

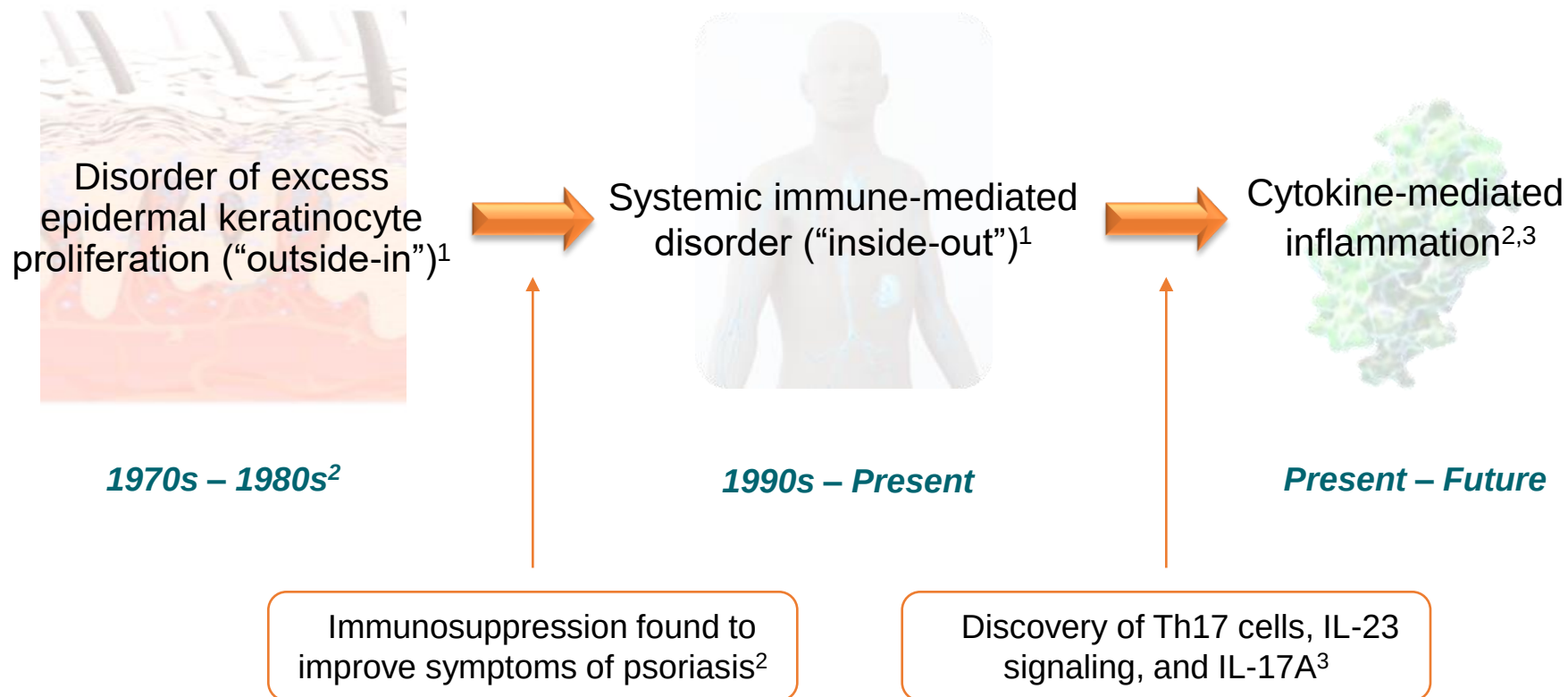
«Μεγαλομοριακοί βιολογικοί παράγοντες
ή ενδοκυττάρια στόχευση με μικρομόρια;

ΨΩΡΙΑΣΗ

Αικατερίνη Πατσατσή

Αναπληρώτρια Καθηγήτρια Δερματολογίας – Αφροδισιολογίας ΑΠΘ

Μοντέλο παθογένειας ψωρίασης: From 'Skin Deep' to Immune-Mediated



Nickoloff BJ, Nestle FO. *J Clin Invest.* 2004;113:1664-1675;

Griffiths CE, Barker JN. *Lancet.* 2007;370:263-271

Johnson-Huang LM et al. *Dis Model Mech.* 2012;5:423-433.

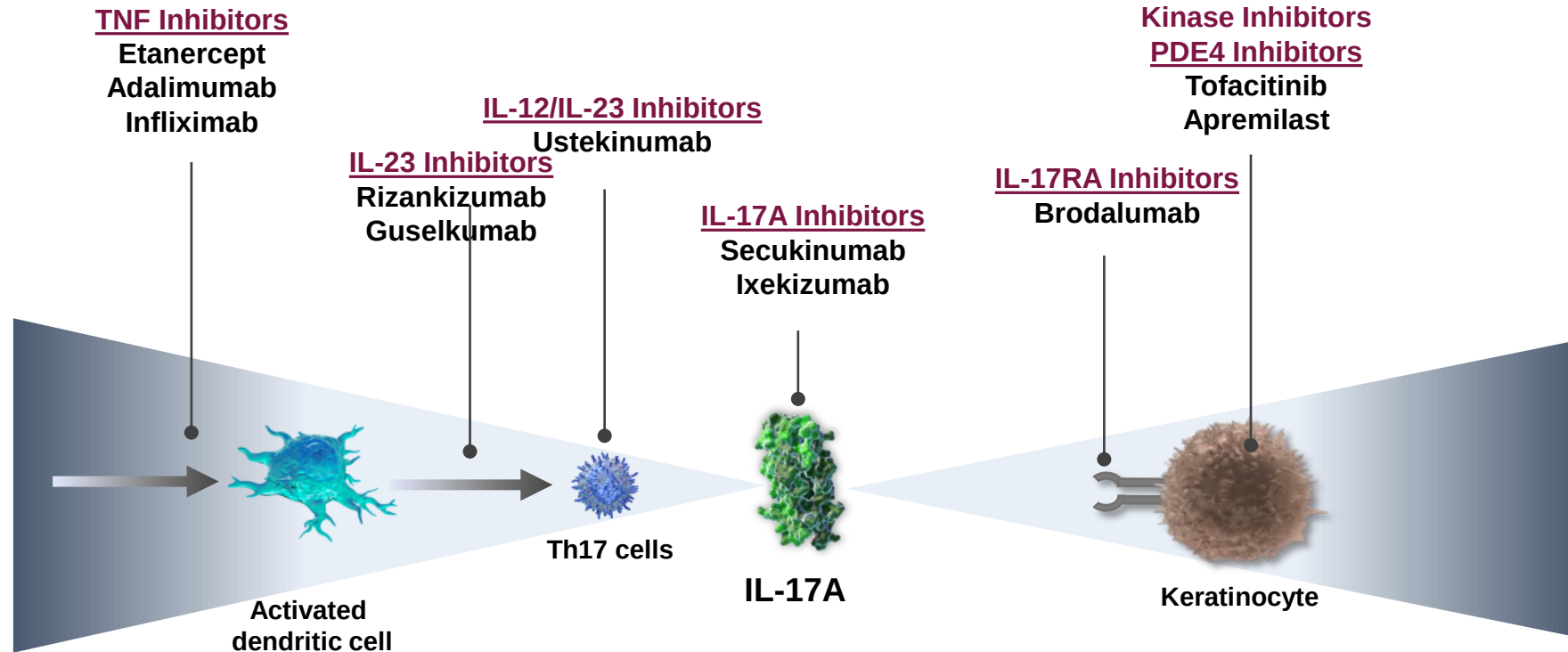
Psoriasis

Underlying Cause: A Complex Interplay

“The exact pathogenesis of plaque psoriasis remains to be fully determined, but it is thought to depend on **environmental** and **genetic** factors that stimulate dysregulated innate and adaptive immune responses in the skin.”

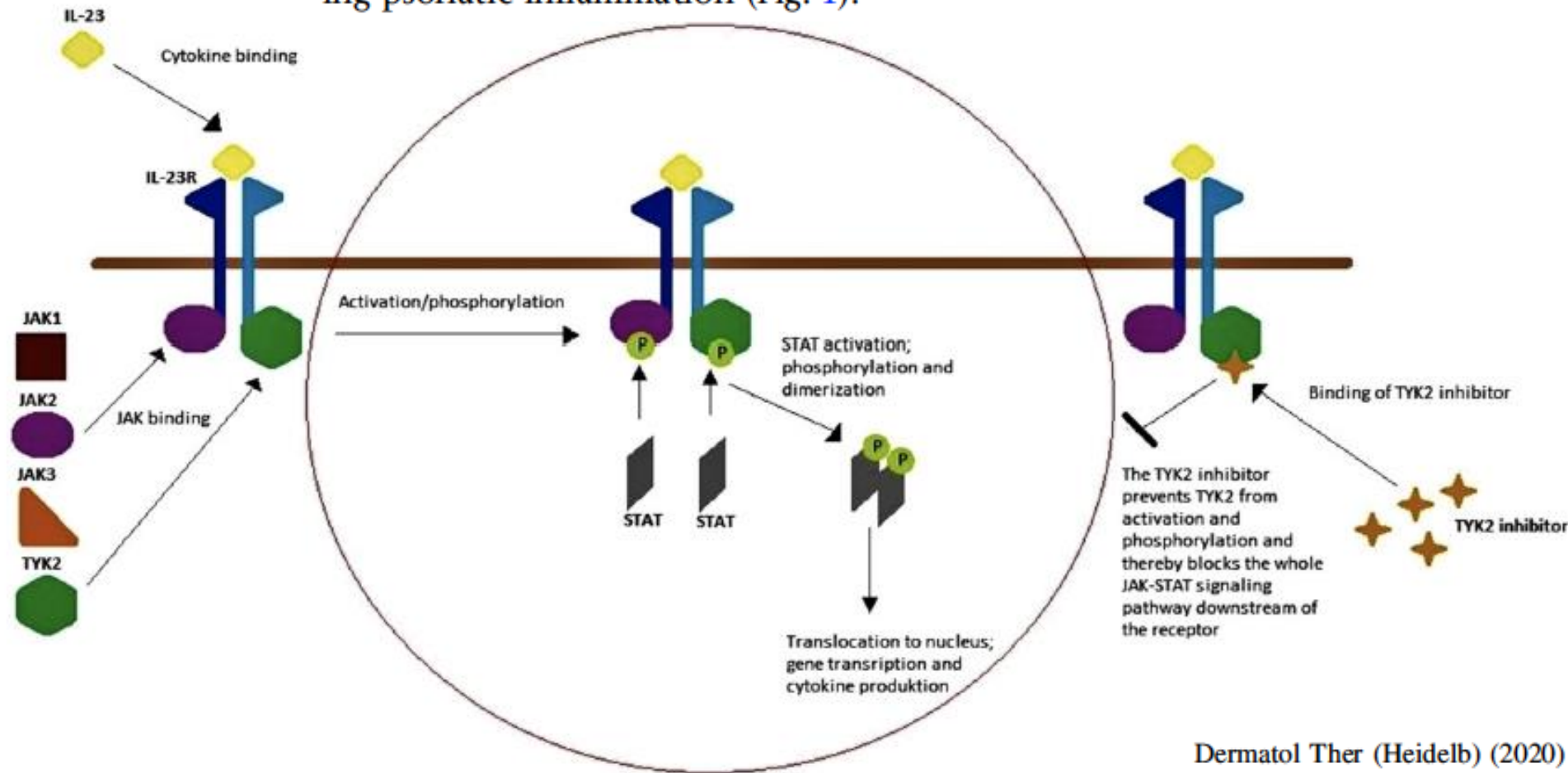
Girolomoni G et al. *Br J Dermatol*. 2012;167:717-724.

Σύγχρονη Θεραπευτική στην Ψωρίαση: ειδική στόχευση με οδηγό την τρέχουσα γνώση της παθοφυσιολογίας



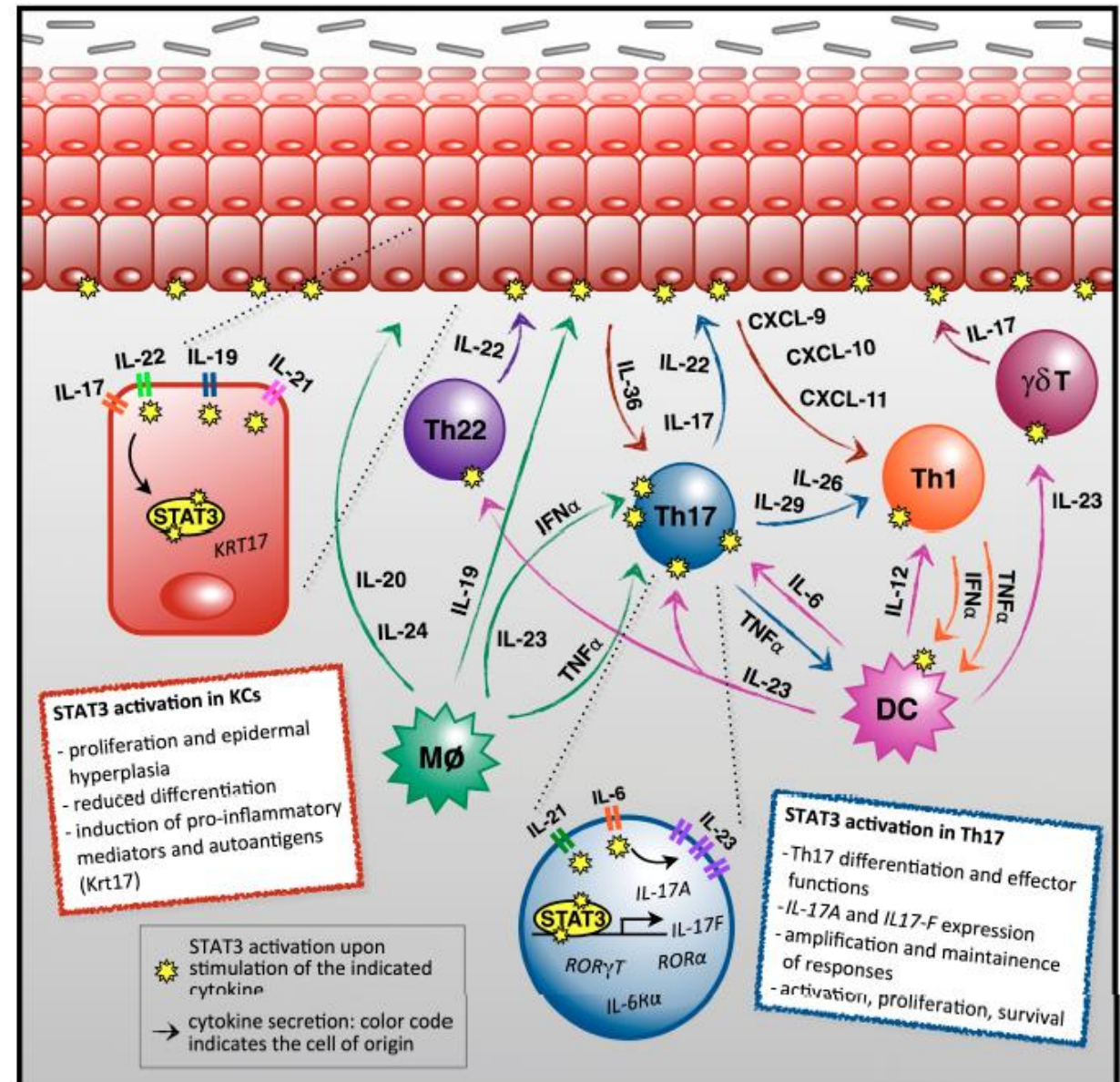
Systemic Treatment of Psoriasis with JAK Inhibitors: A Review

inhibition of JAKs results in inhibition of the signal pathway and gene transcription, leading to further production of inflammatory cytokines, thereby reducing psoriatic inflammation (Fig. 1).



Several biologics used for psoriasis, such as ustekinumab, secukinumab, ixekizumab, guselkumab, risankizumab, tildrakizumab, and brodalumab, target this axis. The IL-23 receptor relies on a heterodimer of JAK2 and TYK2 for signal transduction, thus highlighting the role of JAKs in the pathogenesis of psoriasis and the therapeutic potential of JAK inhibitors [10].

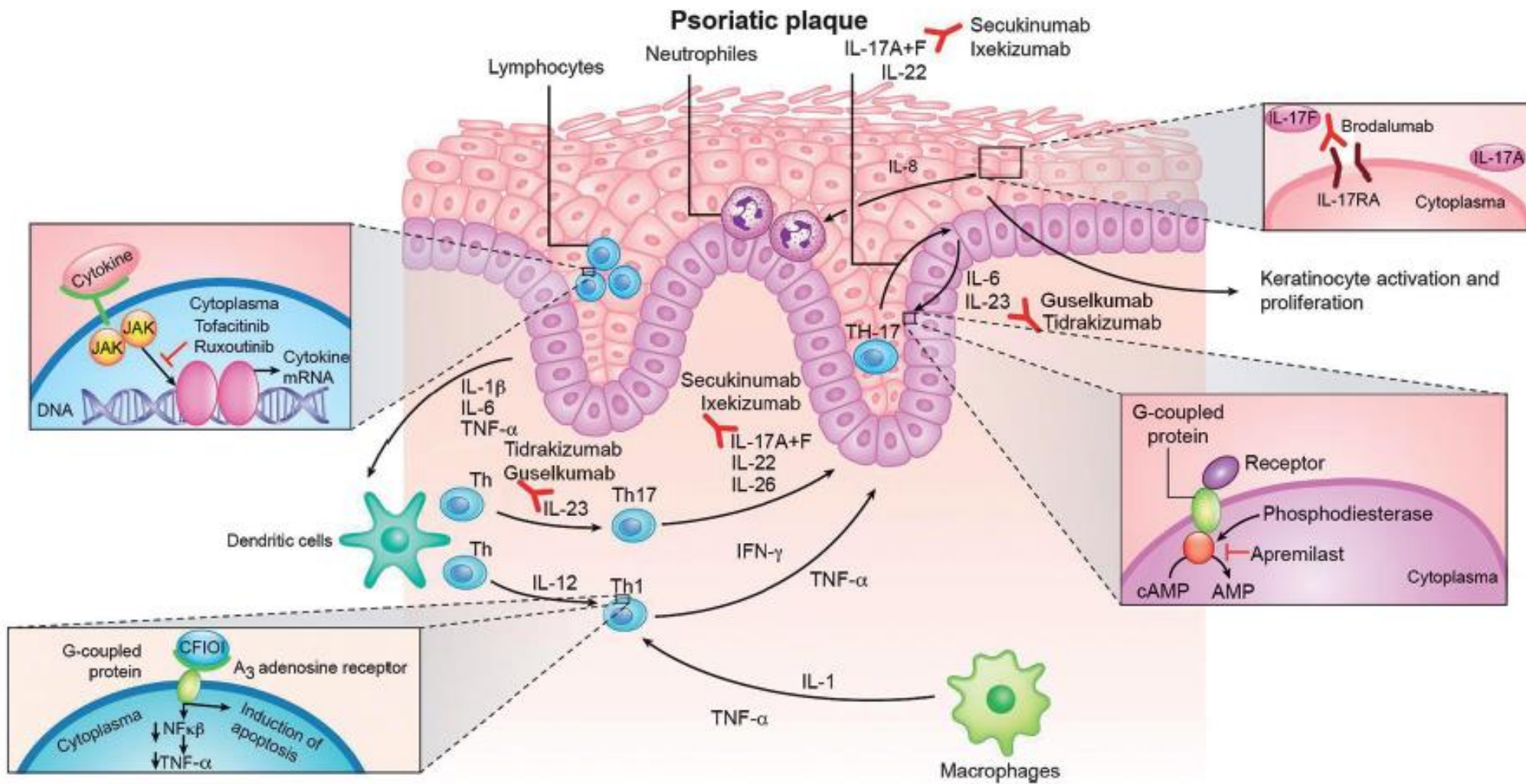
Psoriasis: A STAT3-Centric View

Enzo Calautti *, Lidia Avalle and Valeria Poli * 

New Drugs and Treatment Targets in Psoriasis

Kristian KOFOED, Lone SKOV and Claus ZACHARIAE

Department of Dermato-allergology, Gentofte Hospital, University of Copenhagen, Denmark



Newer small molecules

Group	Molecule	Molecule
PDE-4 inhibitors	Apremilast	Psoriasis, psoriatic arthritis
	Crisaborole	Atopic dermatitis
	Roflumilast	Chronic obstructive pulmonary disease
	RVT-501	Atopic dermatitis
JAK-STAT inhibitors	Tofacitinib	Rheumatoid and psoriatic arthritis, ulcerative colitis. Atopic dermatitis, alopecia areata, psoriasis, and vitiligo
	Ruxolitinib	Myelofibrosis, polycythemia vera. Atopic dermatitis, alopecia areata, psoriasis, and vitiligo
	Baricitinib	Psoriasis
Protein kinase C inhibitors	Sotrastaurin	Prevention of transplant rejection, psoriasis
Tyrosine kinase Inhibitors	Masitinib	Amyotrophic lateral sclerosis
	CT327	Pruritus in psoriasis
MAPK inhibitors	BMS-582949	Atherosclerosis
Adenosine A3 receptor agonist	CF101	Rheumatoid arthritis, and psoriasis
Fumaric acid esters		Psoriasis

Μικρά μόρια και Βιολογικοί Παράγοντες Κύριες Διαφορές

Παράμετροι	Μικρά Μόρια	Βιολογικοί Παράγοντες
Μοριακό Βάρος	Μικρό <1000 Da	Μεγάλο >1000 Da
Χημική Σύνθεση	Οργανικό Μικρό Μόριο	Πρωτεΐνη
Στόχευση	Ενδοκυττάρια – λιγότερο ειδική	Εξωκυττάρια - Ειδική
Μηχανισμός Δράσης	Ενζυμική Αναστολή	Δέσμευση/ εξασθένιση
Ημίσεια Ζωή	Συνήθως σύντομη	Μακρά
Σταθερότητα	Συνήθως σταθερά	Ευαίσθησία σε θερμότητα/πρωτεάσες
Χορήγηση	Από του στόματος/τοπική	Παρεντερική
Ανοσογονικότητα	Όχι	Ναι
Κόστος Παρασκευής	χαμηλό/ποικίλλει	υψηλό

Οι
διαθέσιμες
θεραπίες
για την
ψωρίαση

Φωτοθεραπεία	Από του στόματος συστηματικές θεραπείες		Ενέσιμες συστηματικές θεραπίες
UVB / nb UVB	Κλασσικές θεραπίες	Μικρά μόρια	Βιολογικοί παράγοντες
PUVA	MTX	Απρεμιλάστη	Etanercept
	Κυκλοσπορίνη		Adalimumab
	Ασιτρετίνη		Infliximab
			Certolizumab Pegol
			Ustekinumab
			Secukinumab
			Brodalumab
			Ixekizumab
			Guselkumab
			Rizankizumab





THERAPY REVIEW

Tailored treatment options for patients with psoriatic arthritis and psoriasis: review of established and new biologic and small molecule therapies

Sarah Elyoussfi¹ · Benjamin J. Thomas¹ · Coziana Ciurtin²

Level of evidence classification (Oxford Centre of Evidence-based Medicine, 2009)

- 1a** Systematic reviews (with homogeneity) of randomized controlled trials
- 1b** Individual randomised controlled trials (with narrow confidence interval)
- 1c** “All or none” randomised controlled trials
- 2a** Systematic reviews (with homogeneity) of cohort studies
- 2b** Individual cohort study or low-quality randomized controlled trials (e.g. <80 % follow-up)
- 2c** “Outcomes” research; ecological studies
- 3a** Systematic review (with homogeneity) of case–control studies
- 3b** Individual case–control study
- 4** Case series (and poor quality cohort and case– control studies)
- 5** Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”

Treatment	Peripheral arthritis	Sacroiliitis and spinal disease	Enthesitis	Dactylitis	Nail involvement	Skin psoriasis
<i>TNF inhibitors</i>						
ADALIMUMAB	YES (*1a)				YES (*1a)	YES (*1a)
ETANERCEPT	YES (*1a)	YES (*1a)	YES (*1a)	YES (*1a)	YES (*1a)	YES (*1a)
CERTOLIZUMAB	YES (*1a)	YES (*1a)	YES (*1a)	YES (*1a)	YES (*1a)	YES (*1a)
GOLIMUMAB	YES (*1a)	YES (*1a)	YES (*1a)	YES (*1a)	YES (*1a)	YES (*1a)
INFLIXIMAB	YES (*1a)	YES (*1a)	YES (*1a)	YES (*1a)	YES (*1a)	YES (*1a)
<i>Phosphodiesterase 4 Inhibitors</i>						
APREMILAST	YES (*1a)		YES (*1b)	YES (*1b)	YES (*1b)	YES (*1a)
<i>IL inhibition</i>						
USTEKINUMAB	YES (*1a)	YES (*1b)	YES (*1b)	YES (*1b)		YES (*1a)
BRODALUMAB	YES (*1b)	YES (*1b)	NO (*1b)	NO (*1b)		
IXEKIZUMAB	Ongoing study		Ongoing study	Ongoing study	Ongoing study	YES (*1a)
SECUKINUMAB	YES (*1a)	YES (*1a)	YES (*1a)	YES (*1a)		
TOCILIZUMAB	YES (*4)	NO (*1b)				YES (pustular psoriasis) (*4)
<i>Small molecule inhibitors</i>						
TOFACITINIB	Ongoing studies	Under recruitment in AS	Ongoing studies	Ongoing studies		YES (*1a)



Cochrane
Library

Cochrane Database of Systematic Reviews

Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis (Review)

Sbidian E, Chaimani A, Garcia-Doval I, Do G, Hua C, Mazaud C, Droitcourt C, Hughes C, Ingram JR, Naldi L, Chosidow O, Le Cleach L

Cochrane Database of Systematic Reviews 2017, Issue 12. Art. No.: CD011535.

In terms of reaching PASI 90, the biologic treatments anti-IL17, anti-IL12/23, anti-IL23, and anti-TNF alpha were significantly more effective than the small molecules and the conventional systemic agents. Small molecules were associated with a higher chance of reaching PASI 90 compared to conventional systemic agents.

Επίτευξη PASI 90

**σημαντικά πιο αποτελεσματικοί οι βιολογικοί παράγοντες
(anti – IL 17, anti- IL 12/23, anti-TNF)
από τα μικρά μόρια και τις κλασικές θεραπείες**

At drug level, in terms of reaching PASI 90, all of the anti-IL17 agents and guselkumab (an anti-IL23 drug) were significantly more effective than the anti-TNF alpha agents infliximab, adalimumab, and etanercept, but not certolizumab. Ustekinumab was superior to etanercept. No clear difference was shown between infliximab, adalimumab, and etanercept. Only one trial assessed the efficacy of infliximab in this network; thus, these results have to be interpreted with caution. Tofacitinib was significantly superior to methotrexate, and no clear difference was shown between any of the other small molecules versus conventional treatments.

Επίτευξη PASI 90

- **Υπεροχή των anti – IL 17 και anti- IL23 έναντι των anti-TNF (infliximab, adalimumab, etanercept)**
- **Υπεροχή του tofacitinib έναντι της μεθοτρεξάτης**
- **Μη σαφής διαφορά μεταξύ των υπόλοιπων μικρών μορίων έναντι των κλασικών θεραπειών**

Comparison of Biologics and Oral Treatments for Plaque Psoriasis

A Meta-analysis

April W. Armstrong, MD, MPH; Luis Puig, MD; Avani Joshi, PhD; Martha Skup, PhD; David Williams, MD;
Junlong Li, PhD; Keith A. Betts, PhD; Matthias Augustin, MD

Key Points

Question What is the short-term and long-term comparative efficacy among biologics and oral agents for plaque psoriasis?

Findings In a network meta-analysis of 60 clinical trials for short-term efficacy, brodalumab, guselkumab, ixekizumab, and risankizumab-rzaa had the highest Psoriasis Area and Severity Index response rates at 10 to 16 weeks from baseline. A meta-analysis of long-term efficacy suggested that brodalumab, guselkumab, ixekizumab, and risankizumab-rzaa had the highest response rates at 44 to 60 weeks.

Meaning This study provides an assessment of both short-term and long-term comparative efficacy among treatments for moderate to severe plaque psoriasis which can help health care stakeholders optimize treatment regimens.

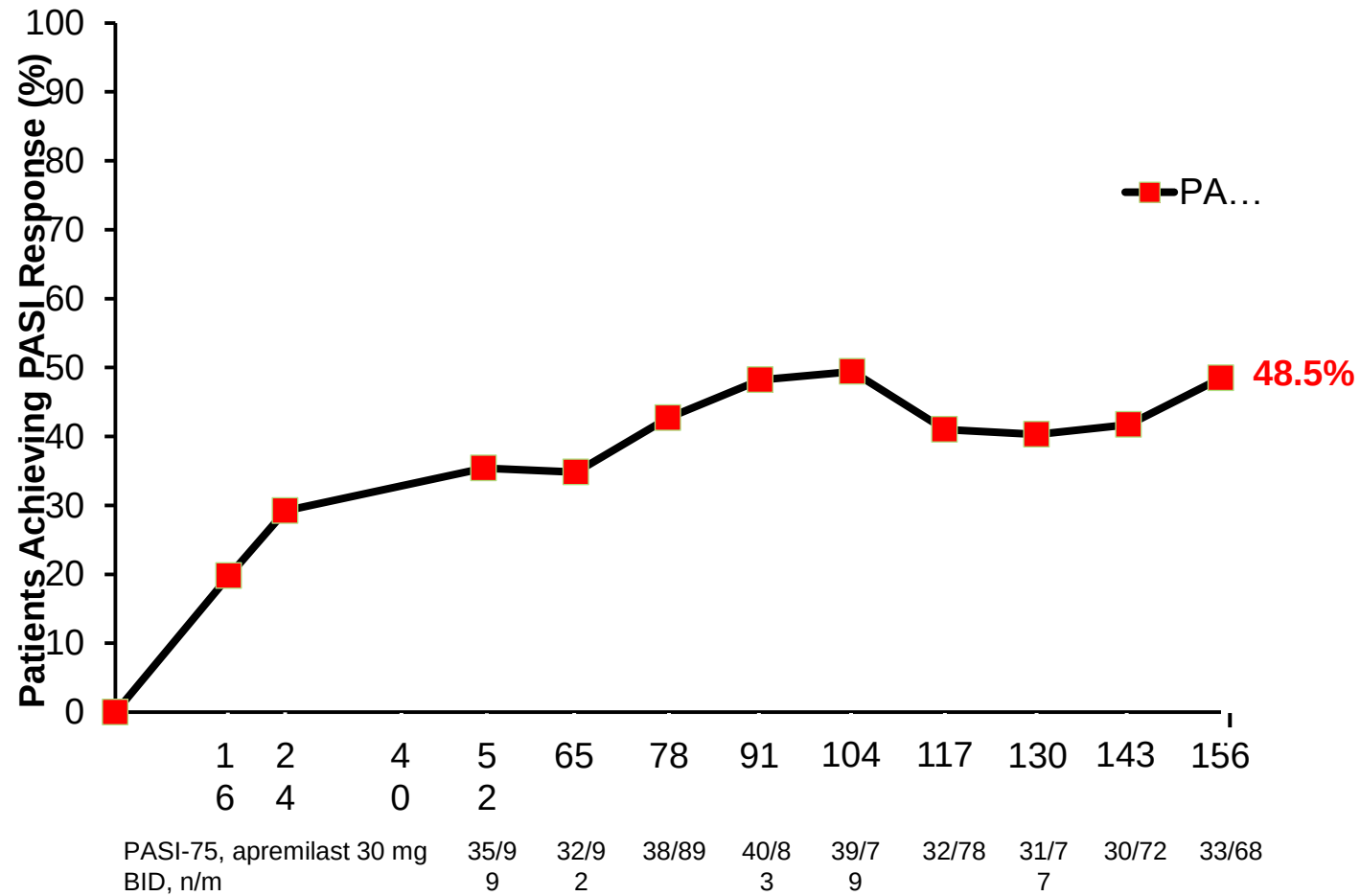
Table. Estimated Response Rates From the NMA of Short-term PASI (Base Case)

Treatment	Posterior Median, % (95% CrI)		
	PASI 75	PASI 90	PASI 100
Risankizumab-rzaa, 150 mg	89.2 (86.9-91.3)	71.6 (67.5-75.4)	40.4 (35.9-45.0)
Ixekizumab, 80 mg	88.8 (86.5-90.9)	70.8 (66.8-74.6)	39.5 (35.2-44.0)
Brodalumab, 210 mg	88.7 (86.5-90.8)	70.6 (66.8-74.6)	39.2 (35.2-43.9)
Guselkumab, 100 mg	86.8 (83.8-89.4)	67.3 (62.5-71.9)	35.7 (30.9-40.7)
Secukinumab, 300 mg	83.1 (80.2-85.7)	61.4 (57.2-65.6)	29.9 (26.3-33.9)
Infliximab, 5 mg/kg	80.4 (76.5-84.0)	57.4 (52.2-62.8)	26.5 (22.3-31.4)
Certolizumab pegol, 400 mg	71.1 (65.4-76.5)	45.6 (39.3-52.2)	17.7 (13.8-22.3)
Ustekinumab, 45 mg ≤100 kg, 90 mg >100 kg	69.7 (66.3-73.1)	43.9 (40.2-47.9)	16.7 (14.4-19.3)
Adalimumab, 40 mg	69.5 (66.0-72.6)	43.7 (40.0-47.4)	16.5 (14.2-19.0)
Certolizumab pegol, 200 mg	66.2 (59.6-72.4)	40.2 (33.5-47.2)	14.4 (10.7-18.8)
Tildrakizumab-asmn, 200 mg	64.9 (59.4-70.3)	38.8 (33.3-44.7)	13.6 (10.6-17.1)
Tildrakizumab-asmn, 100 mg	62.9 (57.3-68.4)	36.8 (31.4-42.5)	12.5 (9.7-15.8)
Etanercept, 25 mg twice weekly/50 mg once weekly	40.1 (35.4-45.1)	17.9 (14.9-21.4)	4.2 (3.1-5.4)
Apremilast, 30 mg	30.8 (26.8-35.0)	12.1 (9.9-14.7)	2.4 (1.8-3.1)
Dimethyl fumarate	29.6 (22.0-38.3)	11.4 (7.5-16.7)	2.2 (1.2-3.8)
Placebo	5.3 (4.8-5.9)	1.1 (1.0-1.2)	0.3 (0.2-0.4)

Απρεμιλάστη – Λόγοι επιλογής θεραπείας Αποτελεσματικότητα σε Κνησμό και Ειδικές Εντοπίσεις

- Μέτρια ψωρίαση
 - Ψωρίαση παλαμών – πελμάτων
 - Ψωρίαση τριχωτού
 - Ψωρίαση ονύχων
-
- Σημαντική ανακούφιση του κνησμού

Μακροχρόνια αποτελεσματικότητα απρεμιλάστης(PASI-75) στα 3 έτη (Μελέτη PALACE 3 -ασθενείς με BSA ≥3% στην έναρξη)

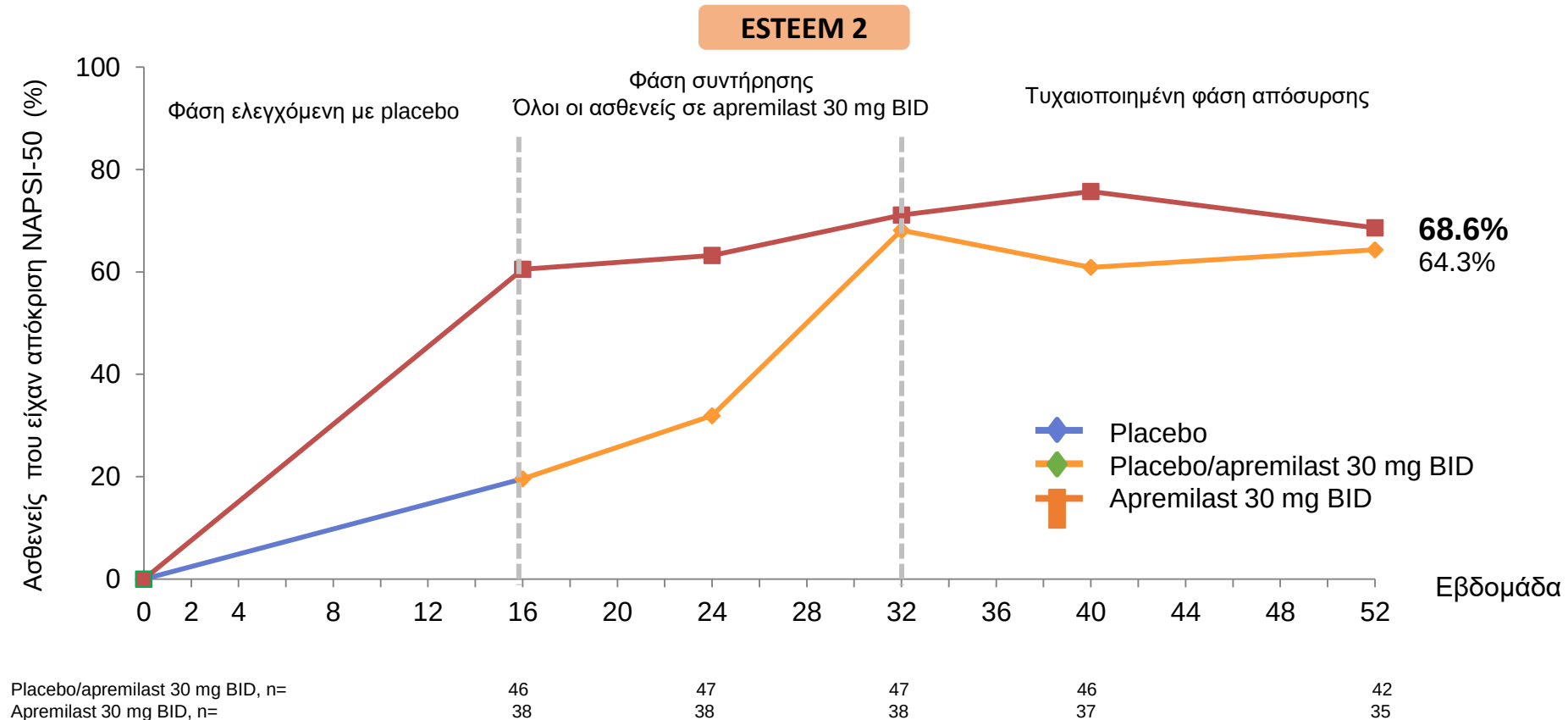


Analyses include all patient data, including the placebo-controlled period, regardless of when patients started taking apremilast (baseline, Week 16, or Week 24).

n/m=number of responders/number of patients with sufficient data for evaluation.

Edwards CJ, et al. EULAR 2016 [poster THU0435].

Αποτελεσματικότητα απρεμιλάστης στην ψωρίαση ονύχων



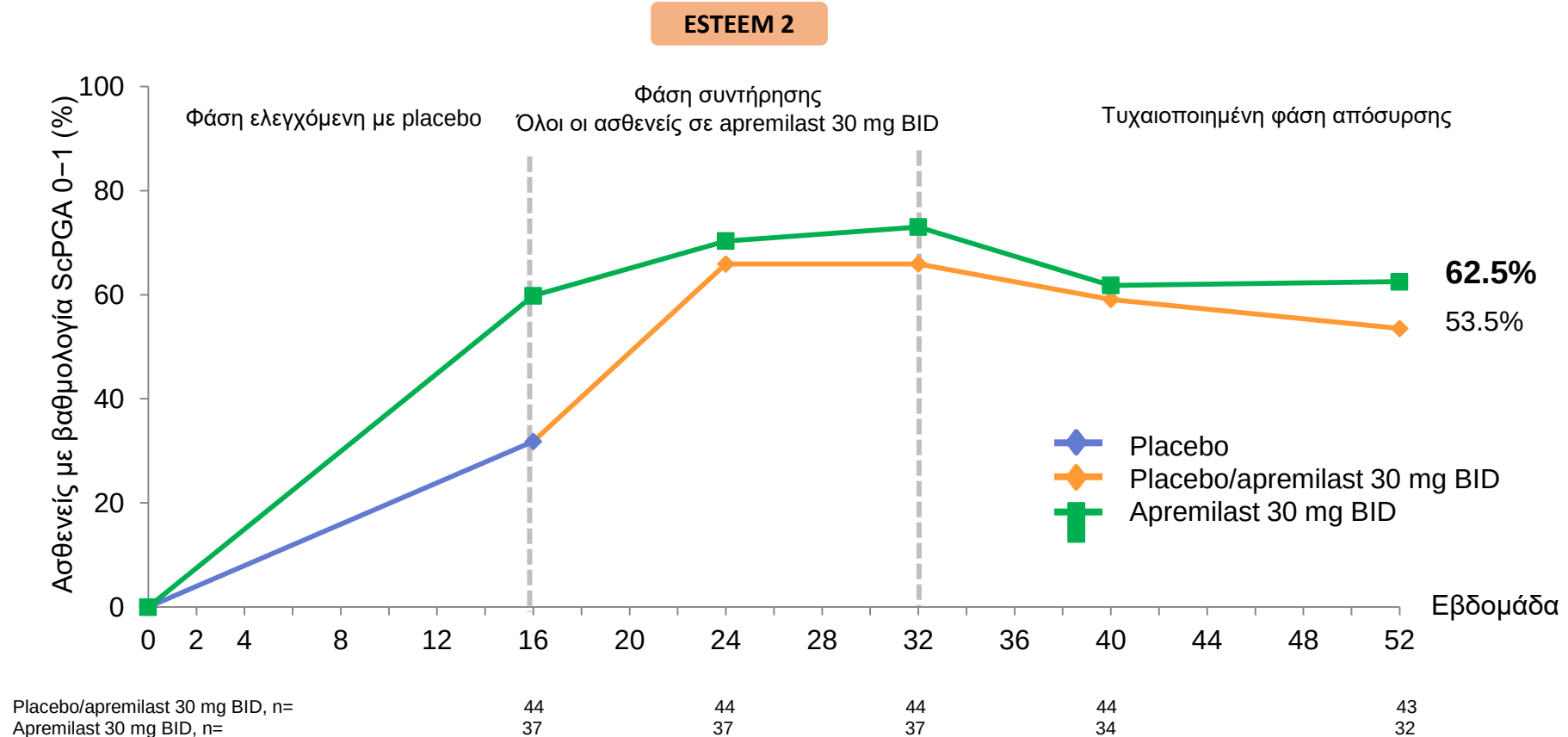
Full analysis set

Patients with a NAPSΙ score ≥ 1 at baseline

PASI=Psoriasis Area and Severity Index; BID=twice daily; NAPSΙ=Nail Psoriasis Severity Index

Crowley J A et al. Poster presented at the 73rd Annual Meeting of the American Academy of Dermatology, 20-24 March 2015, San Francisco, CA (894)

Αποτελεσματικότητα απρεμιλάστης στην ψωρίαση του τριχωτού



Full analysis set

Patients with moderate to very severe scalp psoriasis at baseline (ScPGA score ≥ 3)

PASI=Psoriasis Area and Severity Index; BID=twice daily; ScPGA=Scalp Physician Global Assessment

Crowley JA et al. Poster presented at the 73rd Annual Meeting of the American Academy of Dermatology, 20-24 March 2015, San Francisco, CA (894)

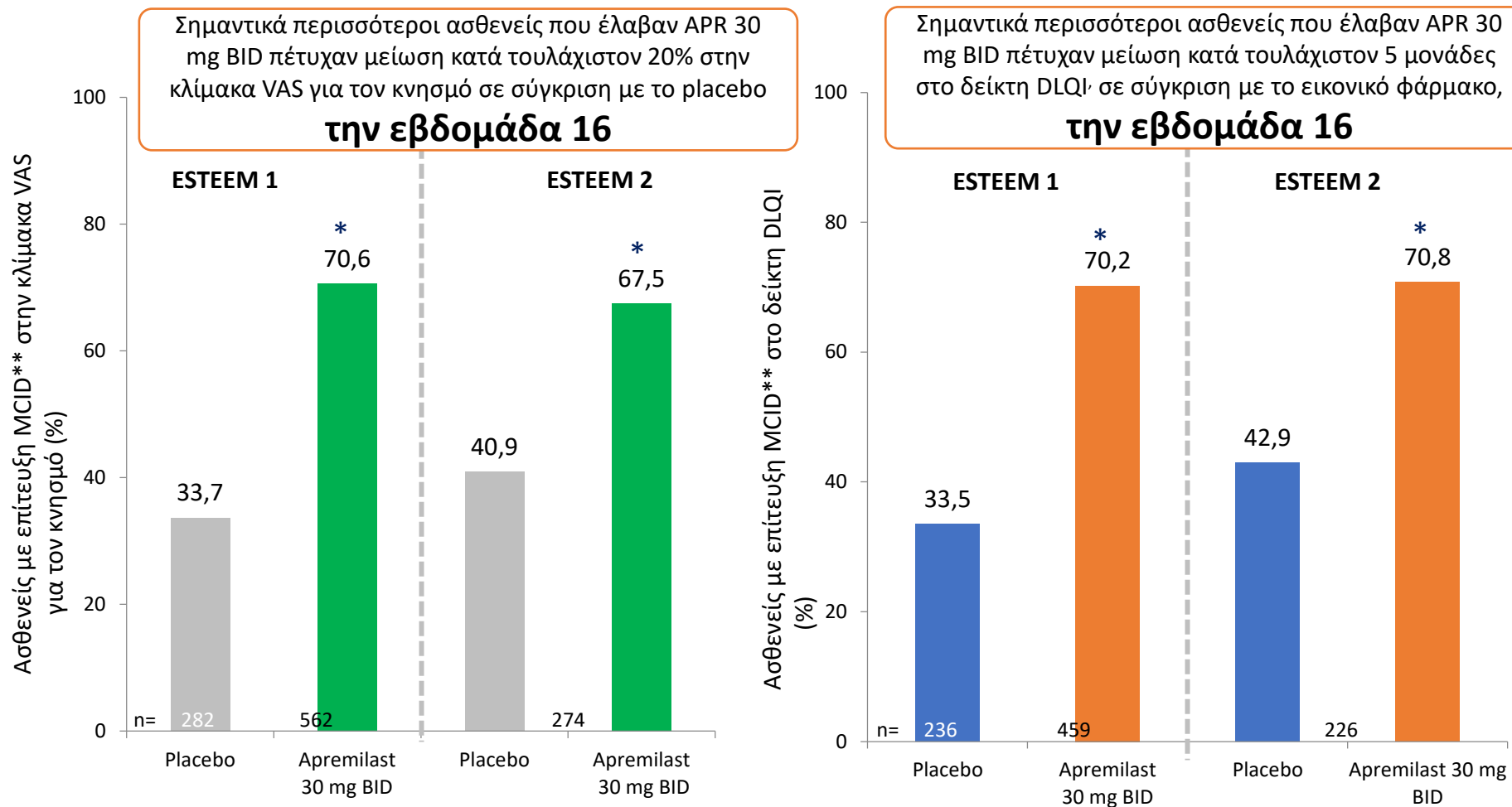
Αποτελεσματικότητα απρεμιλάστης στην ψωρίαση παλαμών - πελμάτων



n=ασθενείς που πέτυχαν PPGA 0 ή 1 με βελτίωση ≥ 1 από την αρχική τιμή
m=ασθενείς με αρχική βαθμολογία PPGA ≥ 1

† Συνολική Εκτίμηση του Ιατρού για την Ψωρίαση σε παλάμες και πέλματα (Palmoplantar Psoriasis Physician Global Assessment)

Αποτελεσματικότητα απρεμιλάστης στην ανακούφιση του κνησμού



** Ελάχιστα κλινικά σημαντική διαφορά: Μεταβολή $\geq 20\%$ στην Οπτική Αναλογική Κλίμακα (VAS) για τον κνησμό και βελτίωση κατά τουλάχιστον 5 μονάδες του DLQI

* $p < 0.001$ vs. placebo

Feldman SR et al. Poster presented at the 73rd Annual Meeting of the American Academy of Dermatology, 20–24 March 2015, San Francisco, CA (1092)

Systemic Treatment of Psoriasis with JAK Inhibitors: A Review

Jak - αναστολείς
Αποτελεσματικότητα
στην ψωρίαση

- 5 κλινικές δοκιμές με tofacitinib στη μέτρια - σοβαρή ψωρίαση κατά πλάκας, μια φάσης II και τέσσερις φάσης III
- **Φάση II**: PASI 75 στην εβδομάδα 12 σε 25.0% (2 mg X 2/ημ), 40.8% (5 mg X 2/ημ), και 66.7% (10 mg X 2/ημ)
- **Φάση III**: PASI 75 στις εβδομάδες 16-24 σε 39.5–54.3% (5 mg X 2/ημ) και 59.2–81.1% (10 mg X 2/ημ)

Systemic Treatment of Psoriasis with JAK Inhibitors: A Review

- Οι Jak αναστολείς δεν φαίνεται να μπορούν να επιτύχουν υψηλά ποσοστά κάθαρσης του ψωριασικού δέρματος (πχ PASI 90) αντίστοιχα των νεότερων βιολογικών παραγόντων
- Φαίνεται να μπορούν να επιτύχουν καλύτερα αποτελέσματα από την απρεμιλάστη και την ετανερσέπτη
- Έχουν θέση στη θεραπευτική φαρέτρα, καθώς λαμβάνονται από του στόματος και είναι φθηνότερα

The number of studies on JAK inhibitors for psoriasis remains limited. Many of the drugs tested have only been examined in phase 2 trials and it is doubtful that they will be tested further. Only tofacitinib has been tested to phase 3, and several phase 3 trials are currently in progress for the TYK2 inhibitor BMS-986165. The selective TYK2 inhibitor BMS-986165 has shown the highest efficacy towards psoriasis of any JAK inhibitor to date, with a PASI75 response of 75% after 12 weeks of treatment in a phase 2 trial [17]. Tofacitinib is the most studied JAK inhibitor for the treatment of psoriasis, with four reported phase 3 trials showing considerable efficacy in terms of the PASI75 response, especially at a high dose of 10 mg twice daily [13–16]. Other JAK inhibitors have also been tested for psoriasis; these have yielded PASI75 responses that are less than or similar to that achieved with tofacitinib. However, none of these have been tested beyond phase 2 [18–21].

Small Molecules and Biologics in the Treatment of Nail Psoriasis

Skin Appendage Disord 2020;6:134–141

Dimitrios Rigopoulos Anna Stathopoulou Stamatios Gregoriou

1st Department of Dermatology-Venereology, Andreas Sygros Hospital, Faculty of Medicine, National and Kapodistrian University of Athens, Athens, Greece

Table 1. Major studies with small molecules and biologics in the treatment of nail PsO

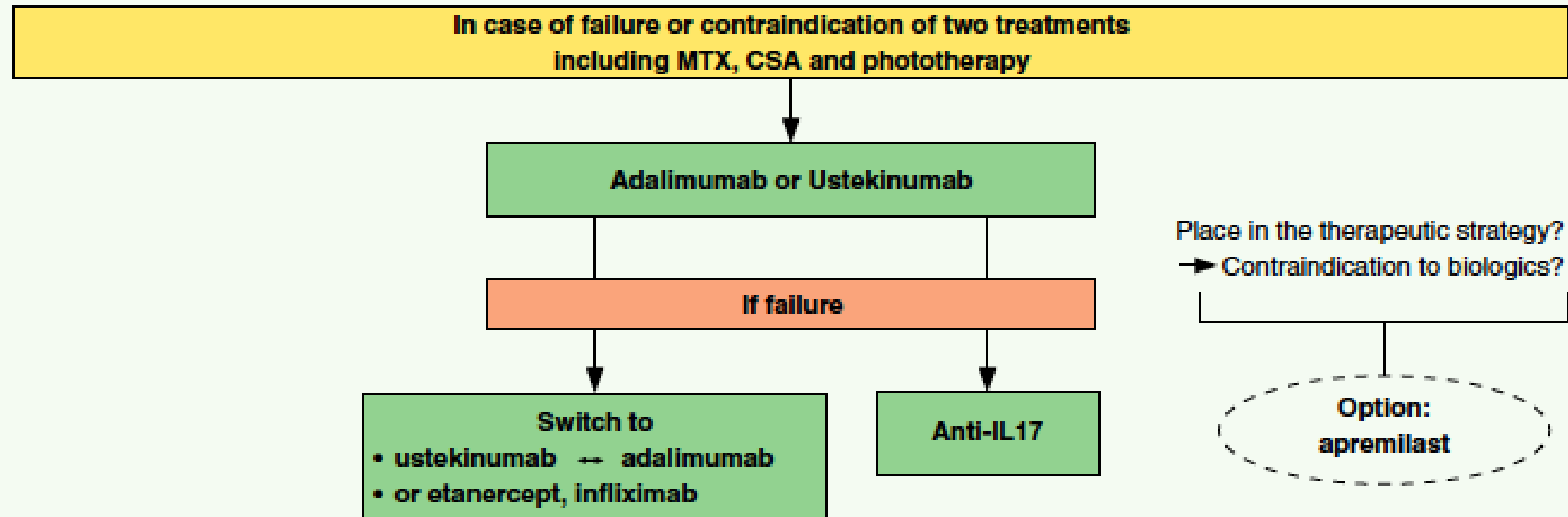
Study	Drug	Patients	NAPSI improvement
Rich P. et al. [13]	Apremilast	1,255	Week 15 NAPSI >50
Reich K. et al. [14]	Apremilast	250	NAPSI mean change from baseline was –48.1 to –51.1%
Merola J.F. et al. [18]	Tofacitinib	1,196	At week 16, patients receiving tofacitinib 5 mg, 10 mg, and placebo achieved, respectively, NAPSI 50 (32.8, 44.2 vs. 12.0%), NAPSI 75 (16.9, 28.1 vs. 6.8%), and NAPSI 100 (10.3, 18.2 vs. 5.1%)
Elewski B.E. et al. [27]	ADA	217	At week 26 to week 52, total fingernail mNAPSI 75 improvement was 47.4–54.5%
Van den Bosch F. et al. [22]	ADA	442	At week 12, the median reduction in the NAPSI score was 57%
Thaçi D. et al. [25]	ADA	730	Decrease from baseline NAPSI at week 16 of 39.5% (9.4±164.5%)
Rich P. et al. [31]	Infliximab	305	Decrease of NAPSI –26.8% at week 10 and –57.2 at week 24
Rich P. et al. [40]	Ustekinumab	766	Improvements in NAPSI ranged from 29.7 to 57.3%
Reich K. et al. [49]	Secukinumab	198	Secukinumab 300 mg demonstrated the highest efficacy, with nearly 50% improvement of total fingernail NAPSI at week 16
Augustin M. et al. [50]	Secukinumab	904	At baseline, 33.3% of PsO patients had nail involvement and at year 1, only 15.6% patients were affected by nail PsO
Van de Kerkhof P. et al. [53]	Ixekizumab	1,346	At week 60, mean per cent NAPSI improvement was >80%, regardless of initial treatment

French guidelines on the use of systemic treatments for moderate-to-severe psoriasis in adults

JEADV 2019, 33, 464–483

F. Amatore,^{1,†} A.-P. Villani,^{2,†} M. Tauber,^{3,†}  M. Viguier,^{4,5,*} B. Guillot,^{5,6} on behalf of the Psoriasis Research Group of the French Society of Dermatology (Groupe de Recherche sur le Psoriasis de la Société Française de Dermatologie)

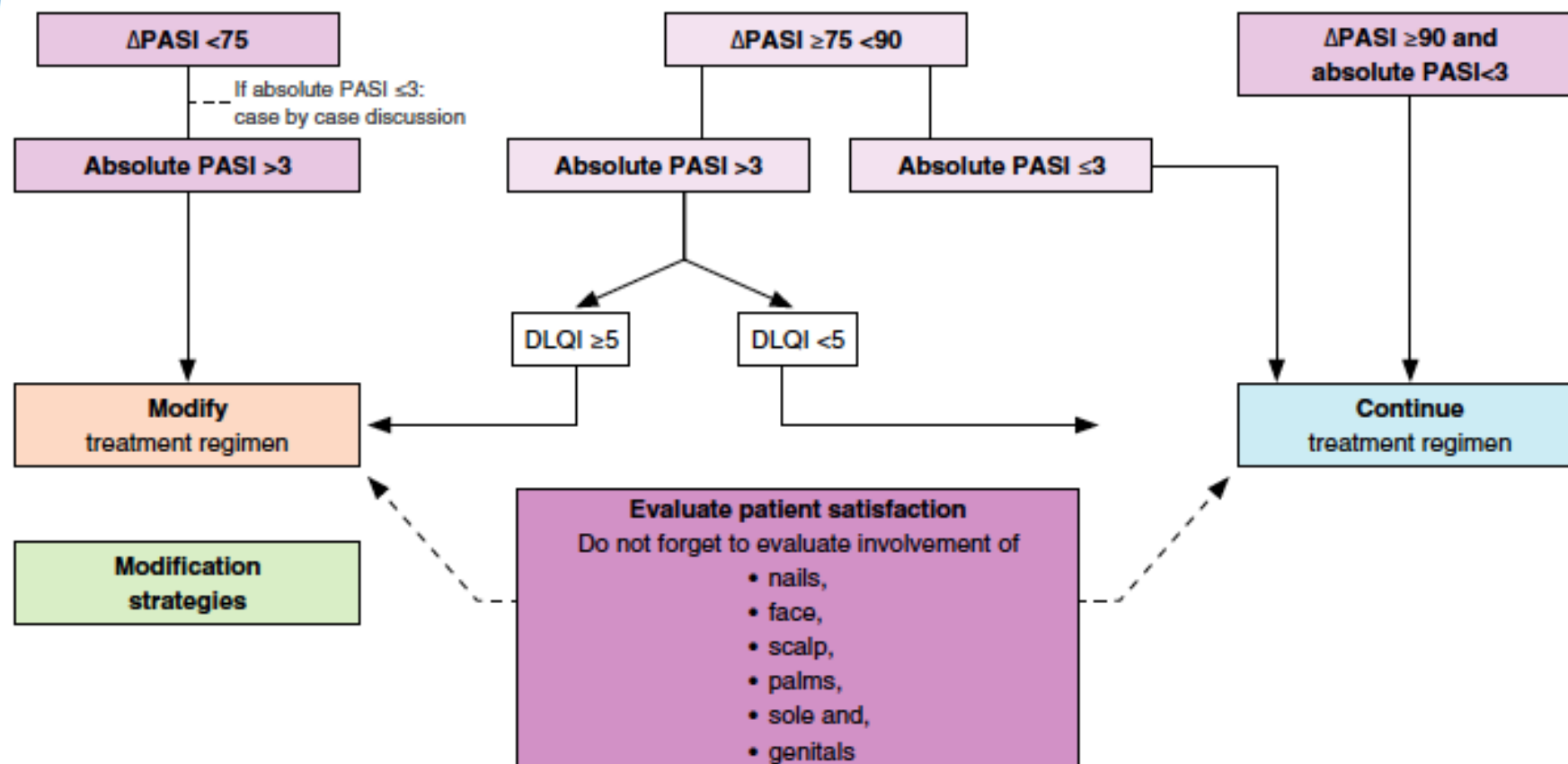
2nd line



French guidelines on the use of systemic treatments for moderate-to-severe psoriasis in adults

F. Amatore,^{1,†} A.-P. Villani,^{2,†} M. Tauber,^{3,†}  M. Viguier,^{4,5,*} B. Guillot,^{5,6} on behalf of the Psoriasis Research Group of the French Society of Dermatology (Groupe de Recherche sur le Psoriasis de la Société Française de Dermatologie)

(b)



Practical recommendations for systemic treatment in psoriasis according to age, pregnancy, metabolic syndrome, mental health, psoriasis subtype and treatment history (BETA-PSO: Belgian Evidence-based Treatment Advice in Psoriasis; part 1)

JEADV 2020, 34, 1654–1665

[illegible]

Practical recommendations for systemic treatment in psoriasis in case of coexisting inflammatory, neurologic, infectious or malignant disorders (BETA-PSO: Belgian Evidence-based Treatment Advice in Psoriasis; part 2)

JEADV 2020, 34, 1914–1923

	APR	IFX	ETA	ADA	CERT	USTE	GUS	RIS	TIL	SECU	IXE	BROD
PsA peripheral	A	A	A	A	A	A	A	A	B	A	A	A
PsA spine	A	A	A	A	A	A	A	A	NA	A	A	A
PsA enthesitis/dactylitis	A	A	A	A	A	A	A	A	B	A	A	A
Inactive IBD	C	A	C	A	A	A	C	A	C	C	C	C
Active IBD	C	A	A	A	A	A	C	A	C	A	A	A
HIV active	C	C	C	C	C	C	C	C	C	C	C	C
HIV non-active	B	B	B	B	B	B	B	B	B	B	B	B
Chronic Hep C	C	B	B	B	B	C	C	C	C	C	C	C
Chronic Hep B	B	B	B	B	B	B	NA	NA	NA	B	C	C
Latent TB	A	A	A	A	A	C	C	C	C	C	C	C
Demyelinating disease	NA	A	A	A	A	A	NA	NA	NA	C	NA	NA
Cancer	C	B	B	B	B	B	NA	NA	NA	NA	NA	NA

«Μεγαλομοριακοί βιολογικοί παράγοντες
ή ενδοκυττάρια στόχευση με μικρομόρια;

«Μεγαλομοριακοί βιολογικοί παράγοντες ή ενδοκυττάρια στόχευση με μικρομόρια;

- Οι νεότεροι μεγαλομοριακοί παράγοντες υπερτερούν σε ταχύτητα δράσης και ποσοστά επίτευξης PASI 90
- Η απρεμιλάστη είναι χρήσιμη στη μέτρια ψωρίαση και σε ειδικές εντοπίσεις
- Οι Jak αναστολείς φαίνεται να έχουν μέτρια – καλή επίτευξη κάθαρσης των δερματικών βλαβών
- Τρόπος χορήγησης – πλεονέκτημα ανάλογα με τον ασθενή
- **Κυριότερο κριτήριο επιλογής η έκταση της ψωρίασης και οι συννοσηρότητες**

