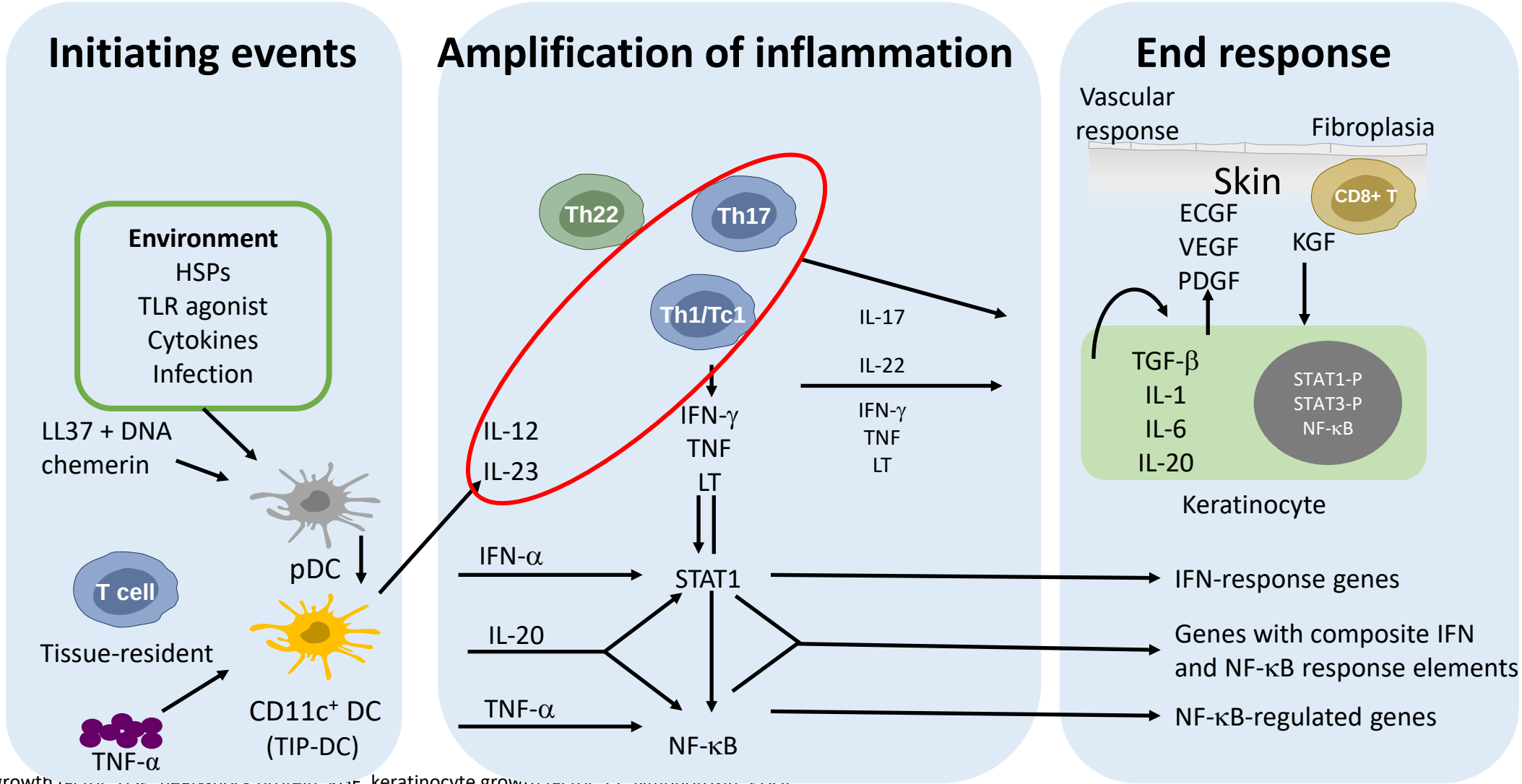
Psoriasis essentials

- **Most cases present before age 40**
- **55% HLA Cw6 + (Early-Onset)**
- **> 81 susceptibility loci**
- **30% psoriatic arthritis**
- **30% depression /anxiety**
- **Obesity**
- **Cardiovascular disease**
- **Inflammatory bowel disease**



Conrad et al

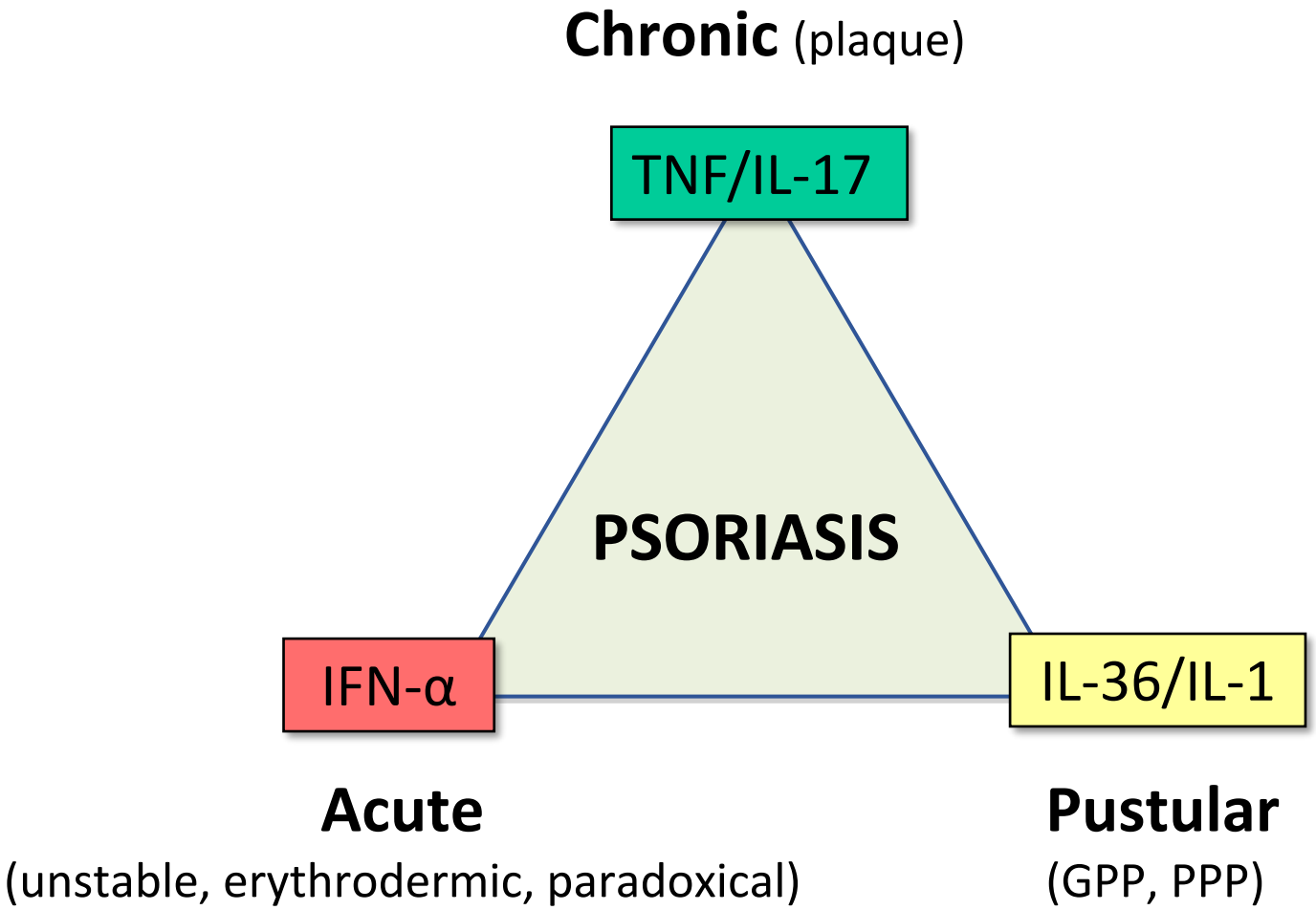
Psoriasis plaque development



ECGF, endothelial cell growth factor; HSP, heat-shock protein; KGF, keratinocyte growth factor; LT, lymphotoxin; PDGF, platelet-derived growth factor; STAT, signal transducers and activators of transcription; VEGF, vascular endothelial growth factor.

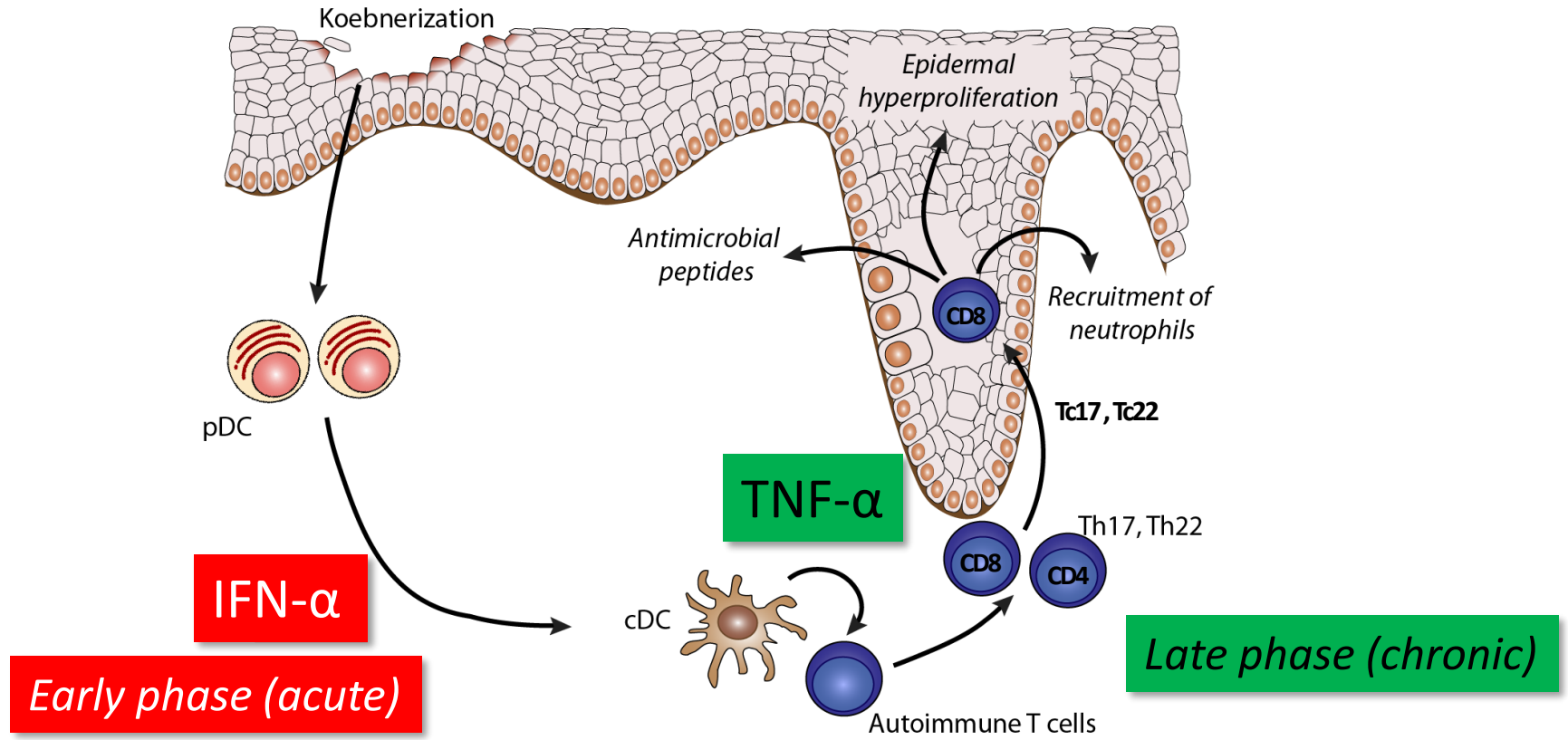
Adapted from Lowes MA, et al. Nature. 2007;445:866-73.

Inflammatory pathways in psoriasis



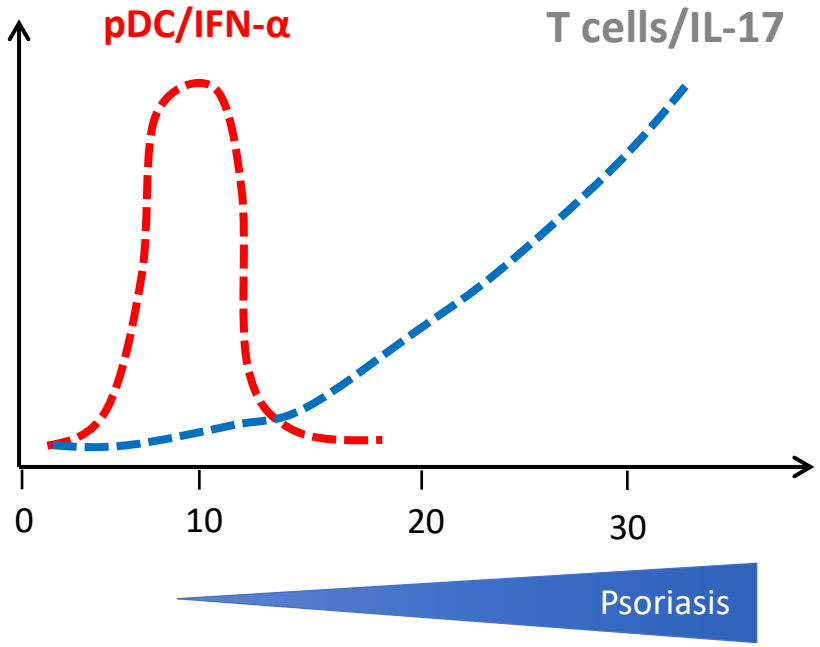
Adapted from 1. Conrad C & Gilliet M *Schweiz Med Forum* 2016; 2. Mylonas A & Conrad C. *Front Immunol* 2018.

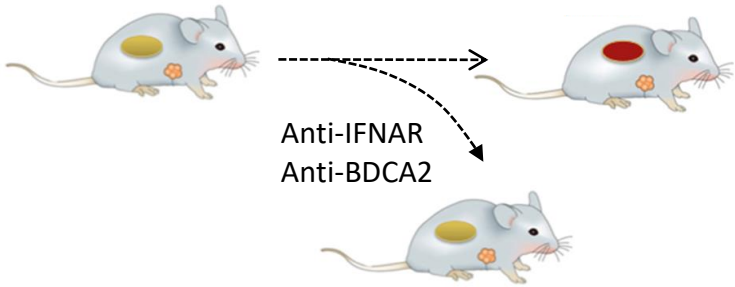
Psoriasis – Pathogenesis



Nestle et al. *J Exp Med*. 2005

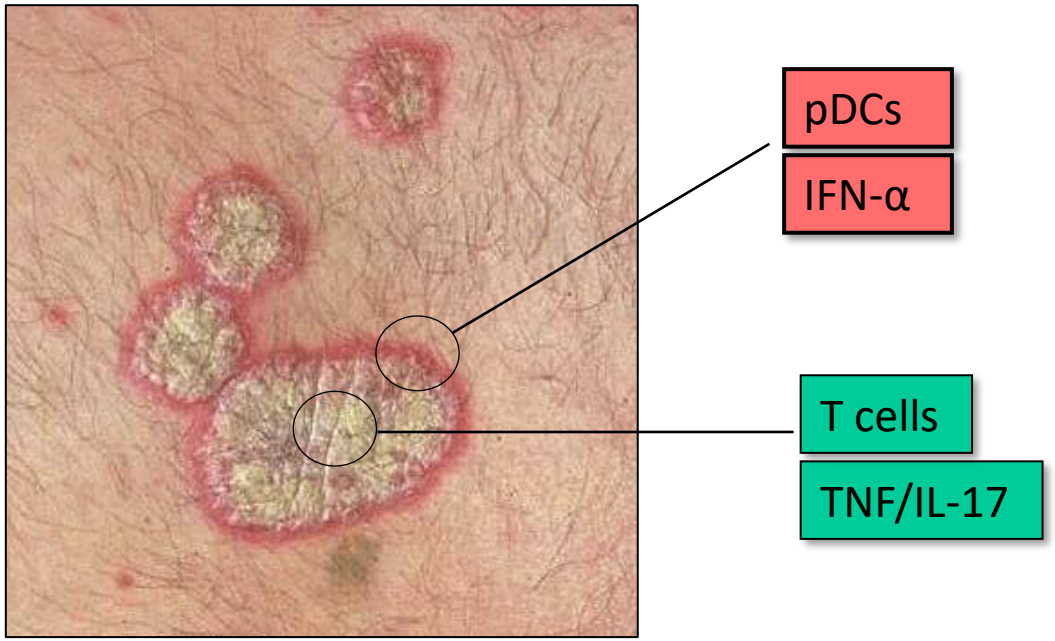
pDCs in the Development of Psoriasis





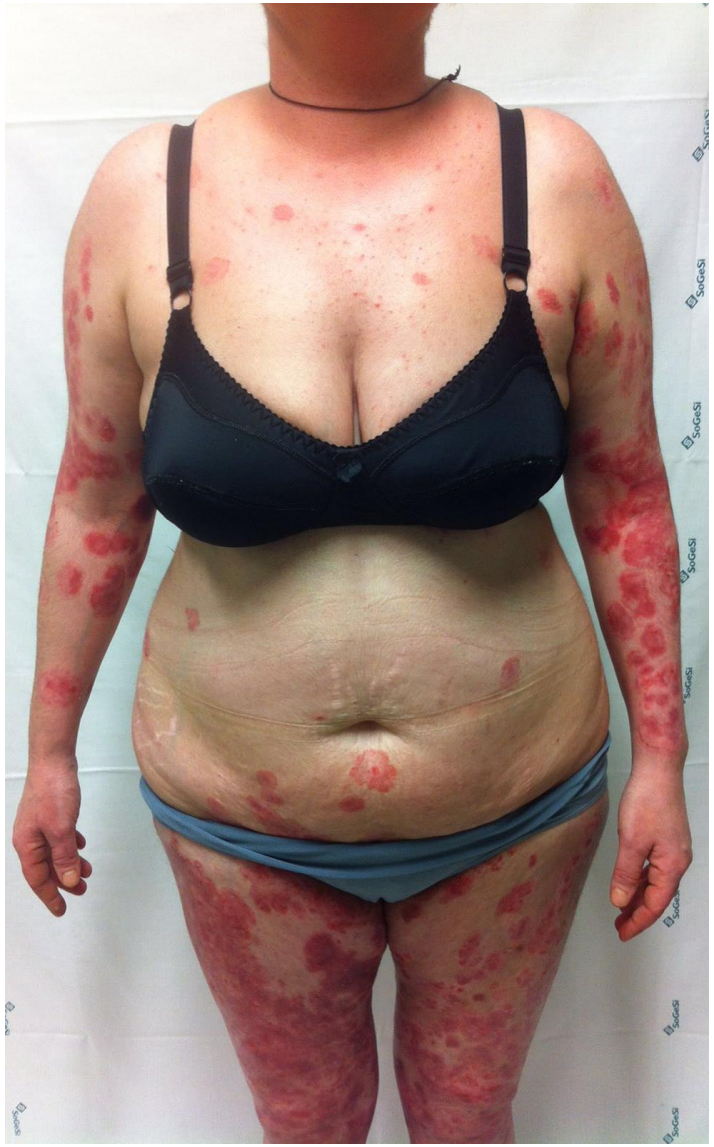
Nestle et al. *J Exp Med*. 2005; Conrad et al. *Nat Med*. 2007

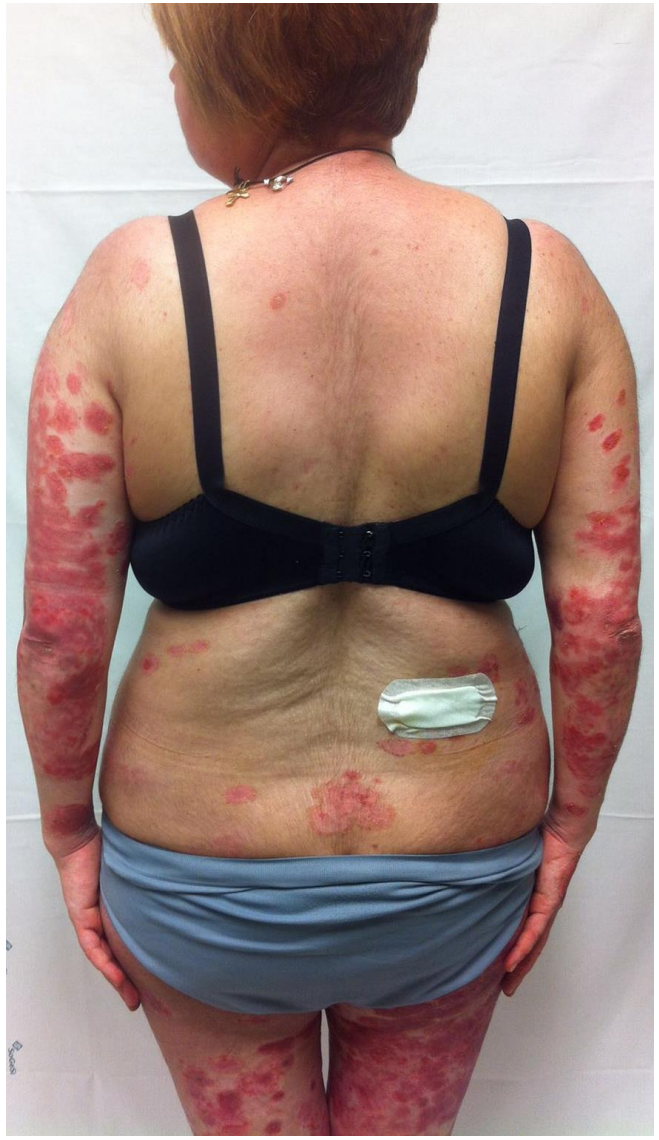
Instable/advancing psoriasis plaques



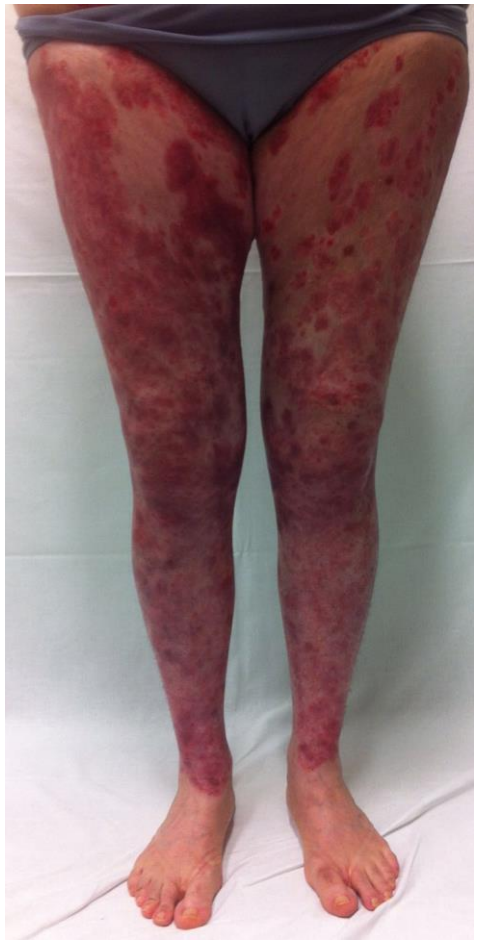
Conrad and Gilliet, *unpublished data*

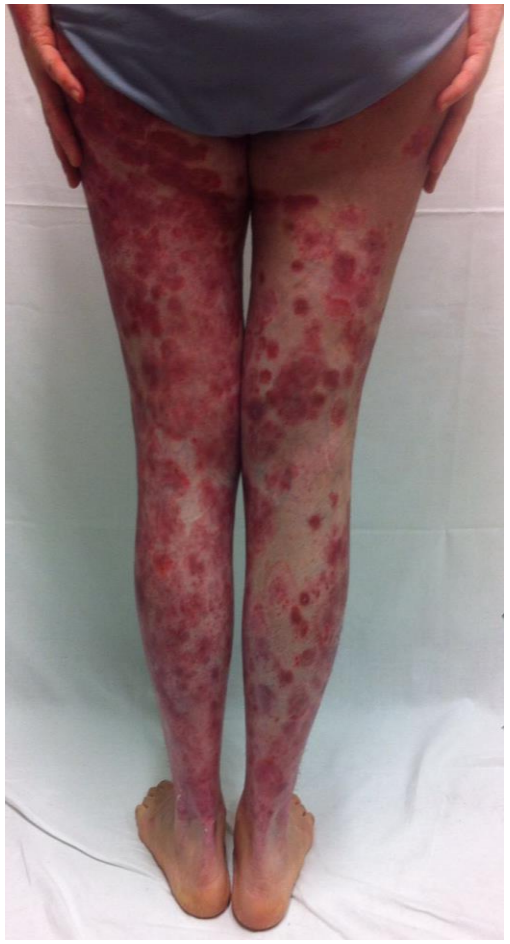
Unstable Psoriasis



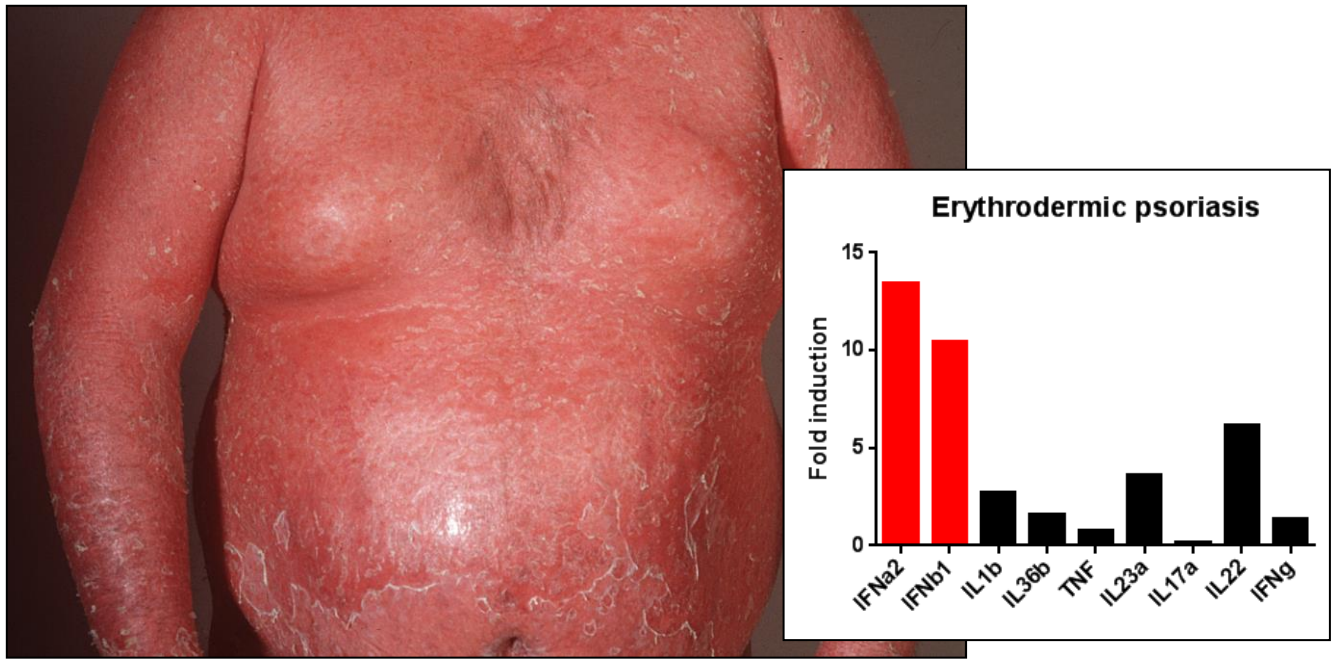


PASI: 21



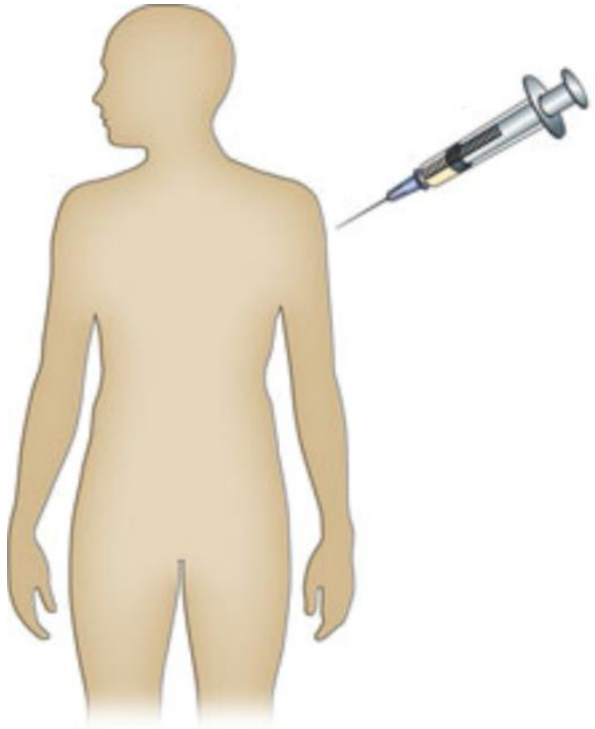


Erythrodermic psoriasis



Conrad and Gilliet, *unpublished data*

Targeting the IFN-α Pathway



Anti-BDCA2
Anti-ILT-7

Phase I studies
(Biogen, Medimmune)

TLR7/9 inhibitors

Phase II studies
(Idera)

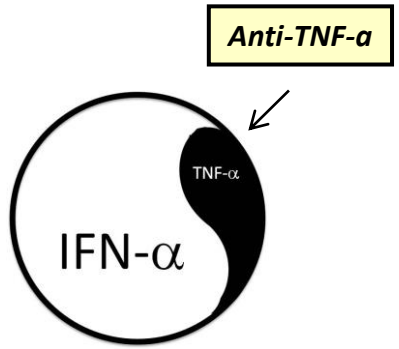
Anti-IFN-a
Anti-IFNAR
TYK2 inhibitor
(**Deucravacitinib**)

Phase II/III studies
(Medimmune, BMS)

Indications:

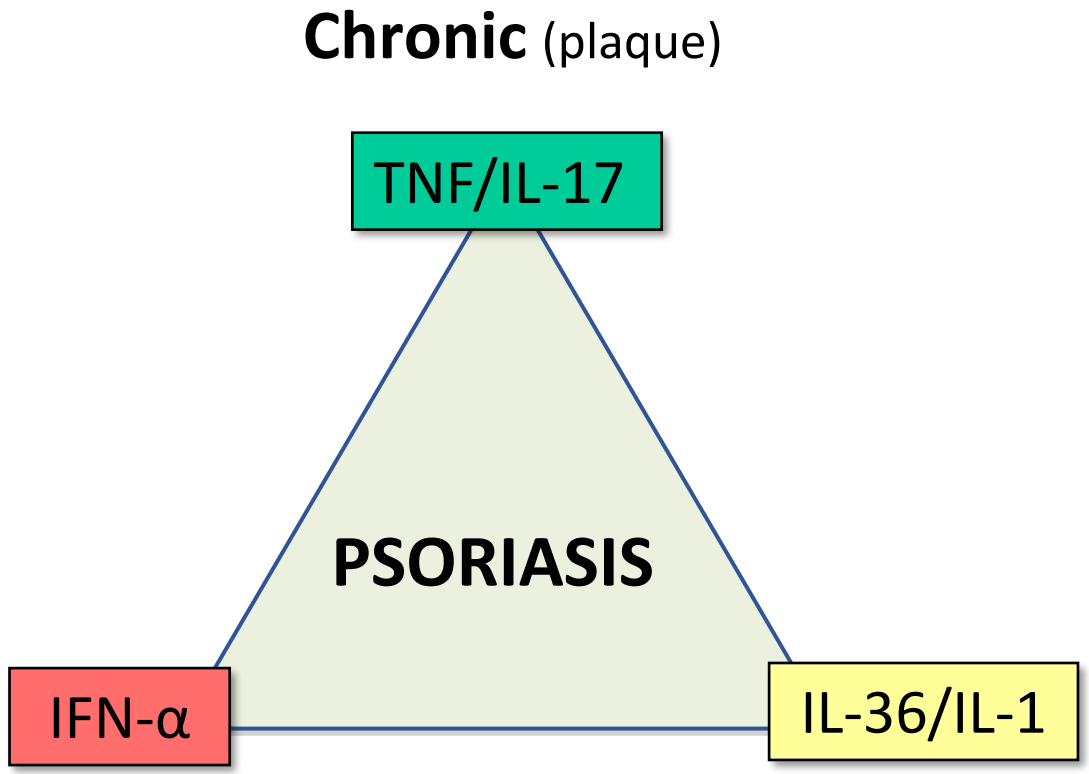
- ***Acute forms of psoriasis (erythrodermic, instable)***
- ***Paradoxical psoriasis***
- ***Prevention of relapses***

Paradoxical psoriasis



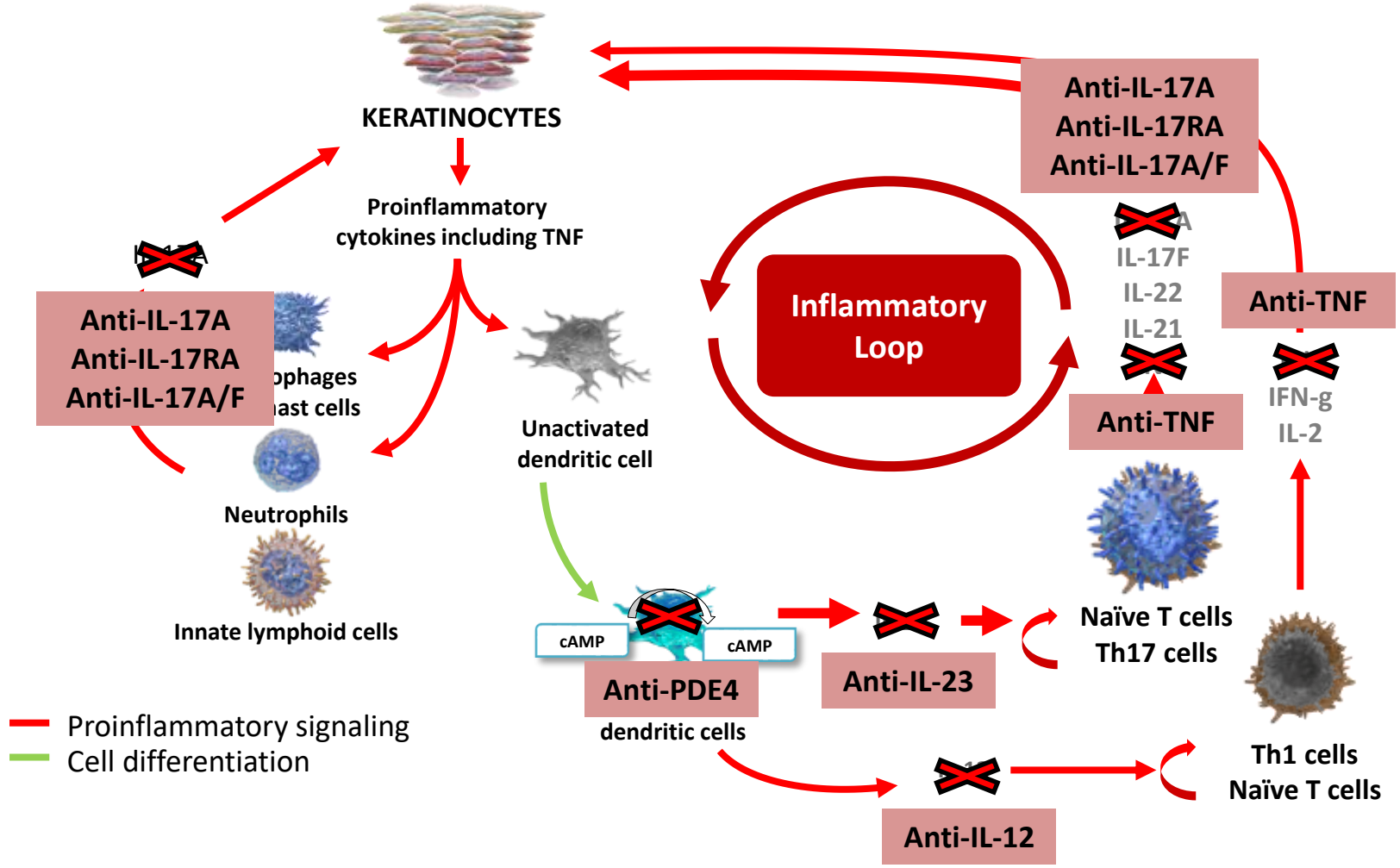
Conrad et al. *Nat Commun.* 2018

Inflammatory pathways in psoriasis



Adapted from 1. Conrad C & Gilliet M *Schweiz Med Forum* 2016; 2. Mylonas A & Conrad C. *Front Immunol* 2018.

Pathogenesis-based Approach to Treatment of Psoriasis in 2022



Adapted from Nestle FO, et al. *N Engl J Med.* 2009;361:496–509; Lowes MA, et al. JID. 2008;128:1207–1211;

Korn T, et al. *Annu Rev Immunol* 2009;27:485–571; Biedermann T, et al. *J Investig Dermatol Symp Proc* 2004;9:5–14;

Onishi RM, et al. *Immunol.* 2010;129:311–321; Lin AM, et al. J Immunol. 2011;187:490–500. Bruin G, et al. Poster presented at: EADV Conference; Istanbul, Turkey; 2–6 October 2013. E-Poster #P1498.

When to Prescribe Biologic Therapy?

Inadequate control with topical therapy and

Significant impact on:

Physical,psychological,social wellbeing and

one or more of: > 10% BSA, or PASI >10

Phototherapy ineffective/rapid relapse

Localized disease: significant functional impact/distress
e.g genital, nail, palmoplantar, face localizations

Considerations when Prescribing

Patient age

Disease phenotype

Disease severity and impact

Psoriatic arthritis

Conception plans

Patient's views (social habits)

Ideal therapeutical Target

- **PASI 90** Clinical improvement
- - 90% reduction in PASI from Pre-Treatment
- PASI 75 Clinical improvement
- - 75% reduction in PASI from Pre-Treatment
- **Absolute PASI<2** is equivalent to PASI 90

Biologics Available for the Treatment of Psoriasis and their Molecular Structure

Approved	Class	Target	Molecular Structure	IG Type
Etanercept[1]	TNFα inhibitor	TNFα	Receptor fusion protein	-
Infliximab[2]	TNFα inhibitor	TNFα	Chimeric monoclonal antibody	IgG_1
Adalimumab[3]	TNFα inhibitor	TNFα	Fully human monoclonal antibody	IgG_1
Ustekinumab[4]	IL-12/23 inhibitor	p40 subunit	Fully human monoclonal antibody	IgG_1
Secukinumab[5]	IL-17A inhibitor	IL-17A	Fully human monoclonal antibody	IgG_1
Ixekizumab[6]	IL-17A inhibitor	IL-17A	Humanized monoclonal antibody	IgG_4
Brodalumab	IL-17RA inhibitor	IL-17RA	Fully human monoclonal antibody	IgG_2
Guselkumab	IL-23 inhibitor	P19 subunit	Fully human monoclonal antibody	IgG_1
Tildrakizumab	IL-23 inhibitor	P19 subunit	Humanized monoclonal antibody	IgG_1
Risankizumab	IL-23 inhibitor	P19 subunit	Humanized monoclonal antibody	IgG_1
Bimekizumab	IL-17A/F inhibitor	IL17A/F	Humanized monoclonal antibody	IgG_1

1. Papp KA, et al. *Br J Dermatol.* 2005;152:1304–1312; 2. Reich K, et al. *Lancet* 2005;366:1367–1374;
3. Menter A, et al. *J Am Acad Dermatol.* 2008;58:106–115; 4. Papp KA, et al. *Lancet* 2012;380:738–746;
5. Langley RG, et al. *N Engl J Med.* 2014; 371:326–328; 6. Leonardi C, et al. *N Engl J Med.* 2014;366:13:1190–1199.

Anti-TNF Biologics

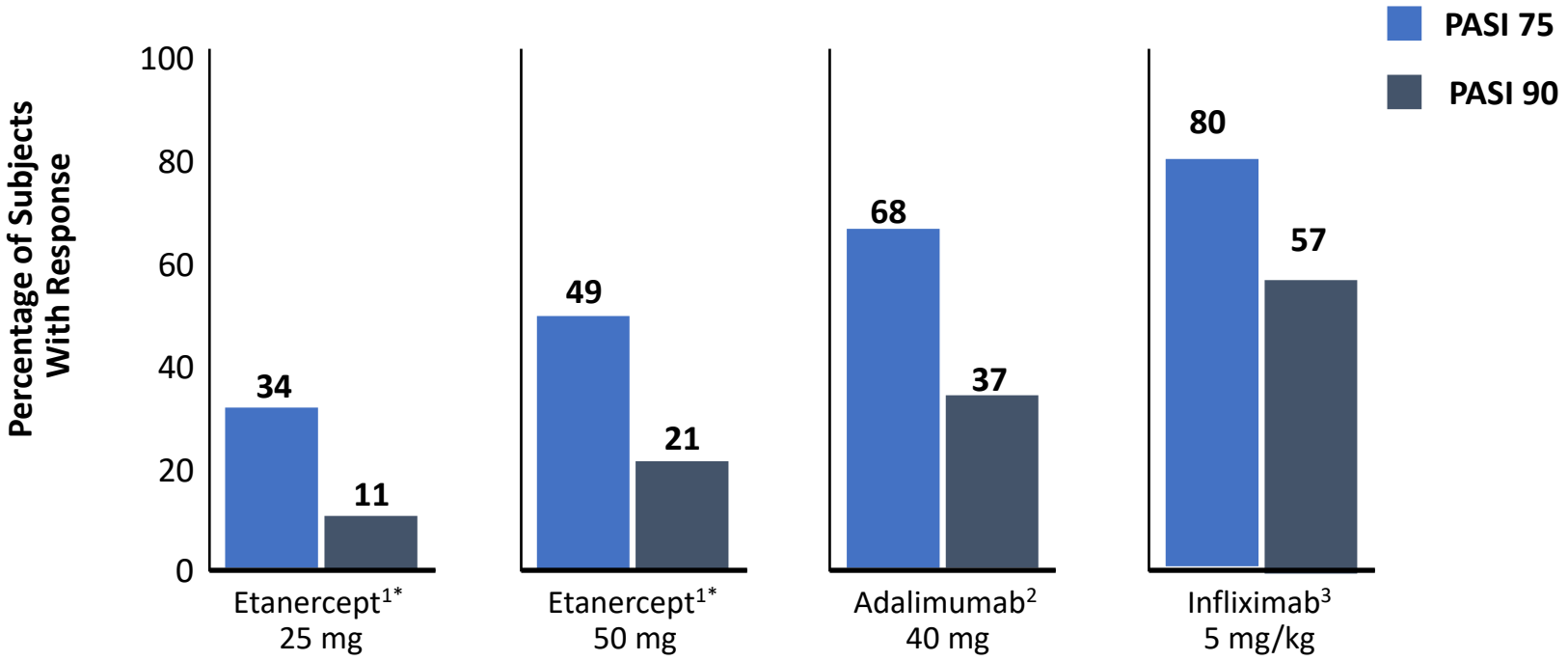
- Greatest experience with this class

- Key considerations
  - TB
  - Demyelination - peripheral and central
  - Cardiac failure
  - Infection - serious more likely with infliximab; also unusual
  - Anti-drug antibodies (ADAs)
  - Weight gain
  - Biosmilars
  - Approved for Psoriatic Arthritis

Anti-TNF Biologics

- Infliximab
  - Weight-based dosing and IV (Smg/Kg, 8 weekly)
  - ADAs high; consider starting with methotrexate
- Etanercept
  - Soluble receptor
  - SOmg SC weekly; least efficacious; many biosimilars
- Adalimumab
  - 40mgs SC 2 weekly;
  - Can increase to weekly
  - Most frequently prescribed biologic in UK; biosimilars now
- Certolizumab
  - 200mg SC 2 weekly pegylated;
  - Good data from pregnancy- use throughout

PASI Responses Achieved With TNFα Inhibition



PASI Responses at Week 12†

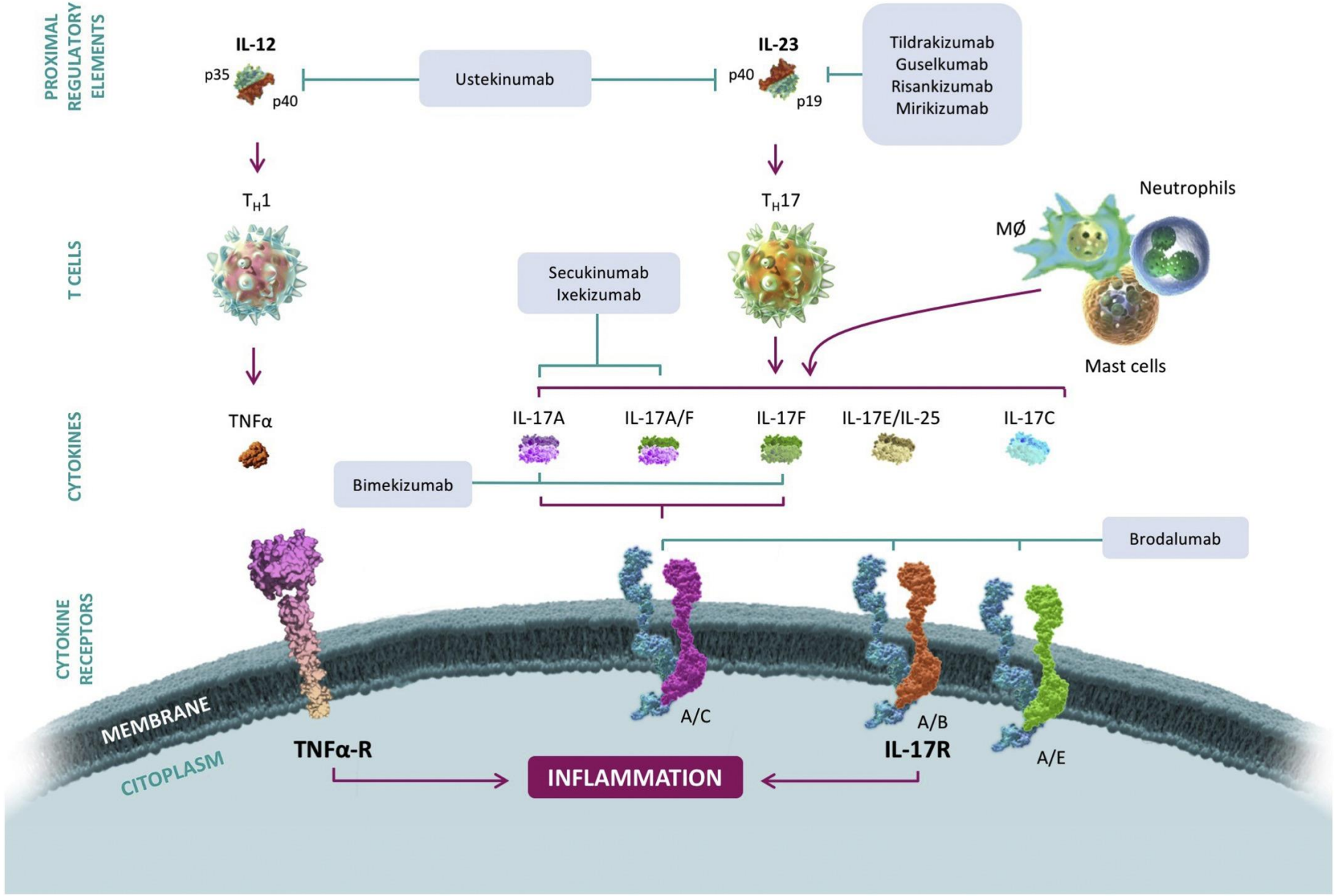
Comparisons not from head-to-head trials

PASI, Psoriasis Area-and-Severity Index

†Week 10 results shown for infliximab (primary endpoint);
*The recommended dose of etanercept is 25 mg administered twice weekly or 50 mg administered once weekly.
1. Papp KA, et al. *Br J Dermatol*. 2005;152:1304–1312.
2. Menter A, et al. *J Am Acad Dermatol*. 2008;58:106–115;

3. Reich K, et al. *Lancet*. 2005;366:1367–1374.

Anti-IL17, Anti-IL12/23 and Anti-IL23 MOA



https://doi.org/10.1016/j.autrev.2019.102429

Anti-IL-17

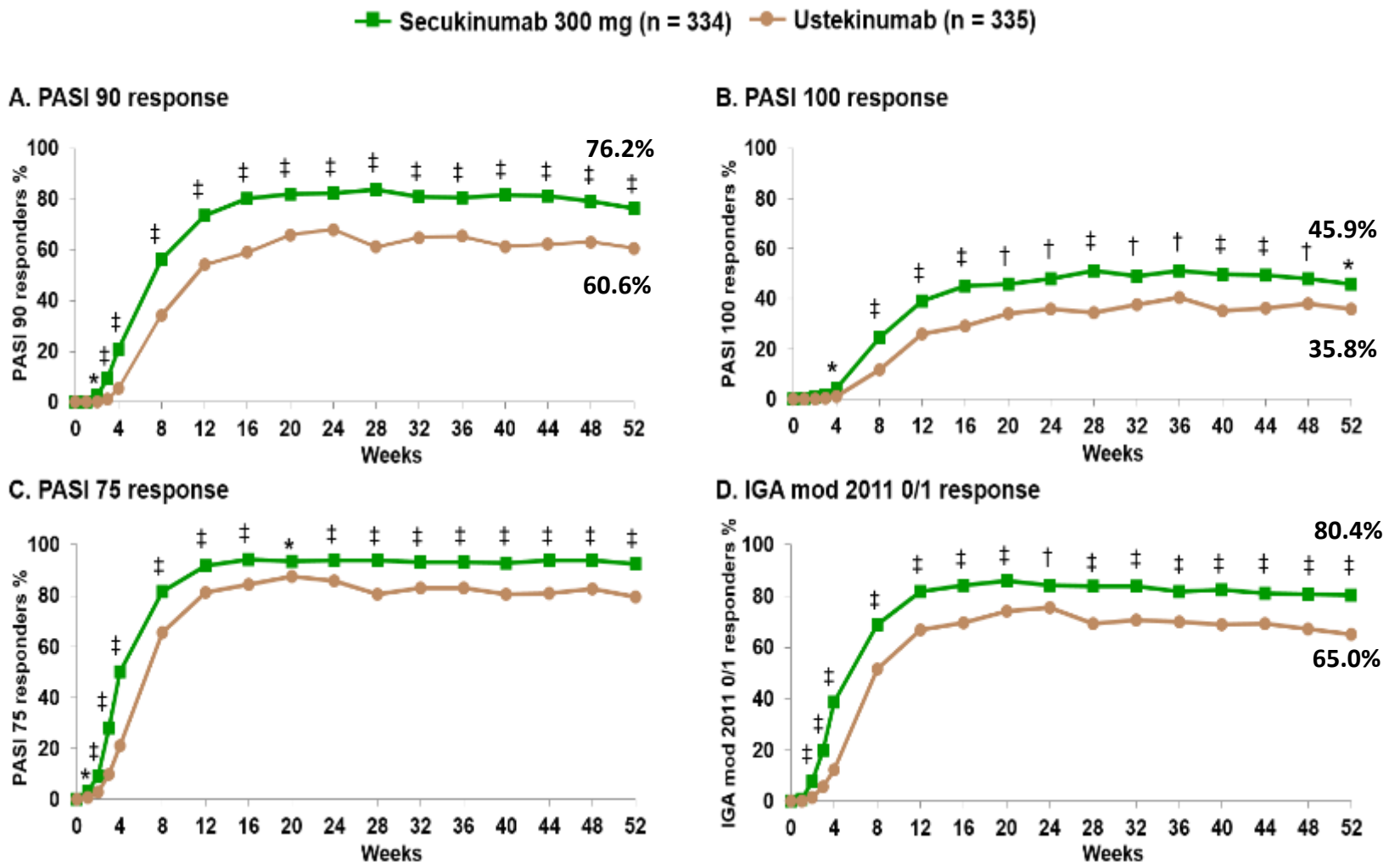
- Secukinumab
  - 300mg SC weekly for 4 weeks; stepping down to monthly, PsA approved
- Ixekizumab
  - 80 mg SC 2 weekly for 12 weeks; stepping down to monthly, PsA approved
- Brodalumab
  - 210 mgs SC 2 weekly throughout following loading

Bimekizumab (anti-IL17A/F) 320 mg every 4 weeks for 16 weeks then 320 mg evrìery 8/weeks

- PASI 90 c.70%;PASI 100 c.40%
- All work in Anti-TNF failure
- Effective for Psoriatic Arthritis...
- Risk of TB very low.

Superiority of Secukinumab vs. Ustekinumab

Superiority of Secukinumab Maintained Over 52 Weeks



Missing data were handled using multiple imputation.

*$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$ vs. ustekinumab by logistic regression. IGA mod 2011 0/1, Investigator's Global Assessment, 2011 modified version, score 0/1; PASI 75/90/100, ≥75%/≥90%/100% improvement from Baseline Psoriasis Area and Severity Index score.

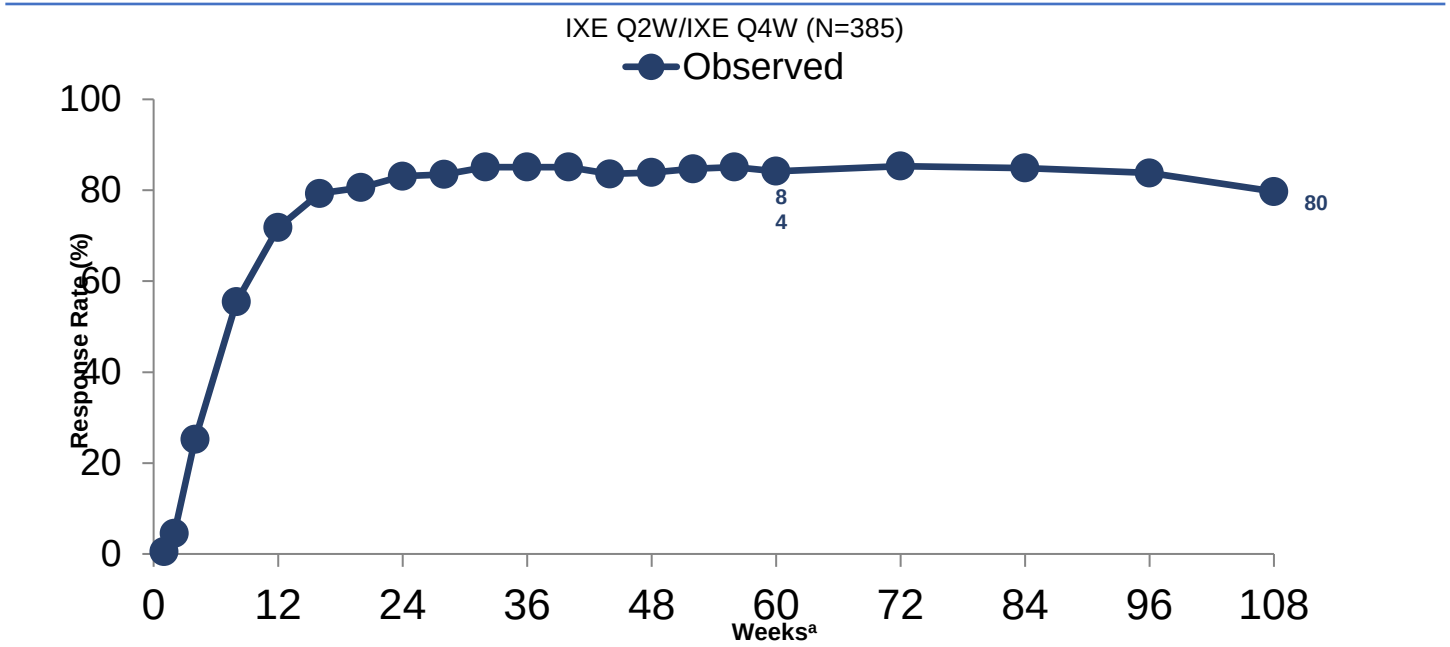
Blauvelt A, et al. Oral presentation at: AAD Annual Meeting; San Francisco, California; 20–24 March 2016. Oral Presentation #3848.

IXEKIZUMAB PASI 90 Response by Treatment Week, Observed

Induction Period and Long Term Externsion, ITT Population

(UNCOVER-3)

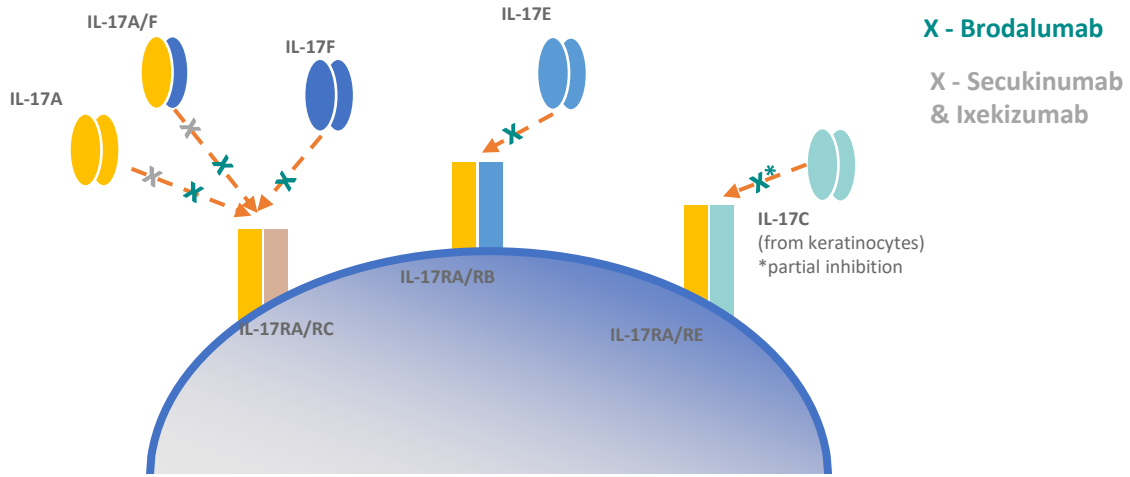
Over 2 years, ixekizumab showed maintenance of efficacy across all endpoints with high skin clearance rates



[a]Per protocol amendment c, patients are allowed to increase dose to IXE Q2W after Week 60 during the long-term extension period.
IXE Q2W=80 mg of Ixekizumab Every 2 Weeks; IXE Q4W=80 mg of Ixekizumab Every 4 Weeks; NRI=Nonresponder Imputation; PASI=Psoriasis Area and Severity Index.

Binding to the IL-17 receptor with brodalumab inhibits multiple pro-inflammatory cytokines

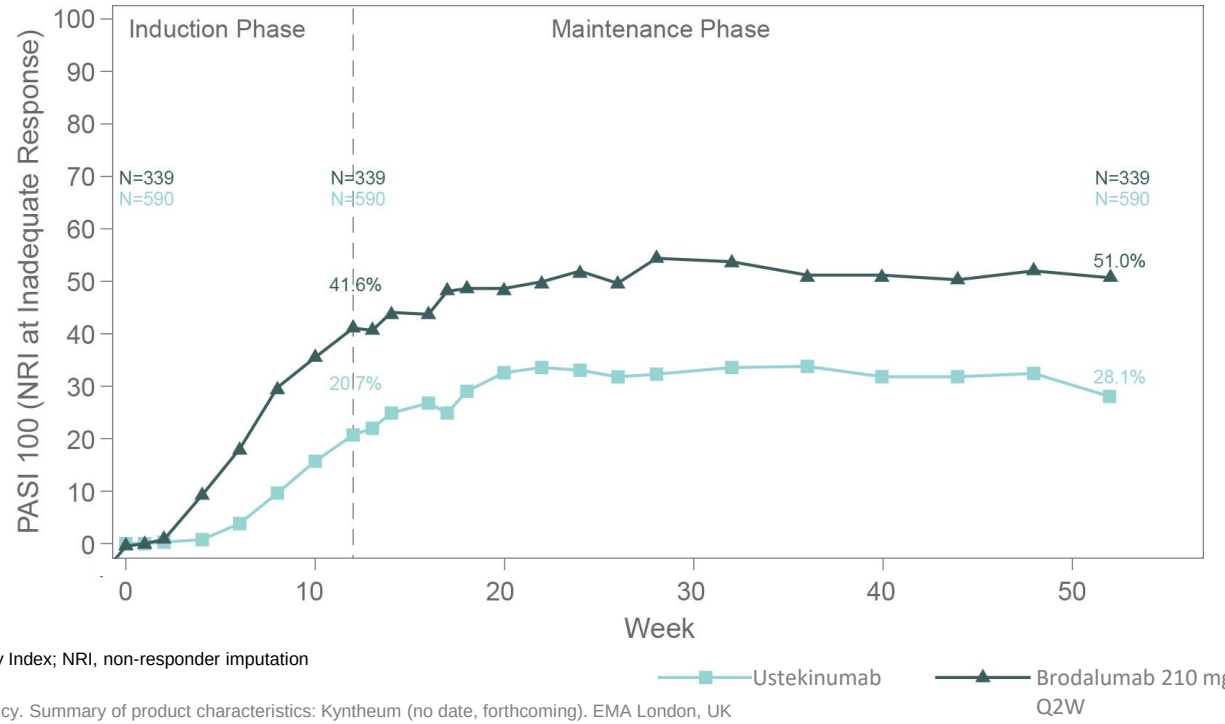
Brodalumab prevents binding of multiple IL-17 isoforms to IL-17 receptor complexes,[1] which inhibits downstream effects of keratinocyte activation such as inflammatory gene expression, skin thickening, and immune cell infiltration[2]



1. Beringer A, *et al., Trends in Mol Med.* 2016;22(3):230–241; 2. Martin DA, *et al., J Invest Dermatol.* 2013;133(1):17-26. doi: 10.1038/jid.2012.194; Image adapted from Beringer A, *et al., Trends in Mol Med.* 2016;22(3):230–241

BRODALUMAB AMAGINE-2 & 3: PASI 100 response rates over time through Week 52 (NRI at inadequate response)

PASI 100 rates during induction and maintenance (pooled AMAGINE-2 and AMAGINE-3)[1,2]



PASI, Psoriasis Area and Severity Index; NRI, non-responder imputation

European Medicines Agency. Summary of product characteristics: Kyntheum (no date, forthcoming). EMA London, UK

BKZ was designed to selectively inhibit IL-17A and IL-17F

Bimekizumab is

a humanized monoclonal IgG1 antibody[1]

Innovative design — Dual specificity for IL-17A and IL-17F[2]

High affinity — pM affinity for both IL-17A and IL-17F[3]

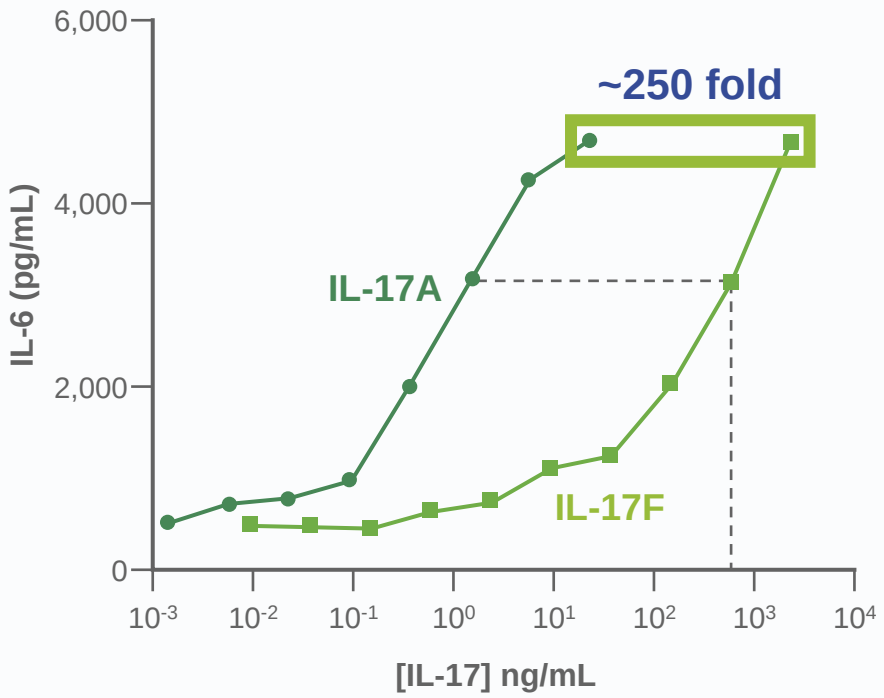
Targets 3 dimers — Binds to IL-17A/A, IL-17A/F & IL-17F/F[3]

Estimated half-life: 22 days.[1] IgG, Immunoglobulin G.

1. Glatt et al. Br J Clin Pharmacol. 2017;83:991–1001. 2. Glatt et al. Ann Rheum Dis. 2018;77:523–32. 3. Adams et al. Frontiers Immunol. 2020;11:1894.

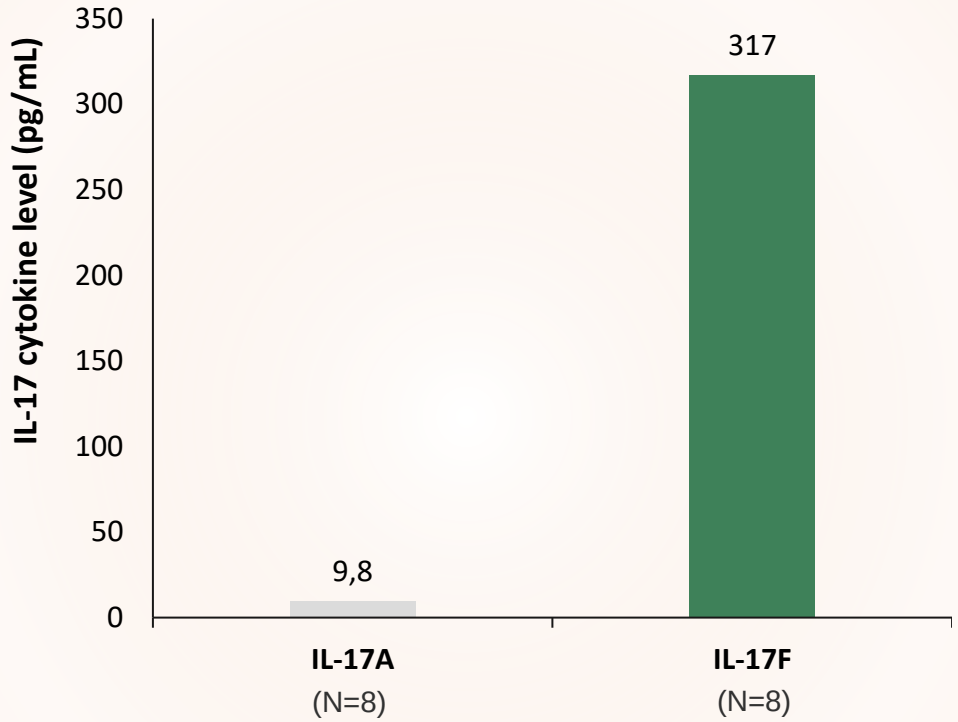
IL-17F is less potent, but more abundant, than IL-17A in psoriasis

Potency in skin[1]
Dermal fibroblasts



IL-17A is 250-fold more potent than IL-17F

Abundance in skin[2]
Transdermal reperfusion (PSO lesions)



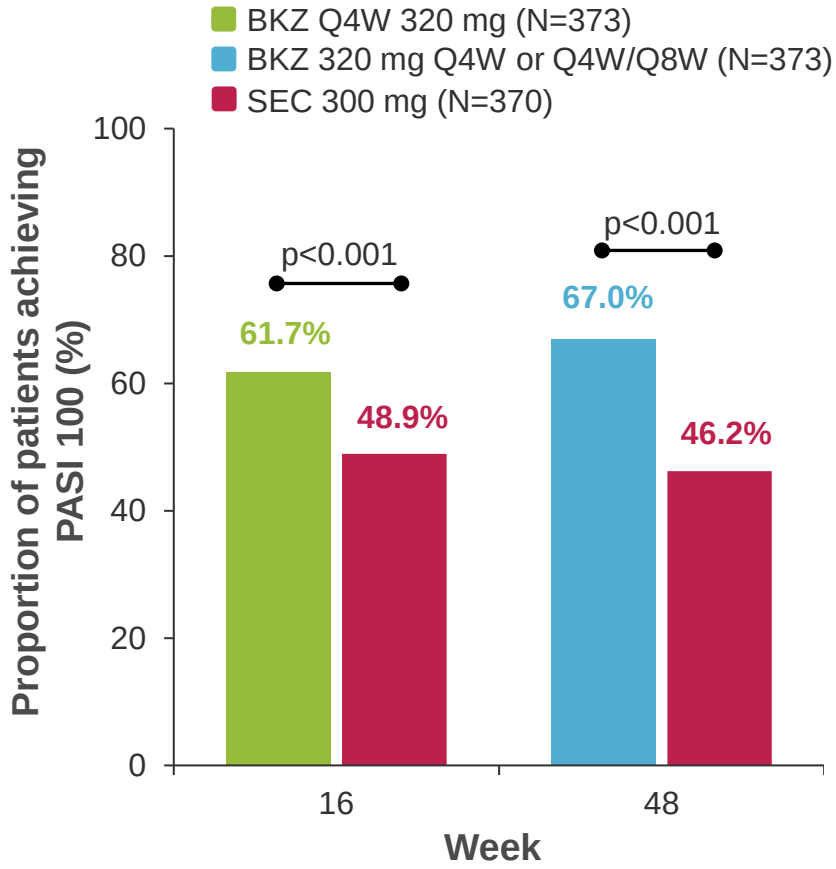
IL-17F levels are approximately 30-fold higher than IL-17A in patients with PSO

- 1.Maroof et al. ESDR 2017;P426. 2. Kolbinger et al. J Allergy Clin Immunol 2017;139:923–32.

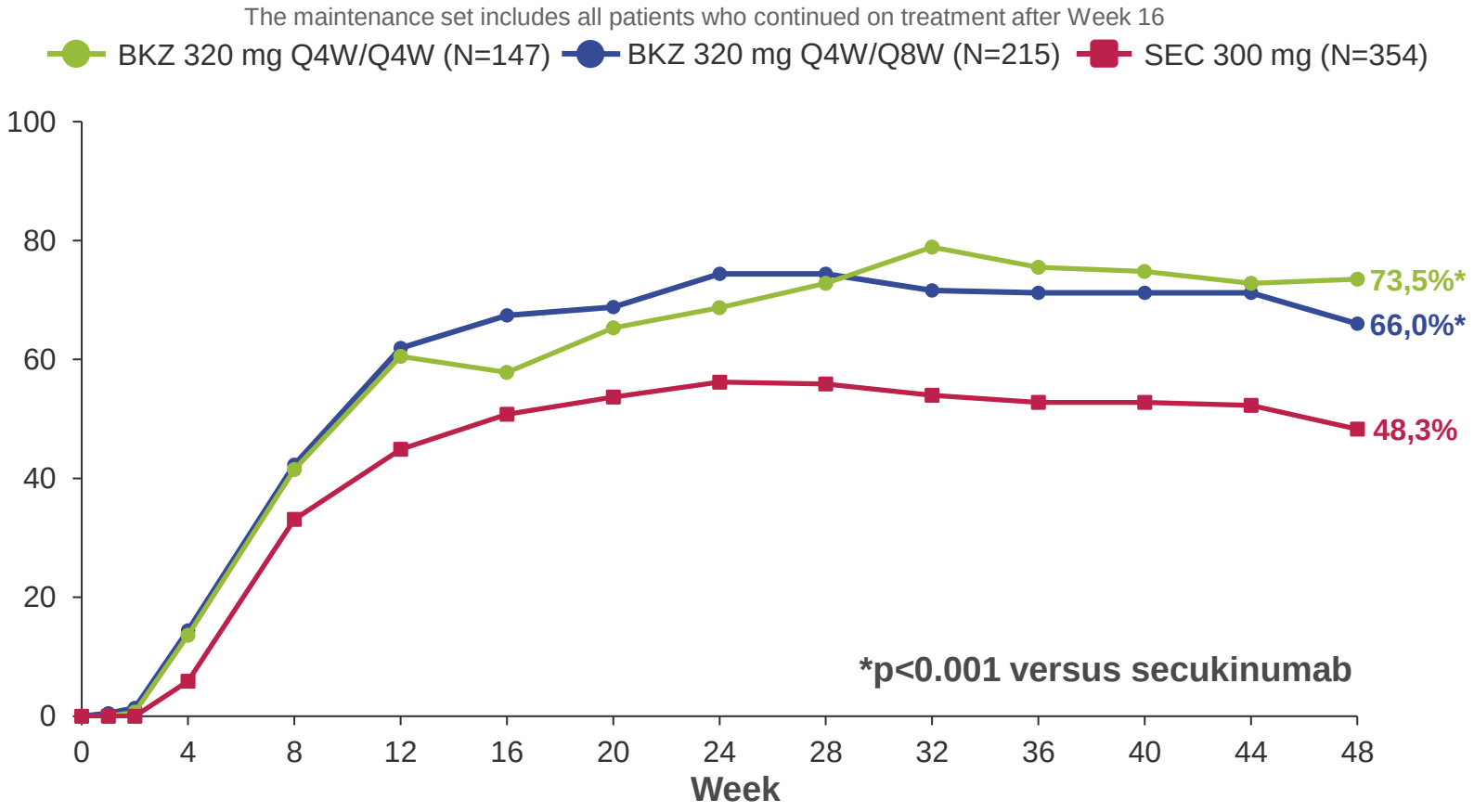
BIMEKIZUMAB BE RADIANT - PASI 100 over 48 Weeks (NRI)

- Primary endpoint PASI 100 response with bimekizumab versus secukinumab at Week 16
- Secondary endpoint PASI 100 response with bimekizumab versus secukinumab at Week 48

PASI 100 at Weeks 16 and 48 (ITT, NRI)



PASI 100 to Week 48 (Maintenance Set, NRI)

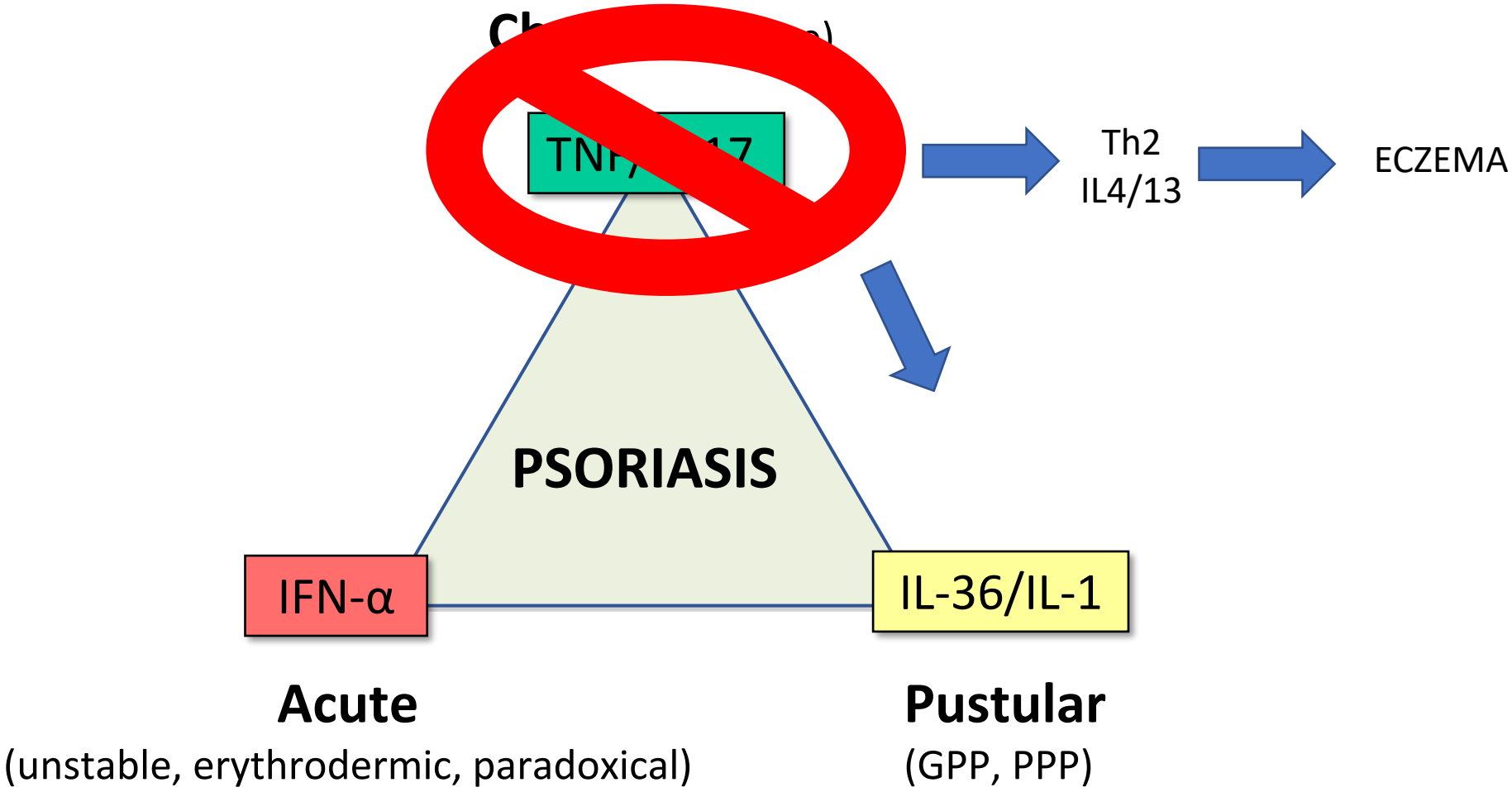


- p values are based on the stratified Cochran Mantel Haenszel test for the general association, with prior biologic exposure and geographic region as stratification factors. BKZ: bimekizumab; ITT: intent-to-treat; NRI: non-responder imputation; PASI 100: 100% improvement from baseline in Psoriasis Area and Severity Index; Q4W: every 4 weeks; Q8W: every 8 weeks; SEC: secukinumab.
- Adapted from: 1. Reich et al. N Engl J Med 2021;doi:10.1056/NEJMoa2102383.

Anti-IL-17: Adverse Events of Special Interest

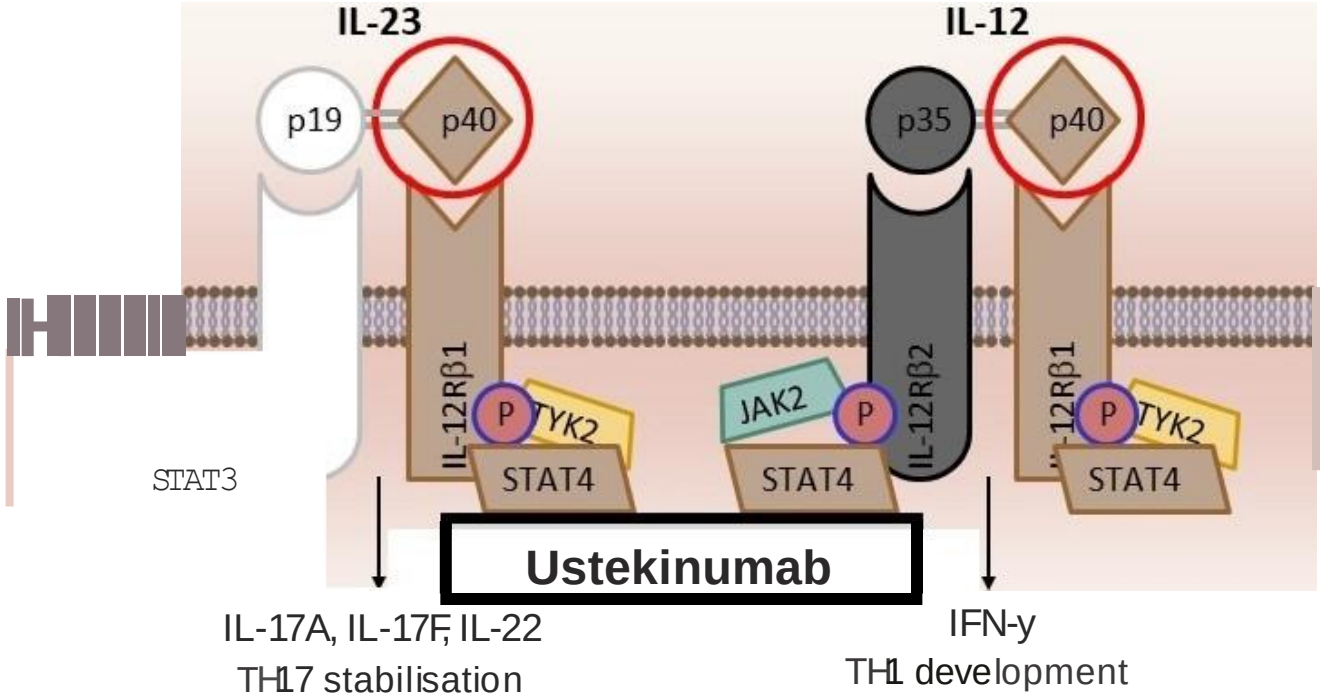
- Candida (10-25% of patients, usually mild)
- Neutropenia (less than 1% of patients)
- Exacerbation of Inflammatory Bowel Disease
- New onset eczema (brodalumab and bimekizumab)
- Pustular reactions

Inflammatory pathways in psoriasis



Adapted from 1. Conrad C & Gilliet M *Schweiz Med Forum* 2016; 2. Mylonas A & Conrad C. *Front Immunol* 2018.

Targeting IL-23p40

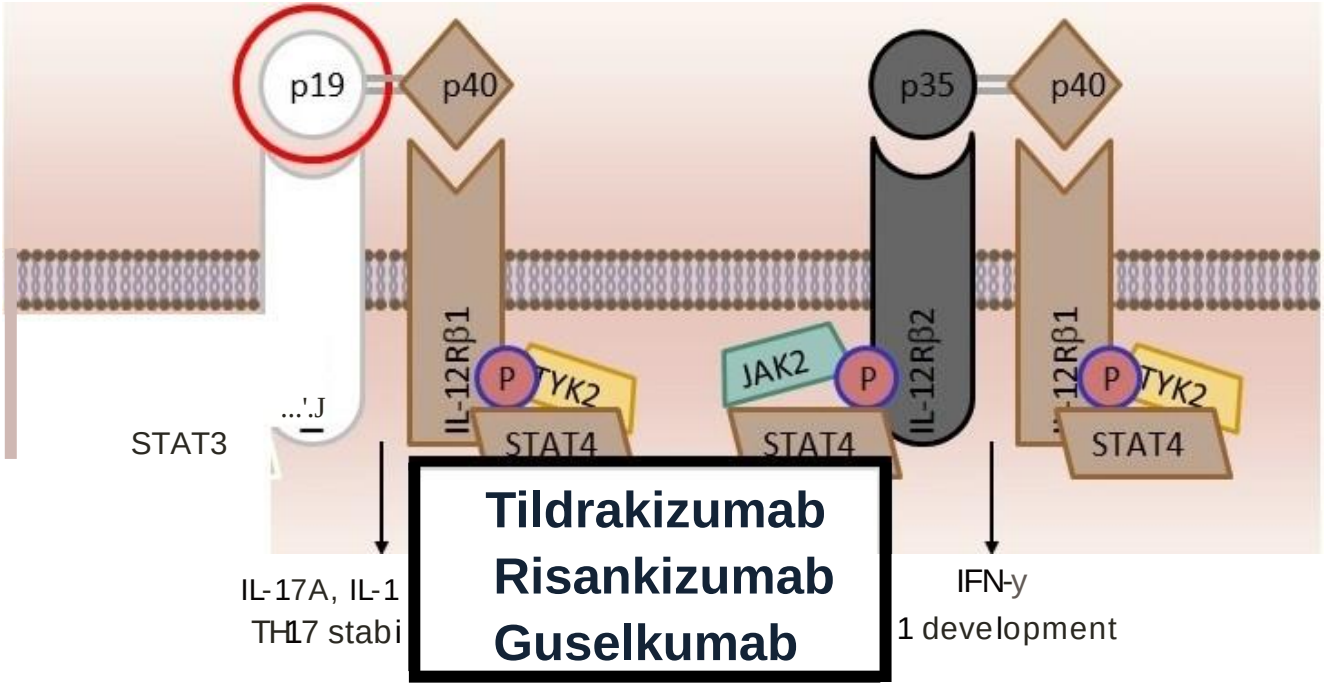


IFN, interferon; IL, interleukin; STAT, signal transducer and activator of transcription; TYK, tyrosine kinase
Teng MW et al. Nat Med 2015; 21: 719–729.

Ustekinumab

- Two doses available
- 45mgs SC 12 weekly (after O and 4 week) for <100Kgs
- 90mgs SC for >100Kgs
- Poorest response in 90-99Kg group
- Risk of TB very low
- Very good drug survival

Targeting IL-23p19

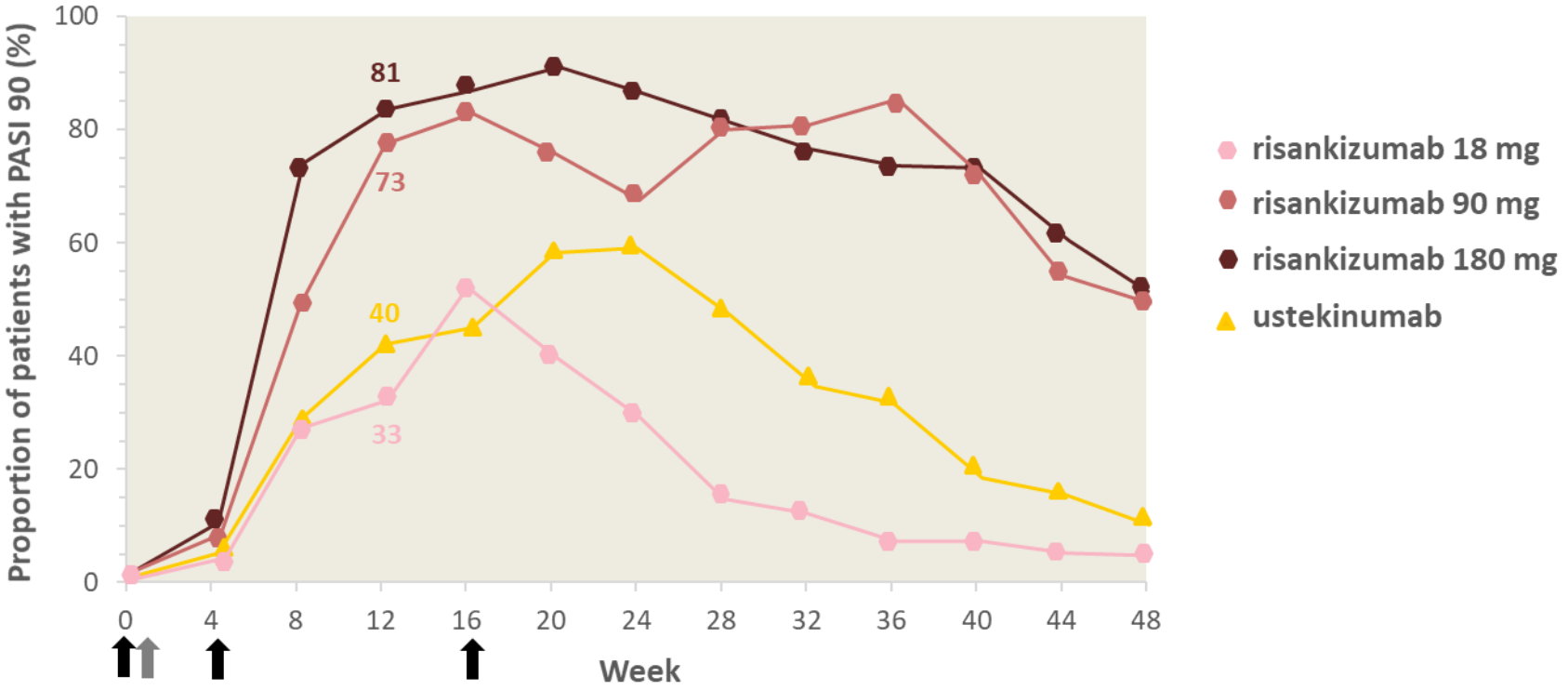


Anti-IL-23p19

- High efficacy PASI 90, 70-80%; PASI 100, 40-50%
- Disease modifying e.g. one injection leading to remission
- Little real world data
- Efficacy in Psoriatic Arthritis ? (Guselkumab approved for PsA)
- Risk of TB very low

Phase II RIS vs UST in PSO

PASI 90 Over Time



Gray arrow=single infusion of risankizumab 18 mg at week 0
Black arrows=infusion of risakizumab (90 mg or 180) or ustekinumab at weeks 0, 4 and 16

50% of patients manitain PASI 90 at week 48 after 3 drug doses

Medical Affairs

Adapted from Papp *et al.* N Engl J Med 2017;376:1551-60.

Comparison of efficacy for biologics targeting IL-23p19

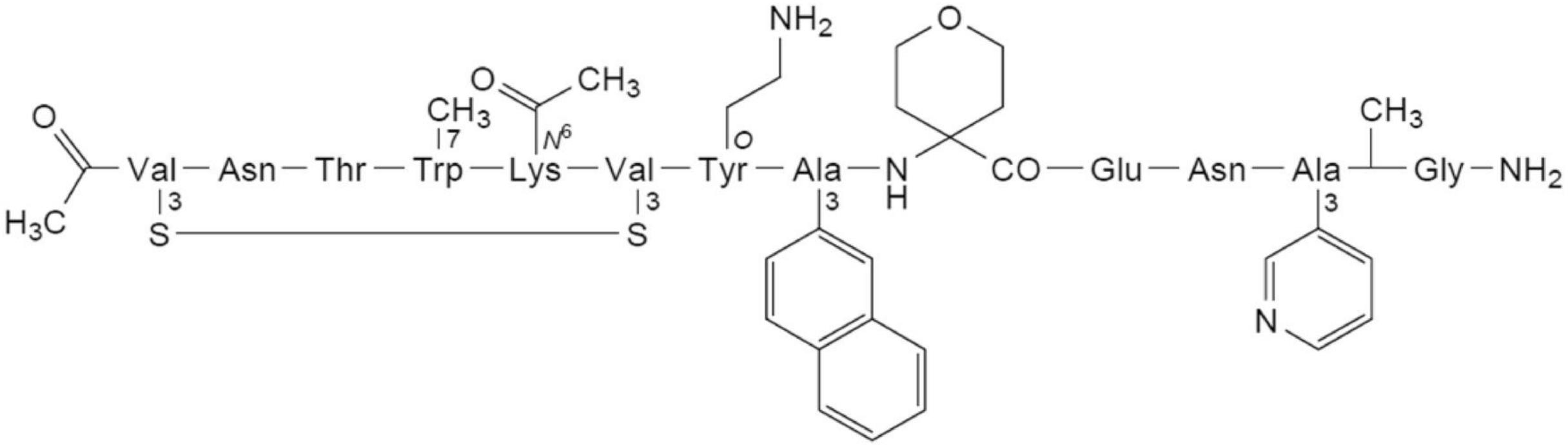
Characteristic	Tildrakizumab† 100 mg[125]	Tildrakizumab† 200 mg[125]	Guselkumab‡ 100 mg[126,127]	Risankizumab 180 mg[130]
Phase	Phase 3	Phase 3	Phase 3	Phase 2
Dosing schedule				
Initial	Weeks 0, 4	Weeks 0, 4	Weeks 0, 4	Week 0
Maintenance	q12w	q12w	q8w	q12w
Efficacy, %	Week 12	Week 12	Week 16	Week 12
PASI 75	61–64	62–66	86–91	88
PASI 90	35–39	35–37	70–73	79
PASI 100	12–14	12–14	34–37	48
PGA 0 or 1	55–58	59	84–85§	NR
Long-term efficacy, %	Week 28¶	Week 28¶	Week 24	Week 36
PASI 75	73–80	73–82	89–91	88
PGA 0 or 1	65–66	69	84§	NR

*Data are not from head-to-head comparisons.
†Data from reSURFACE1 and reSURFACE2 trials.
‡Data from VOYAGE 1 and VOYAGE 2 trails.
§IGA 0 or 1 reported.
¶Responder analysis includes only PASI 75 responders at Week 16.
IGA, investigator global assessment; IL, interleukin; NR, not reported; PASI, Psoriasis Area Severity Index; PGA, Physician's Global Assessment; q8w, every 8 weeks; q12w, every 12 weeks.

Girolomoni et al. JEAD 2017

Medical Affairs

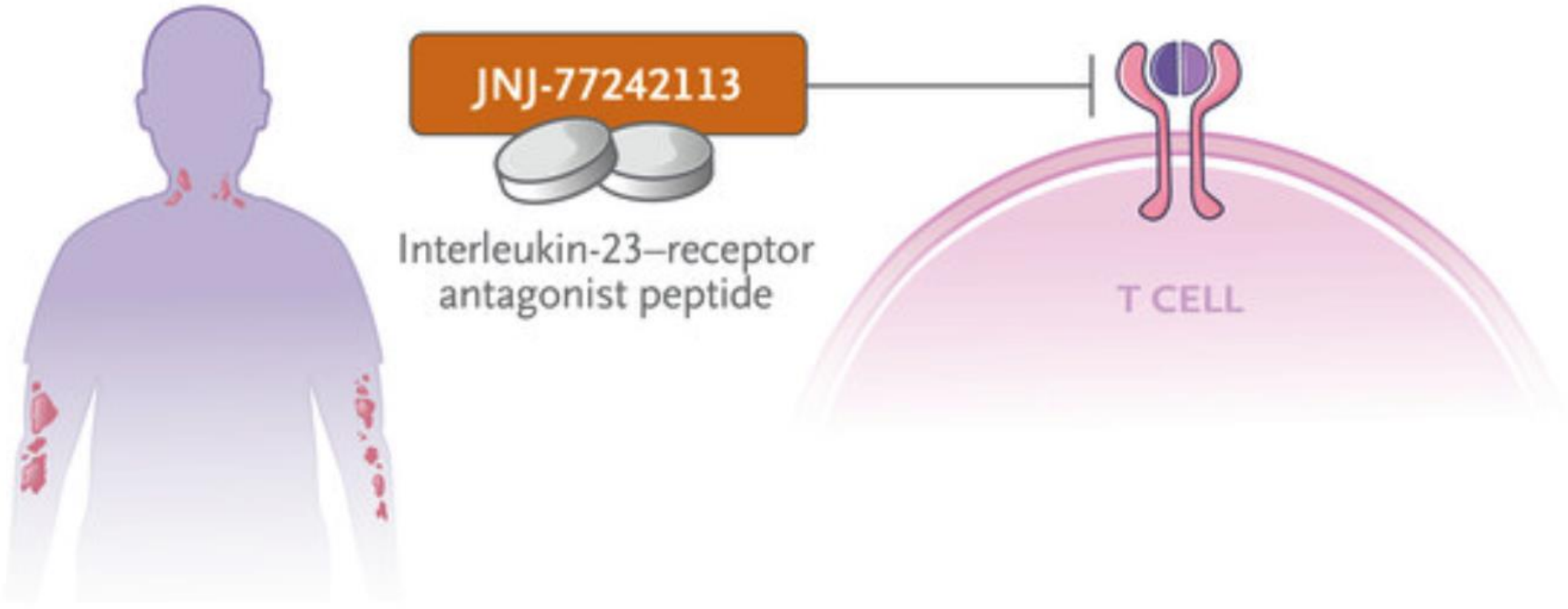
Icotrokinra
(JNJ-2113; JNJ-77242113; PN-235)
είκοσι τρία (íkosi tría)



Inhibits IL-23 activity by an orally administered petide

Scientific Reports **volume 14**, Article number: 17515 (2024)

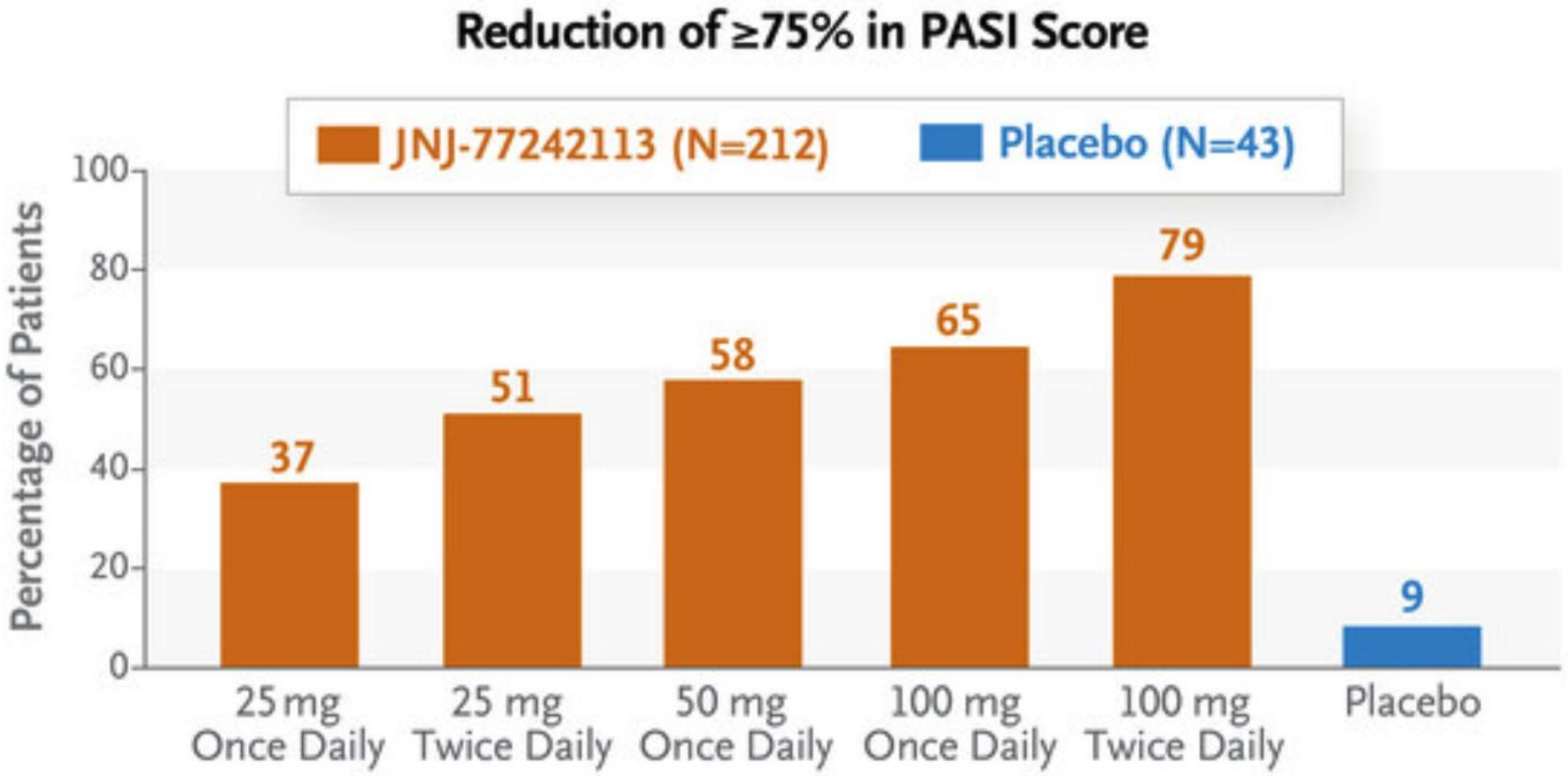
Icotrokinra (JNJ-2113; JNJ-77242113; PN-235)



Icotrokinra antagonizes IL-23 binding to its receptor

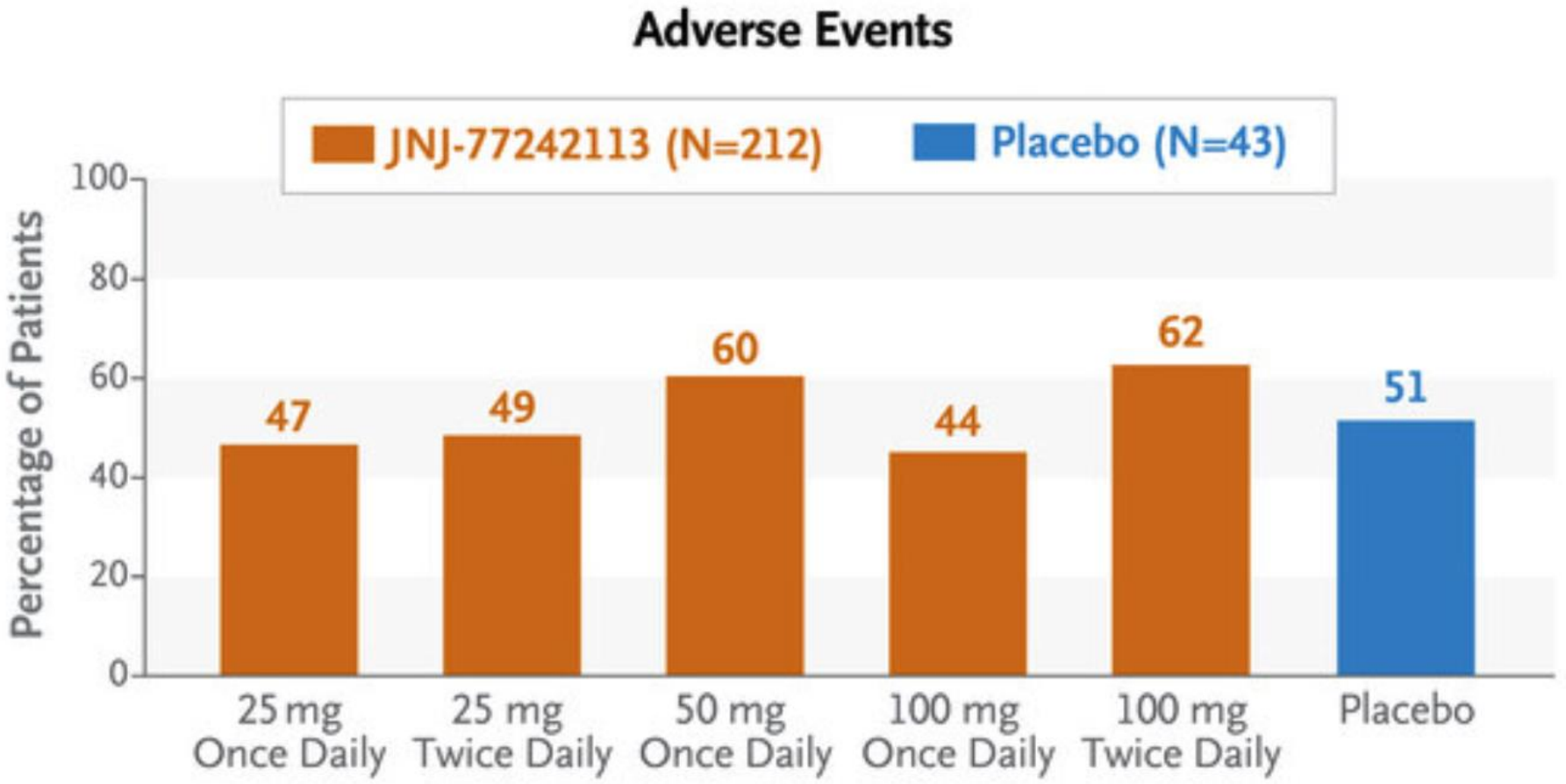
Bissonette R. et al. N Engl J Med 2024;390:510-521 DOI:10.1056/NEJMoa2308713
VOL. 390 NO. 6

Icotrokinra (JNJ-2113; JNJ-77242113; PN-235)



Bissonette R. et al. N Engl J Med 2024;390:510-521 DOI:10.1056/NEJMoa2308713

Icotrokinra (JNJ-2113; JNJ-77242113; PN-235)



Bissonette R. et al. N Engl J Med 2024;390:510-521 DOI:10.1056/NEJMoa2308713
VOL. 390 NO. 6

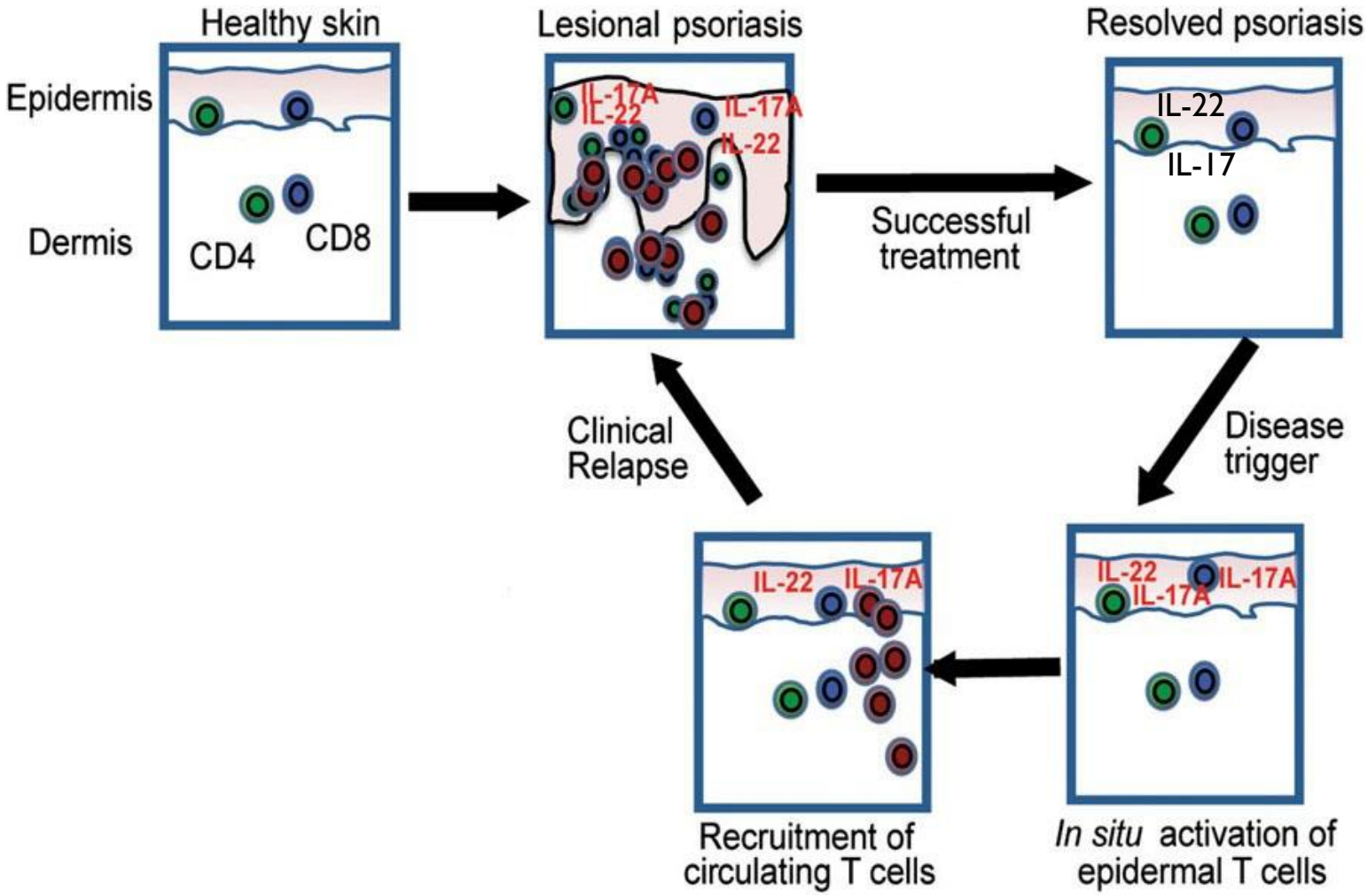
Icotrokinra vs other drugs

		12-16 weeks		52 weeks	
		PASI90	PASI100	PASI90	PASI100
Biologic agents	Bimekizumab	84.4%	58.7%	77.8%	53.8%
	Ixekizumab	70.8%	38.3%	72.7%	51.9%
	Risankizumab	72.7%	42.7%	82.6%	59.9%
	Guselkumab	69.1%	35.9%	76.2%	47.7%
Oral agents	JNJ-77242113 FRONTIER 1 100 mg BID (2b); FRONTIER 2 (52-week extension)	59.5%	40.5%	64.3%	40.5%
	Deucravacitinib 6 mg	29.4%	10.5%	45.2%	20.5%
	Apremilast 30 mg	12.8%	2.6%	31.8%	13.0%

Two Phase III clinical trials are currently active to determine Icotrokinra efficacy and safety on a large number of patients

L. Puig: https://psoriasiscouncil.org/commentaries/oral-interleukin-23-receptor-antagonist-peptide-plaque-psoriasis/

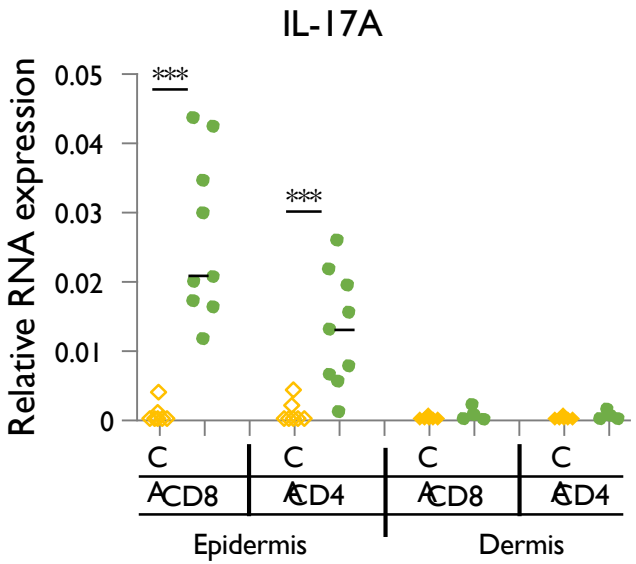
DISEASE MEMORY IN CLINICALLY HEALED SKIN



Cheuk et al. J Immunol. 2014

TRM T CELLS AND DEFECTS IN TREG MAY CONTRIBUTE TO PSORIASIS

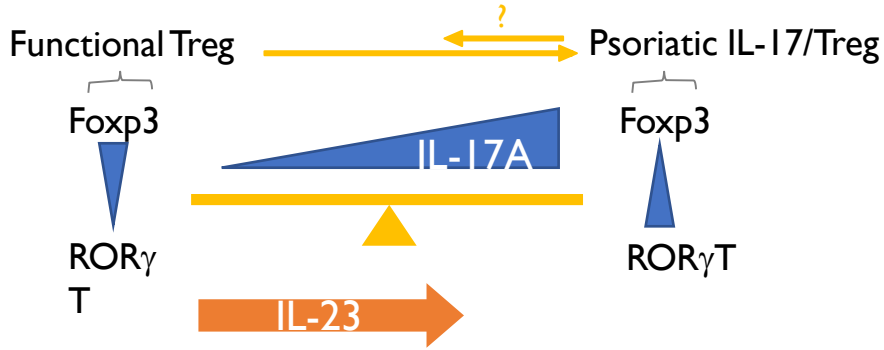
Epidermal TRMs are pathogenic (IL-17A, IL-22 producers)[1]



Are TRMs dependent on IL-23?
Does IL-23 block restore Treg function?

Treg may be defective in psoriasis

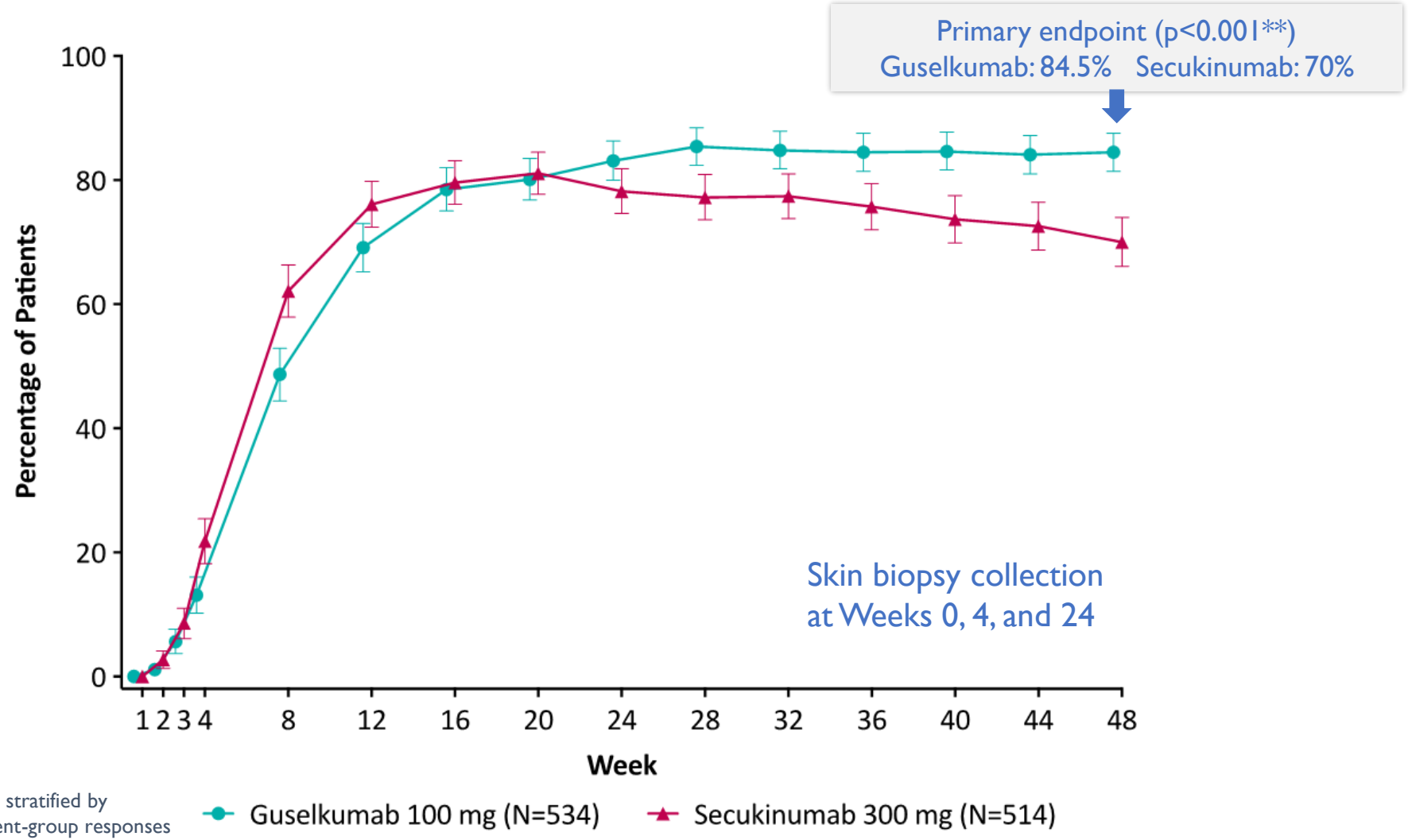
- Foxp3$^+$ Treg in psoriasis skin is increased, but some can produce IL-17A[2]
- Compared with healthy controls, Foxp3$^+$ Treg in psoriasis blood is more easily driven to make IL-17A ex vivo[3]
- Treg defects in psoriasis may be driven by IL-23[4]



- ***$p < 0.001$.
A, active psoriasis lesion; C, healthy skin; TRM, tissue-resident memory T-cell.

- 1. Cheuk S, et al. J Immunol. 2014;192:3111-20.
2. Sanchez Rodriguez R, et al. J Clin Invest. 2014;124:1027-36.
3. Bovenschen HJ, et al. J Invest Dermatol. 2011;131:1853-60.
4. Soler DC, McCormick TS. J Invest Dermatol. 2011;131:1785-6.

Proportion of Patients Achieving PASI 90 Response (With 95% CI) through Week 48 by Visit*[1]



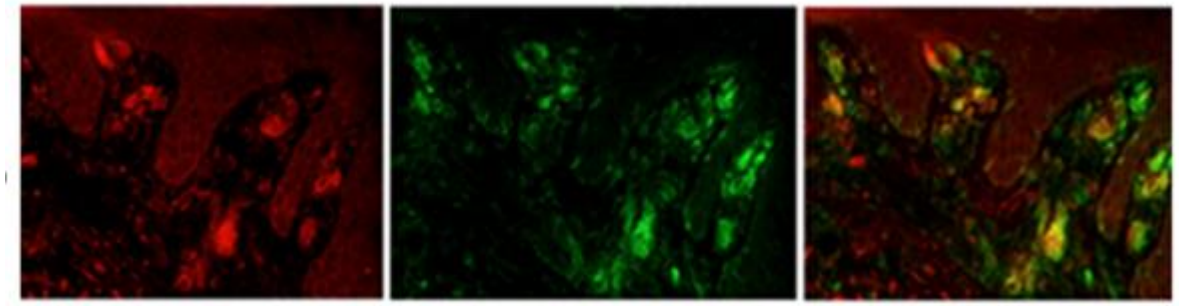
*NRI was used for missing data
**Cochran-Mantel Haenszel chi-square testing stratified by investigator site was used to compare treatment-group responses

1. Reich K., et al. Lancet. 2019 Aug 8. doi:10.1016/S0140-6736(19)31773-8. [Epub ahead of print]

Tissue Resident Memory T cells Contribute to the Pathogenesis of Psoriasis

- Over 10 billion TRMs in healthy skin[1]
- TRMs are found in increased numbers in PSO skin[2,3]
- TRMs are CD103$^+$ (E-cadherin) and/or CD49a$^+$ (collagen IV)

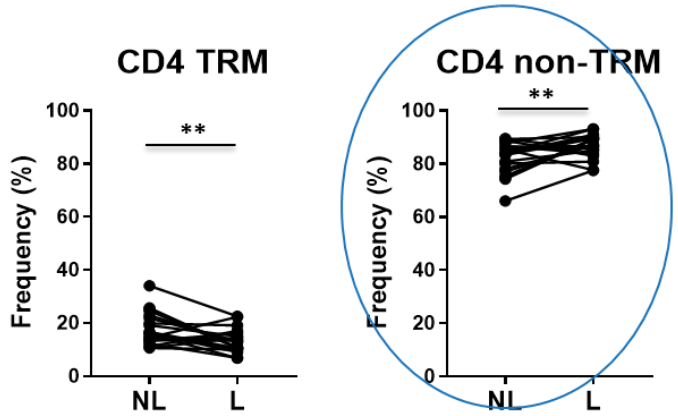
TRMs remain in 'cleared plaques' after anti-TNFα treatment[3]



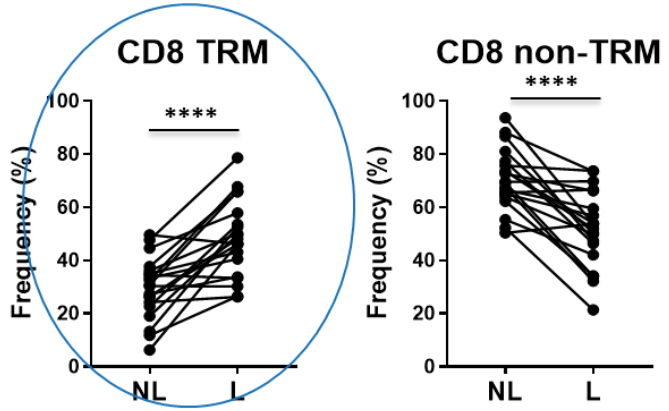
TCR Vβ9 | IL-17A | Merge

ECLIPSE Cellular MOA: Analysis of T cells at baseline:

Relative increase in non-TRMs in CD4$^+$ T cells



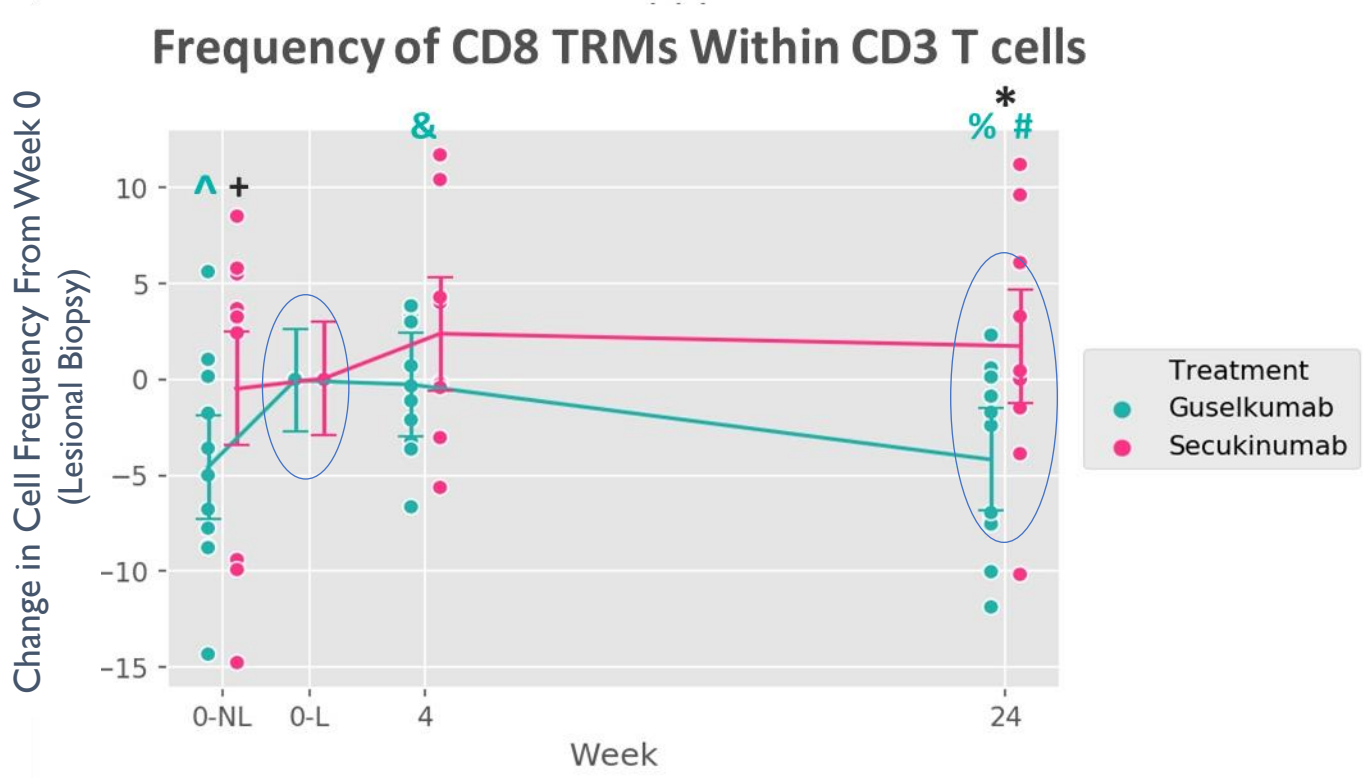
Relative increase in TRMs in CD8$^+$ T cells



L=Lesional
NL=Non-lesional
TRM=Tissue Resident Memory T cells
PSO=Psoriasis
MOA=Mechanism of Action

1. Clark R.A., et al. J Immunol. 2006;176(7):4431-9.
2. Cheuk S., et al. J Immunol. 2014;192(7):3111-20.
3. Matos T.R., et al. J Clin Invest. 2017;127(11):4031-41.

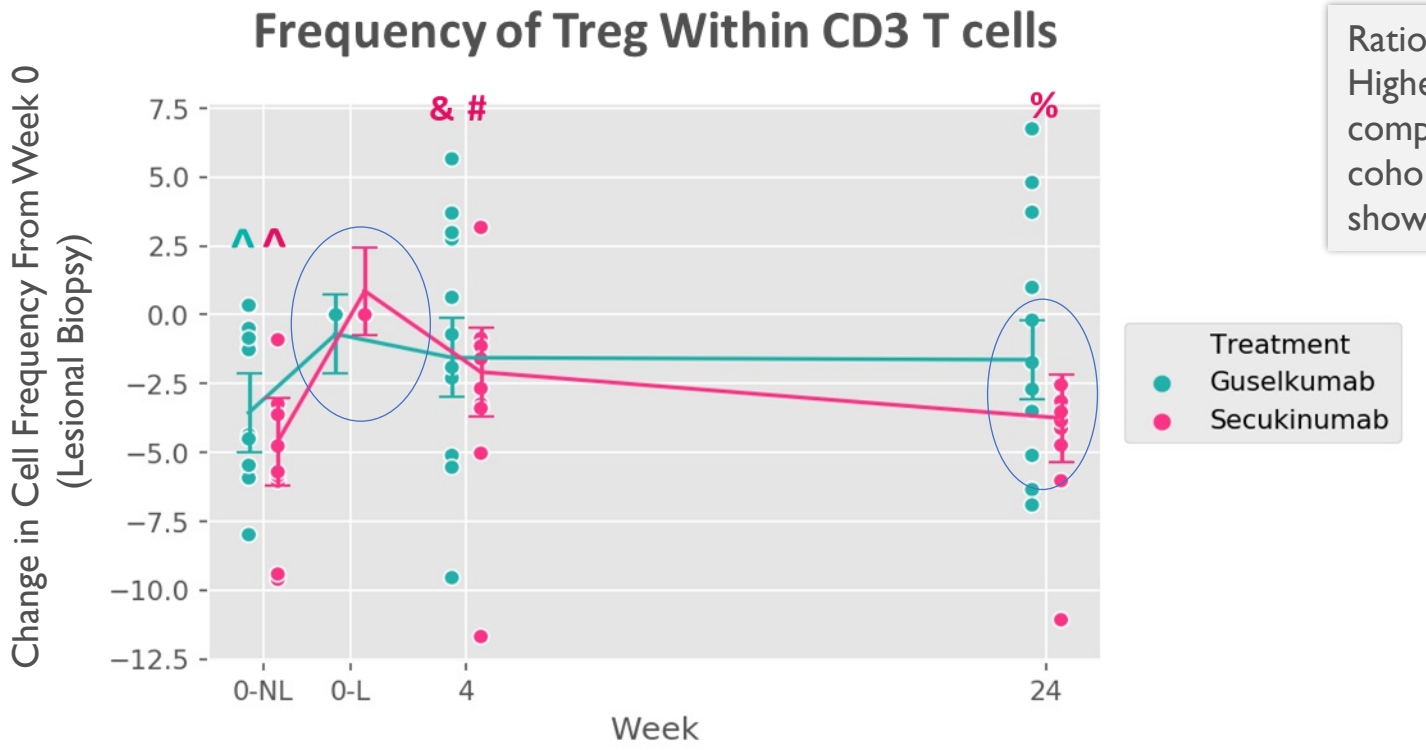
Frequency of CD8+ TRM in Lesional Skin was Reduced More Significantly by Guselkumab Compared to Secukinumab



L=Lesional
NL=Non-lesional
PSO=Psoriasis
TRM=Tissue Resident Memory T cells
Statistical analysis was done with SAS 9.4 software using longitudinal regression model

*guselkumab vs secukinumab, Week 24
+guselkumab vs secukinumab, Week 0
^guselkumab, NL vs L
&guselkumab, NL vs Week 4
#guselkumab, L vs Week 24
%guselkumab, Week 4 vs Week 24
$p<0.05$, all comparisons

Frequency of Regulatory T cells in Psoriatic Skin was Maintained by Guselkumab and Reduced by Secukinumab



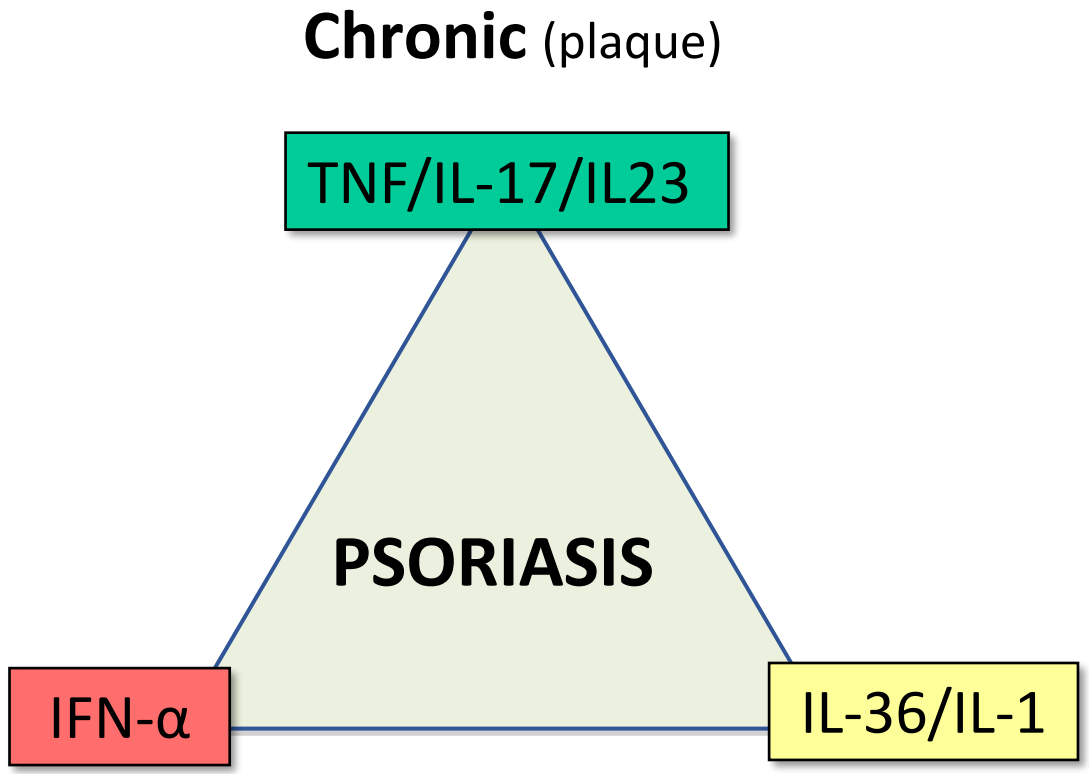
Ratio of Treg to CD8+ TRMs: Higher in guselkumab cohort compared to secukinumab cohort at Week 24 (not shown)

L=Lesional
NL=Non-lesional
TRM=Tissue Resident Memory T cells
Statistical analysis was done with SAS 9.4 software using longitudinal regression model

^guselkumab, NL vs L
^secukinumab, NL vs L
&secukinumab, NL vs Week 4
#secukinumab, L vs Week 4
%secukinumab, L vs Week 24
$p<0.05$, all comparisons

Frequency of Treg ($CD25^+$ /$FoxP3^+$ /$IL\text{-}17A^-$) was maintained in the guselkumab cohort between Weeks 0 and 24.
Frequency of Treg is reduced between Week 0 and Week 24 in the secukinumab cohort.

Inflammatory pathways in psoriasis

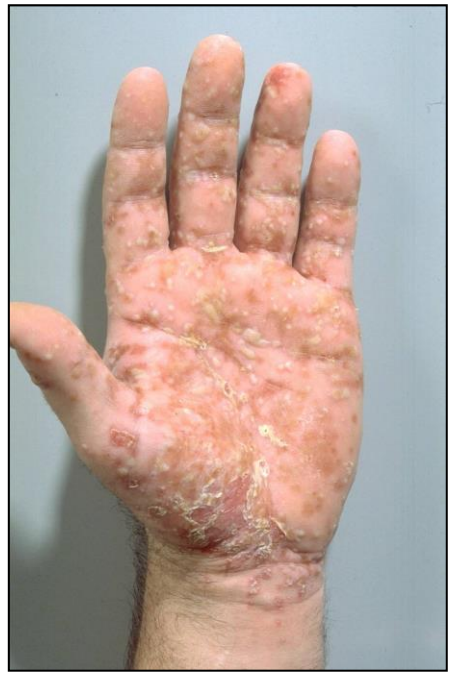


Adapted from 1. Conrad C & Gilliet M *Schweiz Med Forum* 2016; 2. Mylonas A & Conrad C. *Front Immunol* 2018.

Palmoplantar Pustular Psoriasis

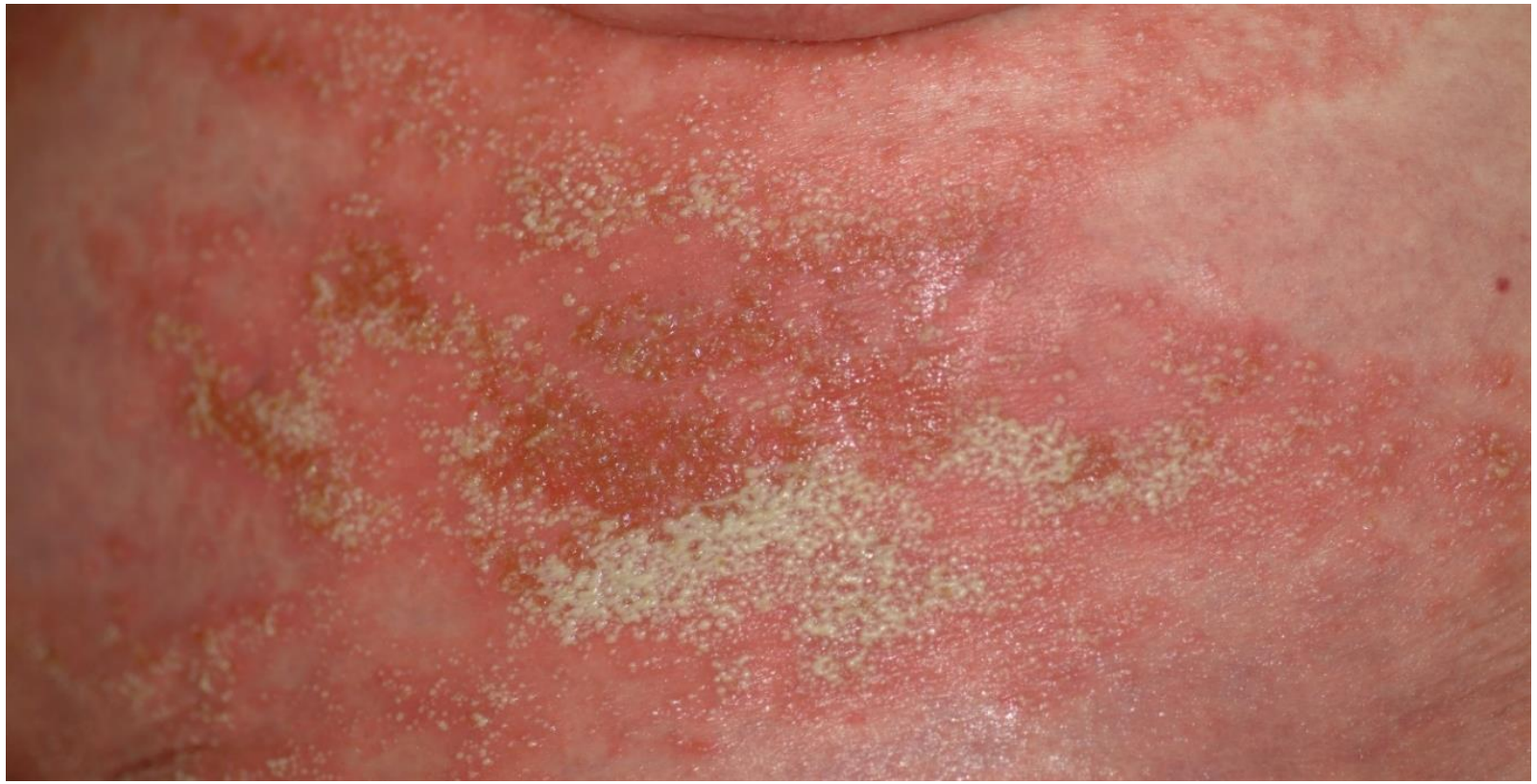
Case:

- Patient, 55 years of age, ♂
- Plaque psoriasis (PASI-12) and palmoplantar pustular psoriasis (PPP)
- Anti-TNF therapy with good clinical response of plaque psoriasis (PASI-3)
- **PPP remains anti-TNF resistant**



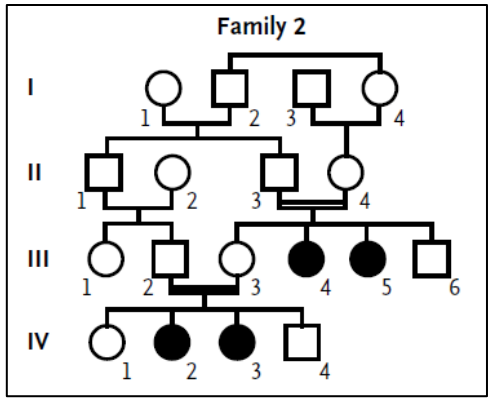
Pustular Psoriasis

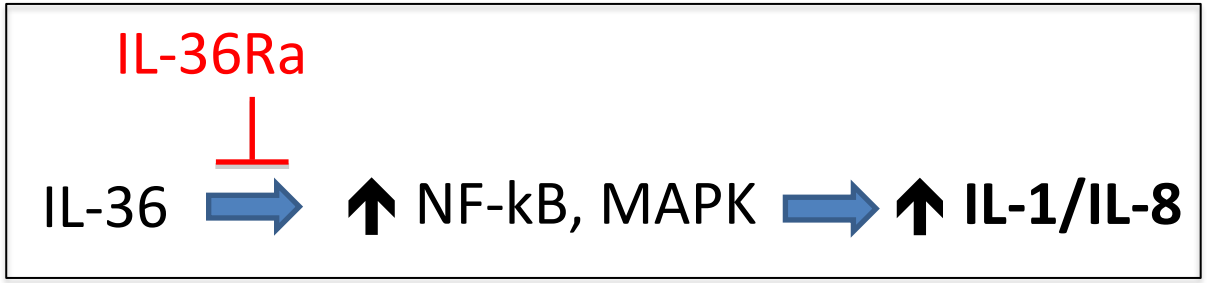
Does pustular psoriasis represent a different form of psoriasis?



Generalized pustular psoriasis: *IL36RN* mutations

- 9 Tunisian families with GPP
- Mutation of *IL36RN*[1]
- *IL36RN* mutations in sporadic GPP cases[2]

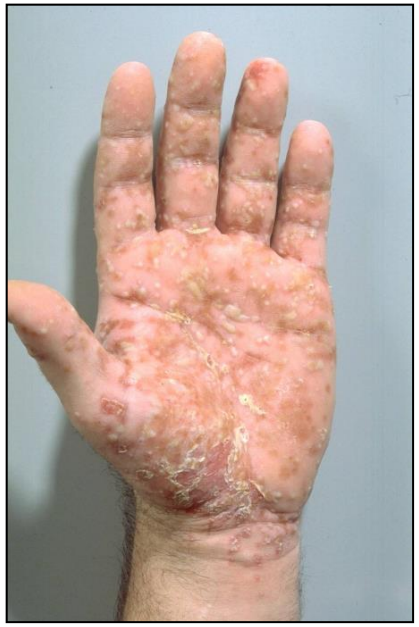


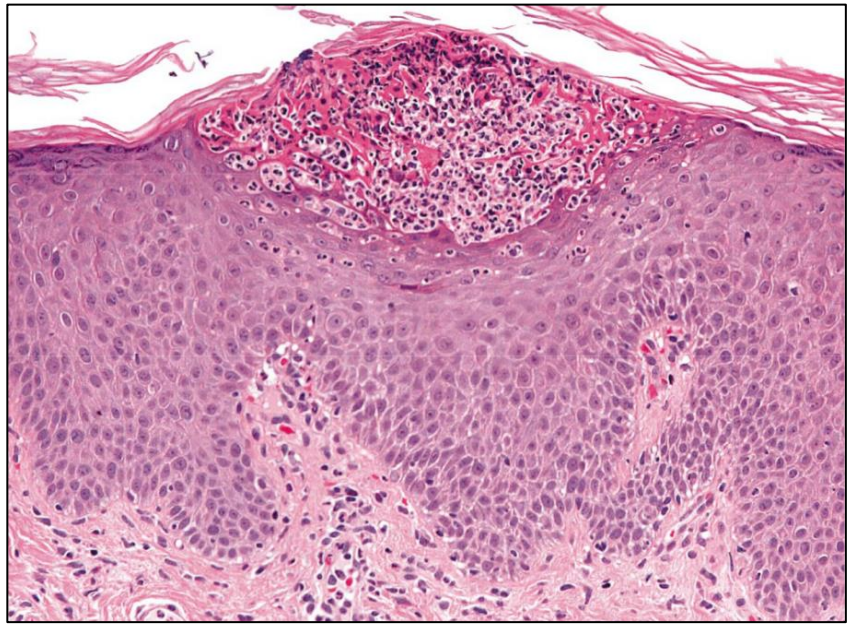


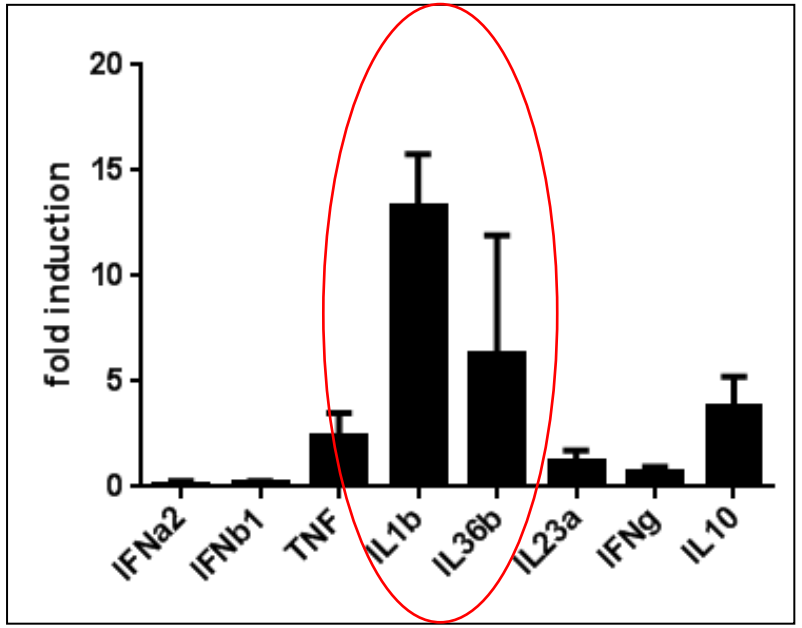
1. Marrakchi S, et al. *N Engl J Med* 2011; 2. Onoufriadis A, et al. *Am J Hum Genet* 2011.

Pustular psoriasis: IL-36/IL-1 pathway

Anti-TNF resistant PPP





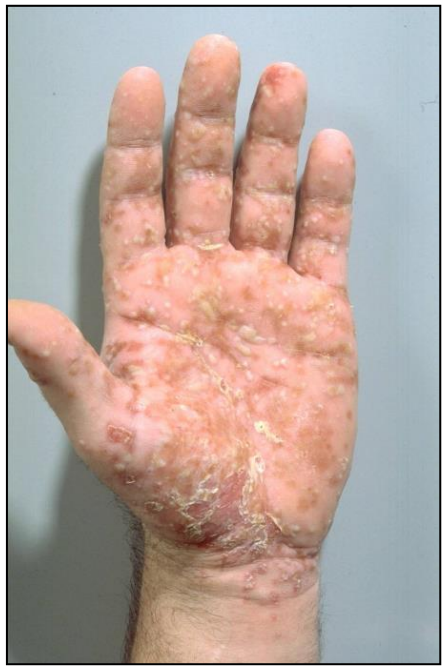


Conrad and Gilliet, *unpublished data*

Pustular psoriasis: IL-36/IL-1 pathway

Palmoplantar pustular psoriasis:

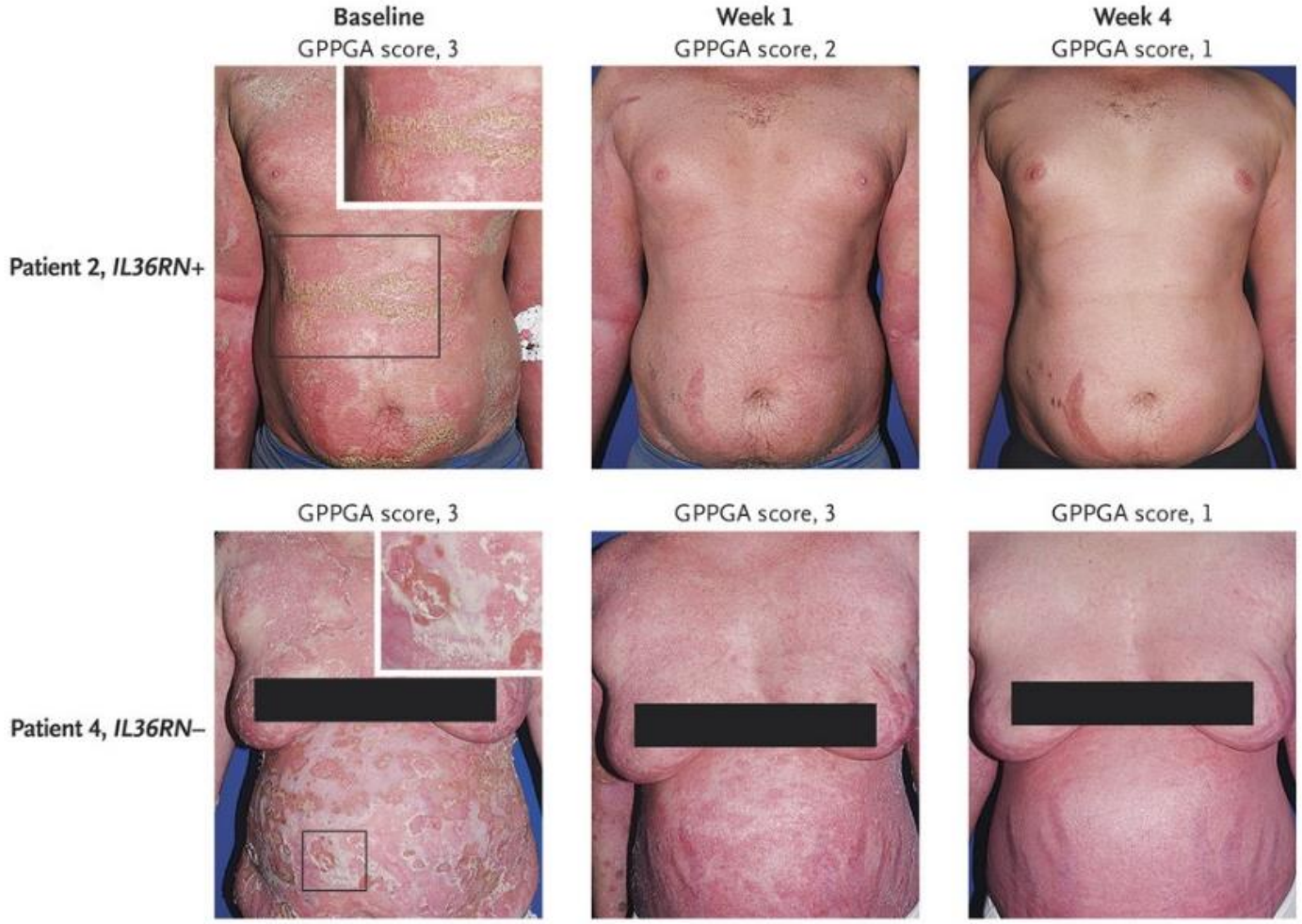
- increased expression of IL-36
- decreased expression of IL-17 and IL-22



⟹ IL-1/IL-36 inflammatory axes are the main drivers in (palmoplantar) pustular psoriasis

Johnston A, et al. *J Dermatol Sci* 2017.

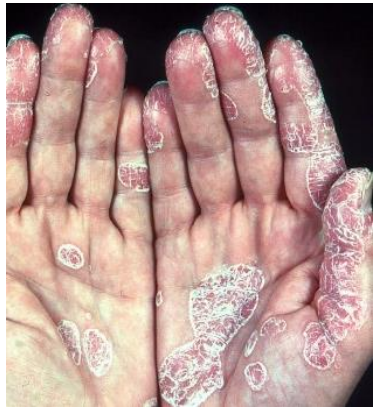
Anti-IL36R – Generalized Pustular Psoriasis



Single intravenous dose of BI 655130 (10mg/kg), a monoclonal antibody against the IL-36 receptor

H Bachelez et al. *N Engl J Med* 2019

Inflammatory pathways in psoriasis



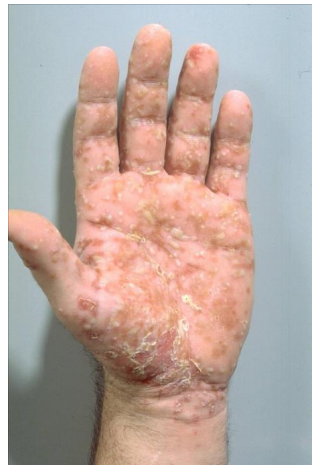
Chronic (plaque)

TNF/IL-17/IL23

PSORIASIS

IFN-α

IL-36/IL-1



Acute

(unstable, erythrodermic, paradoxical)

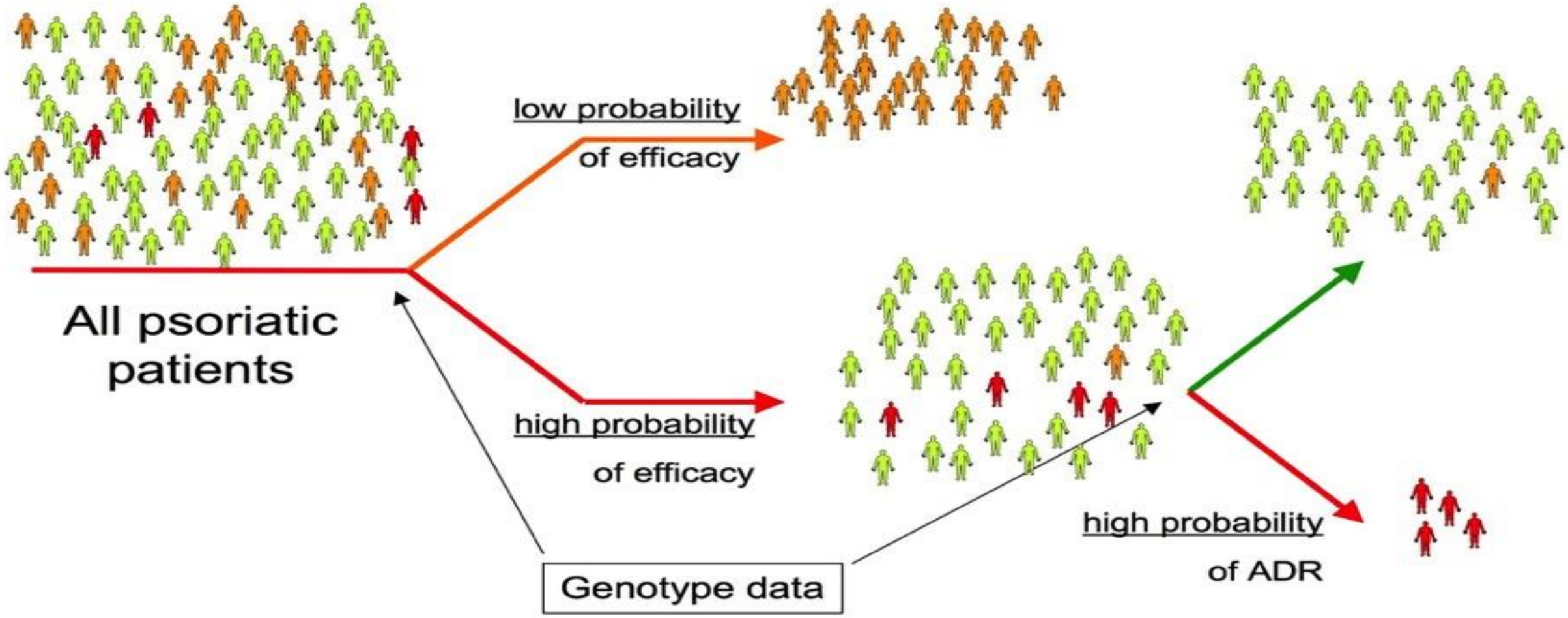
Pustular

(GPP, PPP)

Adapted from 1. Conrad C & Gilliet M *Schweiz Med Forum* 2016; 2. Mylonas A & Conrad C. *Front Immunol* 2018.

How to choose the right treatment?

STRATIFIED MEDICINE



Right medicine, right dose to right patient

THERAPEUTICS

BJD
British Journal of Dermatology

Pharmacogenetics of psoriasis: HLA-Cw6 but not LCE3B/3C deletion nor TNFAIP3 polymorphism predisposes to clinical response to interleukin 12/23 blocker ustekinumab

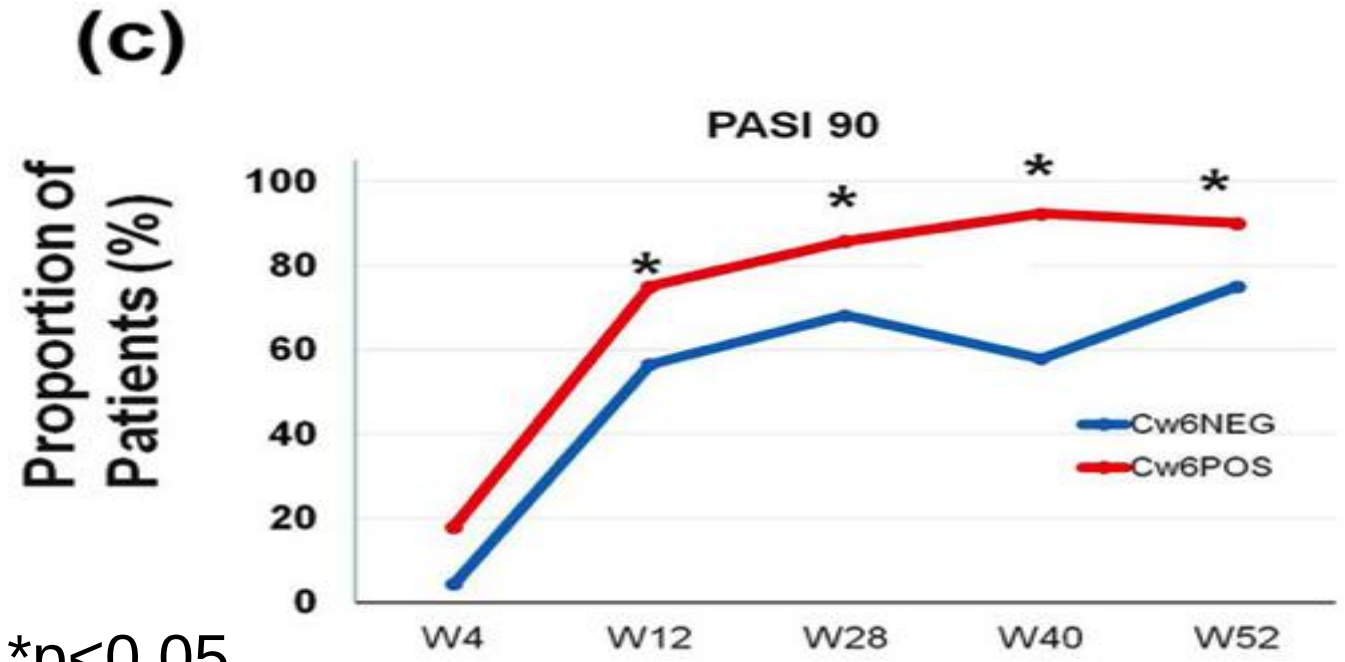
M. Talamonti,[1] E. Botti,[1] M. Galluzzo,[1] M. Teoli,[1] G. Spallone,[1] M. Bavetta,[1] S. Chimenti[1] and A. Costanzo[2]

[1]*Department of Dermatology, University of Rome Tor Vergata, Rome, Italy*
[2]*Dermatology Unit, NESMOS Department, Sapienza University of Rome, Via di Grottarossa 1037 00187, Rome, Italy*

Br J Dermatol. 2013 Mar 23. doi: 10.1111/bjd.12331. [Epub ahead of print]
PMID: 23521149 [PubMed – as supplied by publisher]

Patients harboring the HLA-Cw6 allele respond faster and better to Ustekinumab

HLA-Cw6



*p<0.05

Patients carrying HLA-Cw6 respond earlier and better to Ustekinumab

ORIGINAL ARTICLE

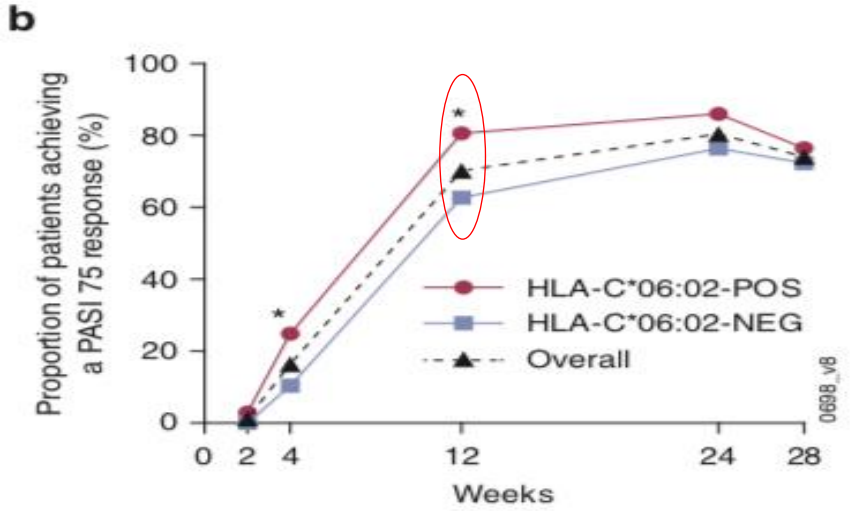
See related commentary on pg 2339

HLA-C*06:02 Allele and Response to IL-12/23 Inhibition: Results from the Ustekinumab Phase 3 Psoriasis Program

Katherine Li[1], C. Chris Huang[1], Bruce Randazzo[1], Shu Li[1], Philippe Szapary[1], Mark Curran[1], Kim Campbell[1] and Carrie Brodmerkel[1]

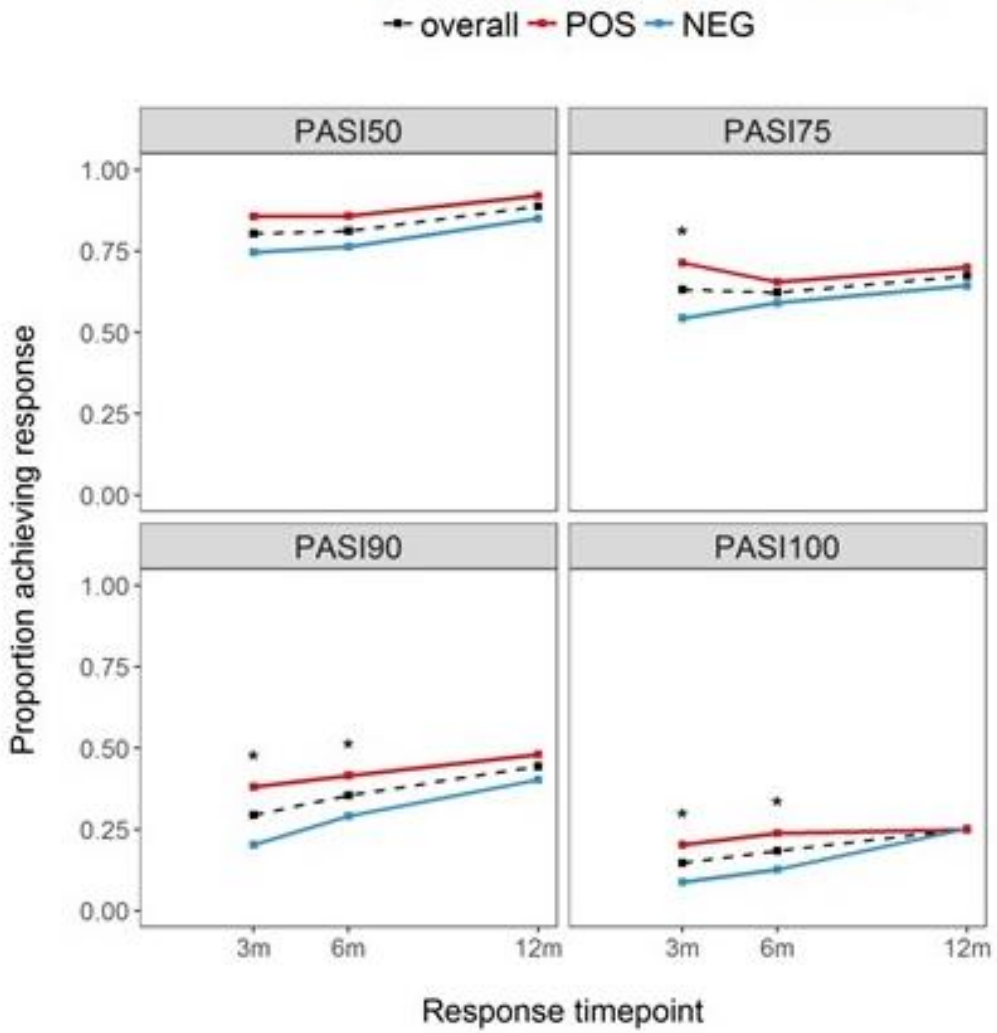
JID Open

A subset of patients from PHOENIX Registrative trials were genotyped for the presence of the HLA-Cw6 allele and their response to ustekinumab was stratified.



Week	2	4	12	24	28
N	331	330	332	255	254
HLA-C*06:02-POS	2.90	24.82	80.58	85.98	76.42
HLA-C*06:02-NEG	0.00	10.36	62.69	76.35	72.30
Overall	1.21	16.36	70.18	80.39	74.02
δ POS vs. NEG	2.90	14.46	17.89	9.63	4.12
δ POS vs. Overall	1.69	8.46	10.40	5.59	2.40

HLA-Cw6+ve patients have significantly faster and greater PASI 90 response compared to Cw6-ve



Permutation testing to preserve **Correlation Structure** between tests:

		Ustekinumab		
		3m	6m	12m
	n	163	223	187
PASI50	OR	2.10	1.92	2.12
	95% CI	0.98-4.47	0.99-3.73	0.87-5.19
	P_{perm}	0.2520	0.2817	0.3526
PASI75	OR	2.16	1.32	1.44
	95% CI	1.18-3.97	0.79-2.20	0.82-2.53
	P_{perm}	0.1036	0.5046	0.4702
PASI90	OR	**2.48**	1.68	1.51
	95% CI	**1.33-4.64**	1.00-2.83	0.90-2.56
	P_{perm}	**0.0377**	0.2846	0.3573
PASI100	OR	2.38	1.96	1.12
	95% CI	1.10-5.12	1.03-3.72	0.62-2.04
	P_{perm}	0.1995	0.2510	0.7016

P_{perm}(# same direction effects) = 0.0403

Dand et al J Allergy Clin Immunol 2019

Presented by Griffiths Euroderm Excellence 2019

HLA-Cw6 influences Guselkumab efficacy

VOYAGE 1 and 2, 1443 subjects were randomized to either guselkumab (100 mg at weeks 0 and 4 and every 8 weeks thereafter); placebo; or adalimumab (80 mg at week 0 and 40 mg at week 1, followed by 40 mg every other week thereafter).
Responses to guselkumab were evaluated at weeks 2, 4, 12, 16, 20, 24, and 28 in 519 Caucasian patients stratified by HLA-Cw6 status.

HLA-Cw6 positive patients respond better to Guselkumab

PASI 90 HLA-Cw6+ better at week 8, 12, 16 and 20 (max diff 18% week 8)

PASI 100 HLA-Cw6+ better at week 8, 12, 16, 22 and (max diff 15.2% week 20)

Association between HLA-Cw6 status and response to guselkumab in patients with moderate to severe plaque psoriasis. X.LiuS.DePrimoY.ChenS.LiE.Munoz-Elias JID Supplement IID 2018 Meeting abstracts https://doi.org/10.1016/j.jid.2018.03.458

1. Which category?

	PASI < 10, no sensitive areas, DLQI < 10	PASI > 10, chronic stable	PASI > 10 (or > 20?), inflammatory instable
1st therapeutic decision	Topical therapy, UV light	Conventional systemics	Biologics 1st line
2nd therapeutic decision	Conventional systemics (if wanted and in label)	Biologics 1st line or 2nd line	Biologics 1st line or 2nd line

2. Which conventional?

PsA, no liver damage	No PsA, no lymphopenia, oral preferred, flexibility	2nd line conventional, nails/ enthesitis, safety profile	Pustular (palmoplantar) with PUVA	Short term, no renal dysfunction
MTX	DMF	Apremilast	Retinoids	Ciclosporine

3. Which biologic?

Comorbidity level		Convenience level	
Candida or IBD	TNF/IL-12/23	Less frequent injections	IL-12/23
TBC or NYHA > 2	IL-17/17R/12/23	Super-quick response	IL-17/17R
Dominant PsA	TNF/IL-17/17R	Overall skin efficacy	IL-17/17R/23
Pregnancy	TNF/(IL-12)	Flexibility	IL-23

DLQI, Dermatology Life Quality Index; DMF, dimethyl fumarate; MTX, methotrexate; TBC, tuberculosis; TNF, tumour necrosis factor.

Information provided by K Eyerich.

Humanitas Dermatology

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Riccardo Borroni
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Federica Sanna
Chiara Perugini
Jessica Avagliano
Mario Valenti

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Andrea Cortese
Giovanni Fiorillo
Francesco Toso
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