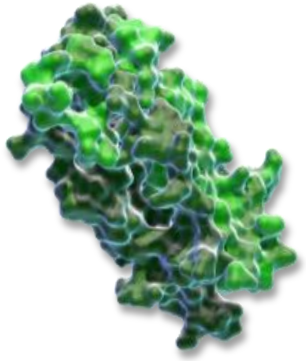

Ιντερλευκίνη-17Α : Ανακαλύπτοντας ένα νεο μονοπάτι στη θεραπεία της ψωρίασης.

ΑΓΓΕΛΙΚΗ ΜΠΕΦΟΝ
ΕΠΙΜΕΛΗΤΡΙΑ Α΄
ΔΕΡΜΑΤΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ ΕΣΥ
ΝΟΣΟΚΟΜΕΙΟ Α. ΣΥΓΓΡΟΣ

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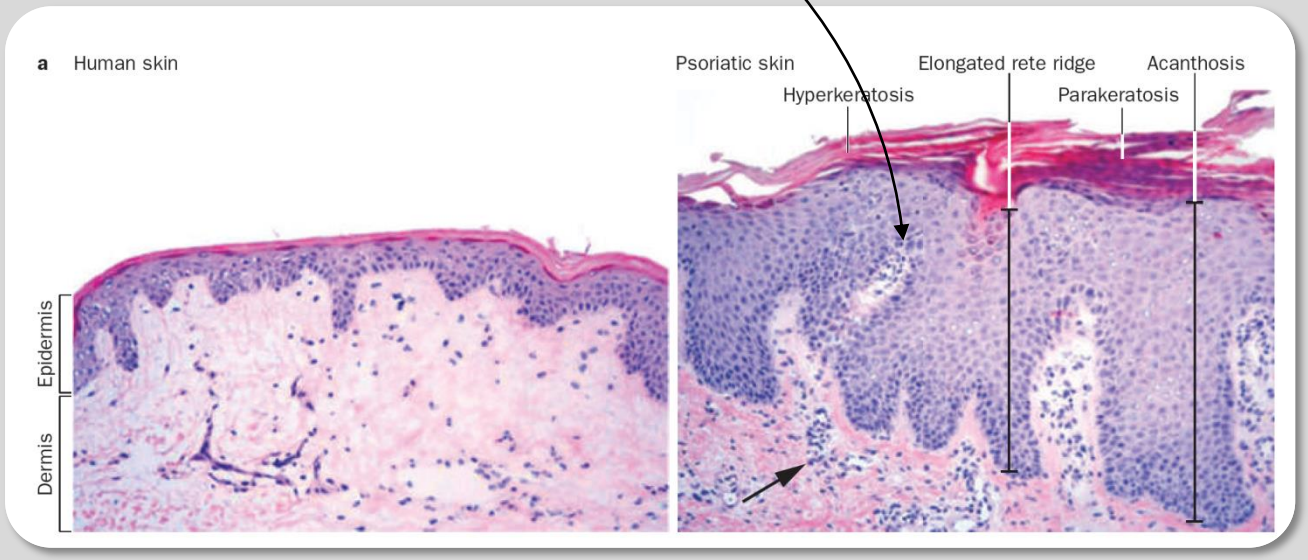
Έχω λάβει τιμητική αμοιβή από την εταιρεία Novartis για τη συμμετοχή μου στο παρόν δορυφορικό συμπόσιο

Psoriasis Is Caused by Keratinocyte Dysregulation
General concept before the 1980s



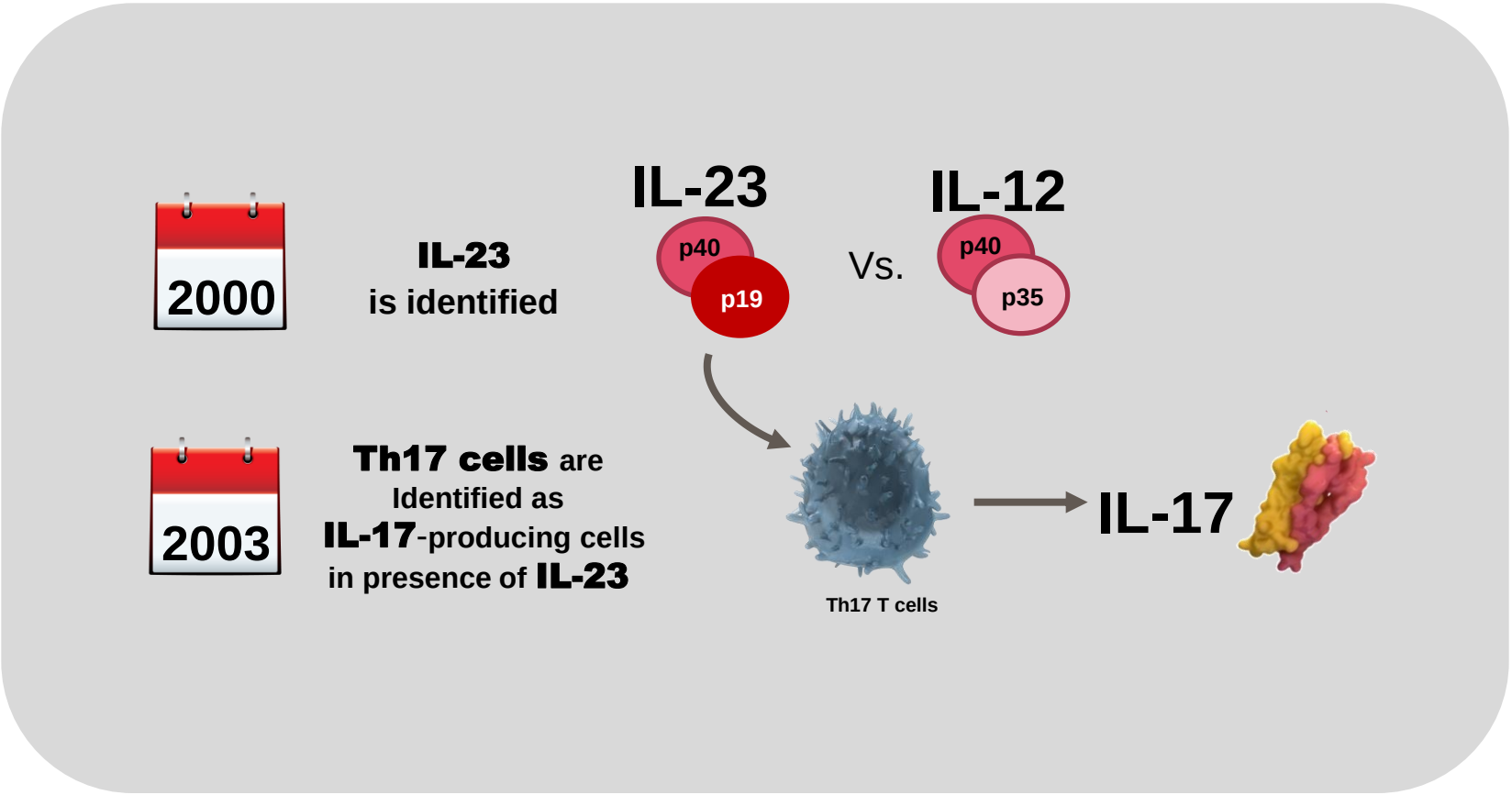
Wagner EF et al. *Nat Rev Rheumatol*. 2010:6:704-714.

Psoriasis Is a T-cell–Mediated Disease

Concepts between 1980 and 2000

Mosmann T et al. *J Immunol*. 1986;136:2348-2357; Kobayashi M et al. *J Exp Med*. 1989;70:827-846; Manetti R et al. *J Exp Med*. 1993;177:1199-1204 .

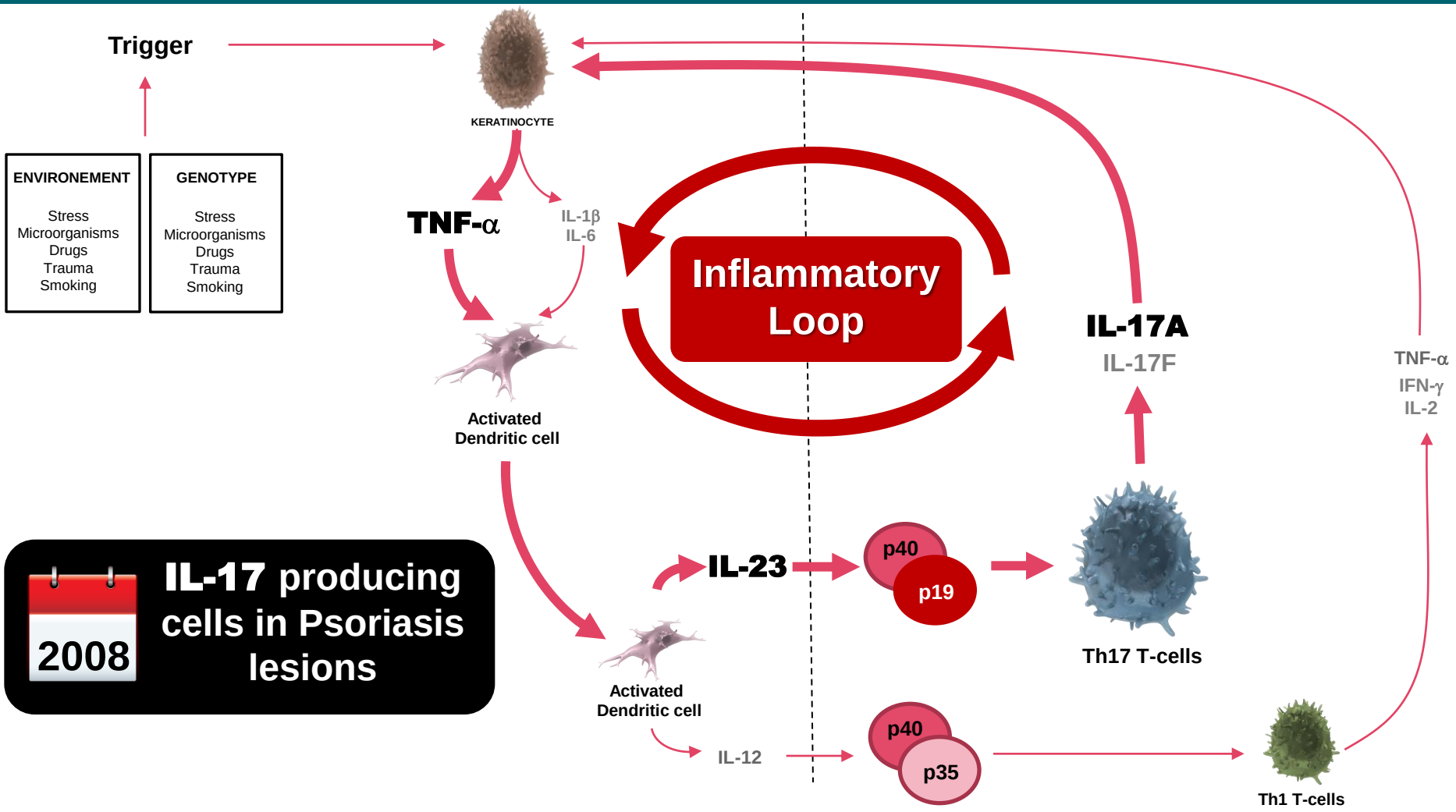
Discovery of IL-23, IL-17, and Th17 Cells
The role of IL-17 and Th17 in chronic inflammation



Oppman B et al. *Immunity.* 2000;13:715–725; Aggarwal S et al. *J Biol Chem*. 2003;278:1910-1914; Lowes M et al. *J Invest Dermatol*. 2008;128:1207-1211.

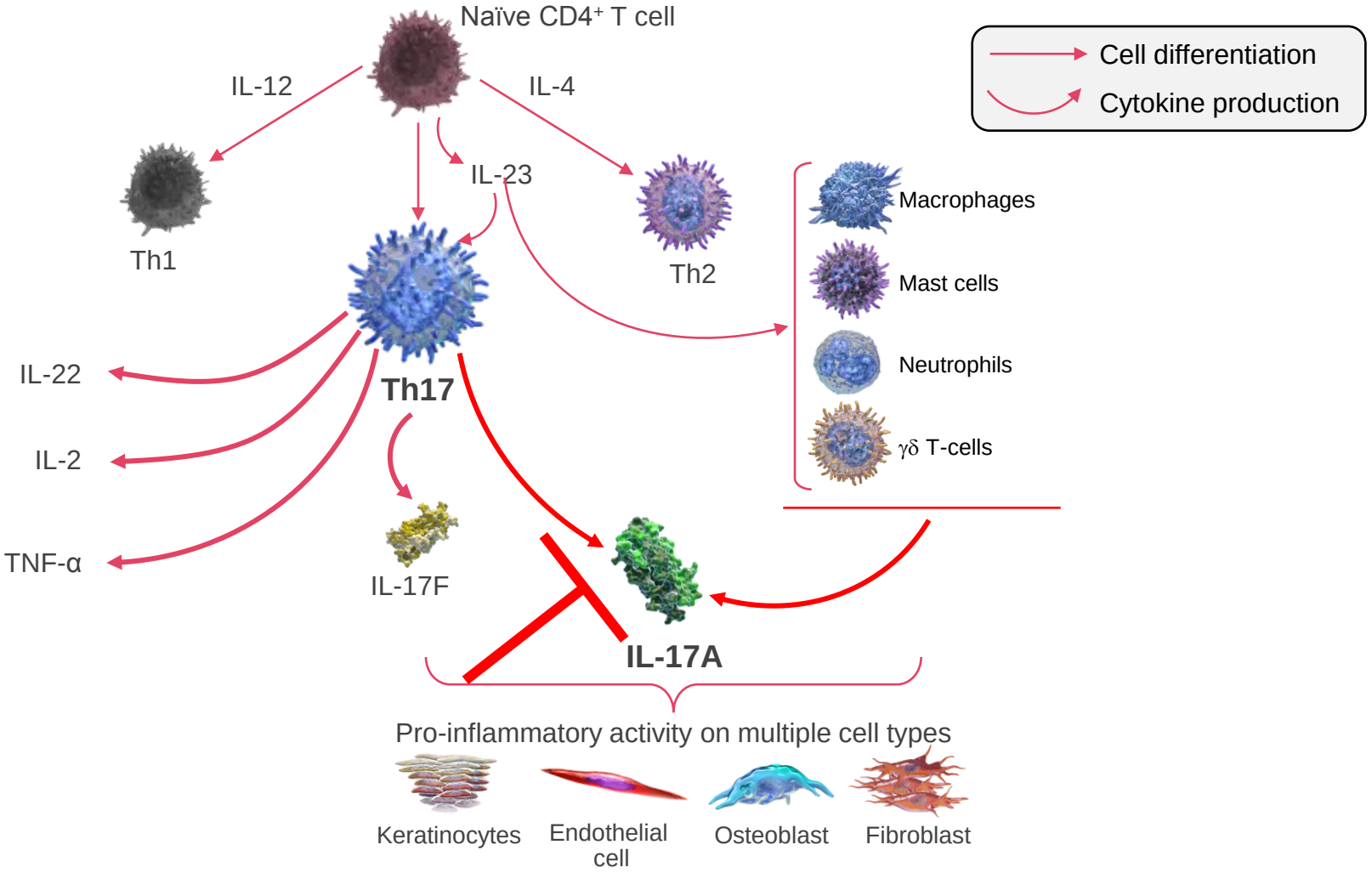
Current Psoriasis Pathogenesis Hypothesis

Th17 cells may be proximal regulators of psoriatic skin inflammation



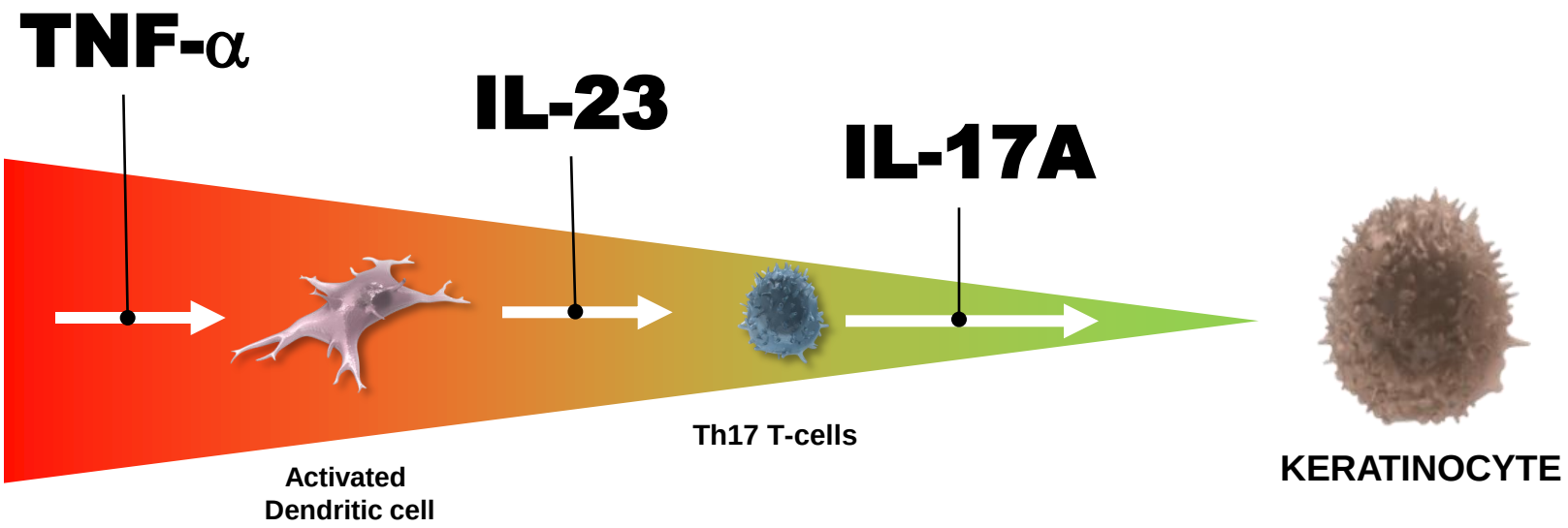
Adapted from Nestle F et al. *N Engl J Med.* 2009;361:496-509; Lowes M et al. *J Invest Dermatol*. 2008;128:1207-1211.

IL-17 : ο νέος στόχος



Iwakura Y et al. *J Clin Invest*. 2006;116:1218-1222; Miossec P, Kolls JK. *Nat Rev Drug Discov.* 2012;11:763-776.

Η IL17A επιδρά απευθείας στο κερατινοκύτταρο



Adapted from Nestle F et al. *N Engl J Med.* 2009;361:496-509.

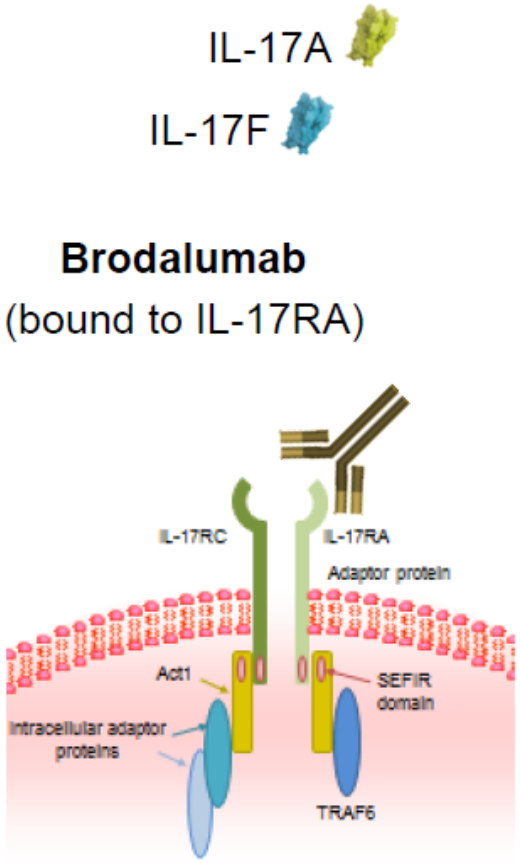
Η στόχευση της IL-17A αποτελεί την απάντηση στη θεραπεία της ψωρίασης?

Στην παρούσα φάση, 3 νέες βιολογικές θεραπείες στοχεύουν αυτό το μονοπάτι

Brodalumab: πλήρως ανθρώπινο αντίσωμα έναντι του υποδοχέα της IL-17 (IL-17A και IL-17F)

	Amgen
USAN name	Brodalumab
Immunoglobulin Type	IgG_2
Target	IL-17RA
Effect	IL-17A, IL-17F, IL-25
Homology	Fully human
Number of patients in phase 2 trials*	198
Indications under development**	Psoriasis (phase 2) Psoriatic arthritis (phase 2)

- Brodalumab blocks IL-17A **and** IL-17F signaling

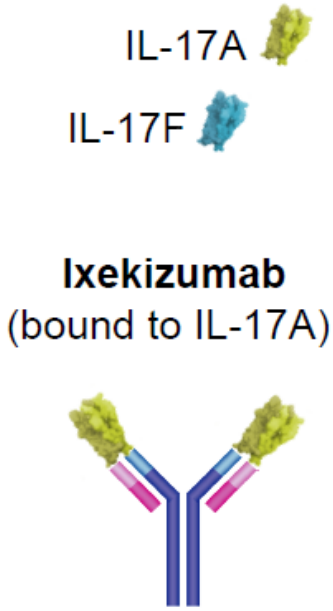


*Leonardi C et al. *N Engl J Med*. 2012;366:1190-1199;

** clinicaltrials.gov accessed June 2012

Ixekizumab: εξανθρωποποιημένο αντίσωμα έναντι της IL-17A

	Eli Lilly
USAN name	Ixekizumab
Immunoglobulin Type	IgG_4
Target	IL-17A
Effect	IL-17A
Homology	Humanized
Number of patients in phase 2 trials*	142
Indications under development**	Psoriasis (phase 3)



- Ixekizumab blocks IL-17A signaling

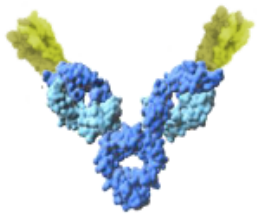
*Papp K et al. *N Engl J Med.* 2012;366:1181-1189.

** clinicaltrials.gov accessed June 2012

Secukinumab: πλήρως ανθρώπινο αντίσωμα εκλεκτικό έναντι της IL-17A

	Novartis
USAN name	Secukinumab
Immunoglobulin Type	IgG_1
Target	IL-17A
Effect	IL-17A
Homology	Fully human
Number of patients in phase 2 trials*	629
Indications under development**	Psoriasis (phase 3) Psoriatic arthritis (phase 3)

Secukinumab
(bound to IL-17A)

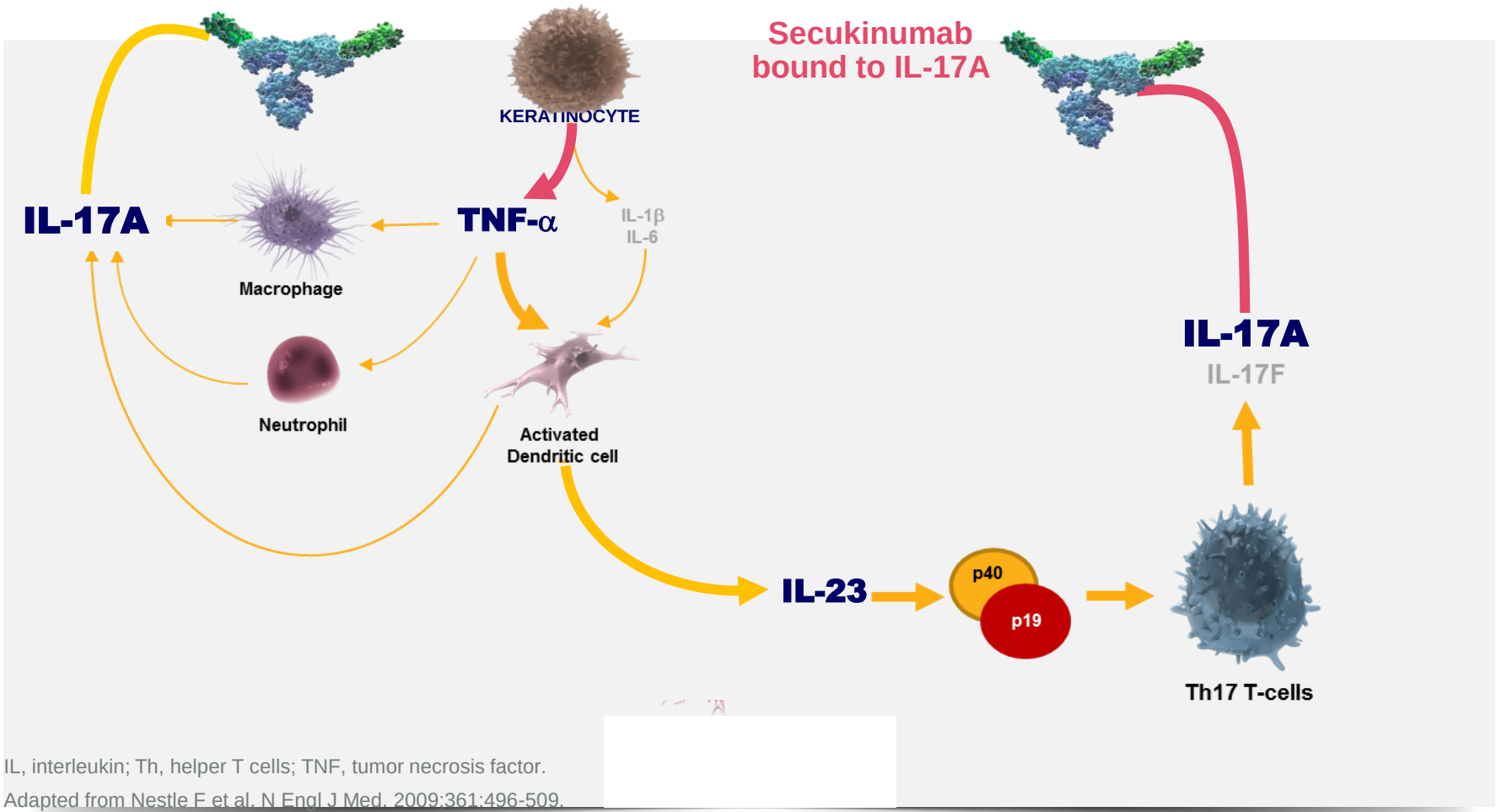


- Secukinumab blocks IL-17A signaling

*Papp KA et al. Presented at: American Academy of Dermatology Annual Meeting 2012; Papp KA et al. Presented at: 20th Congress of the European Academy of Dermatology and Venereology; October 21, 2011; Lisbon, Portugal. Abstract 0626. Rich PA et al. Presented at: 20th Congress of the European Academy of Dermatology and Venereology; October 21, 2011; Lisbon, Portugal. Abstract 0627.

** clinicaltrials.gov accessed June 2012

Το Secukinumab διακόπτει το φλεγμονώδες μονοπάτι, μπλοκάροντας την IL-17A



IL, interleukin; Th, helper T cells; TNF, tumor necrosis factor.

Adapted from Nestle F et al. N Engl J Med. 2009;361:496-509.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Secukinumab in Plaque Psoriasis — Results of Two Phase Three Trials

Richard G. Langley, M.D., Boni E. Elewski, M.D., Mark Lebwohl, M.D., Kristian Reich, M.D., Ph.D., Christopher E.M. Griffiths, M.D., Kim Papp, M.D., Ph.D., Lluís Puig, M.D., Ph.D., Hidemi Nakagawa, M.D., Ph.D., Lynda Spelman, M.B., B.S., Bárður Sigurgeirsson, M.D., Ph.D., Enrique Rivas, M.D., Tsen-Fang Tsai, M.D., Norman Wasel, M.D., Stephen Tyring, M.D., Ph.D., Thomas Salko, B.A., Isabelle Hampele, Ph.D., Marianne Notter, M.S., Alexander Karpov, Ph.D., Silvia Helou, M.D., Ph.D., and Charis Papavassilis, M.D., Ph.D., for the ERASURE and FIXTURE Study Groups*

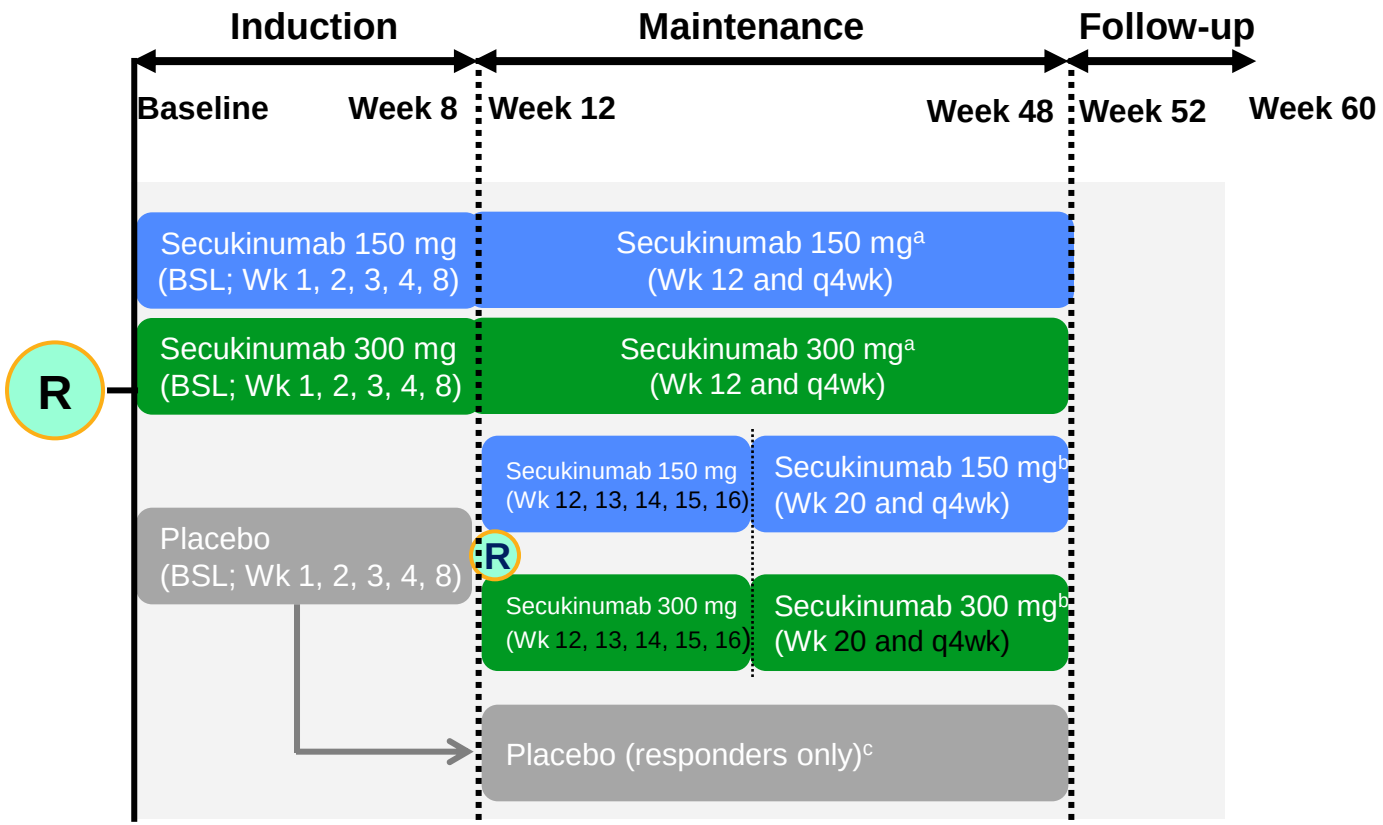
Langley et al. NEJM (2014)

Largest phase 3 program completed to date in Psoriasis (~3,500 pts)

Core submission package

A2302	**ERASURE**	**Secukinumab vs placebo**
A2303	**FIXTURE**	**Secukinumab vs placebo vs Enbrel**
A2308	**FEATURE**	**Secukinumab *prefilled syringe* vs placebo**
A2309	**JUNCTURE**	**Secukinumab *autoinjector/pen* vs placebo**

ERASURE Study Design:
Secukinumab vs placebo

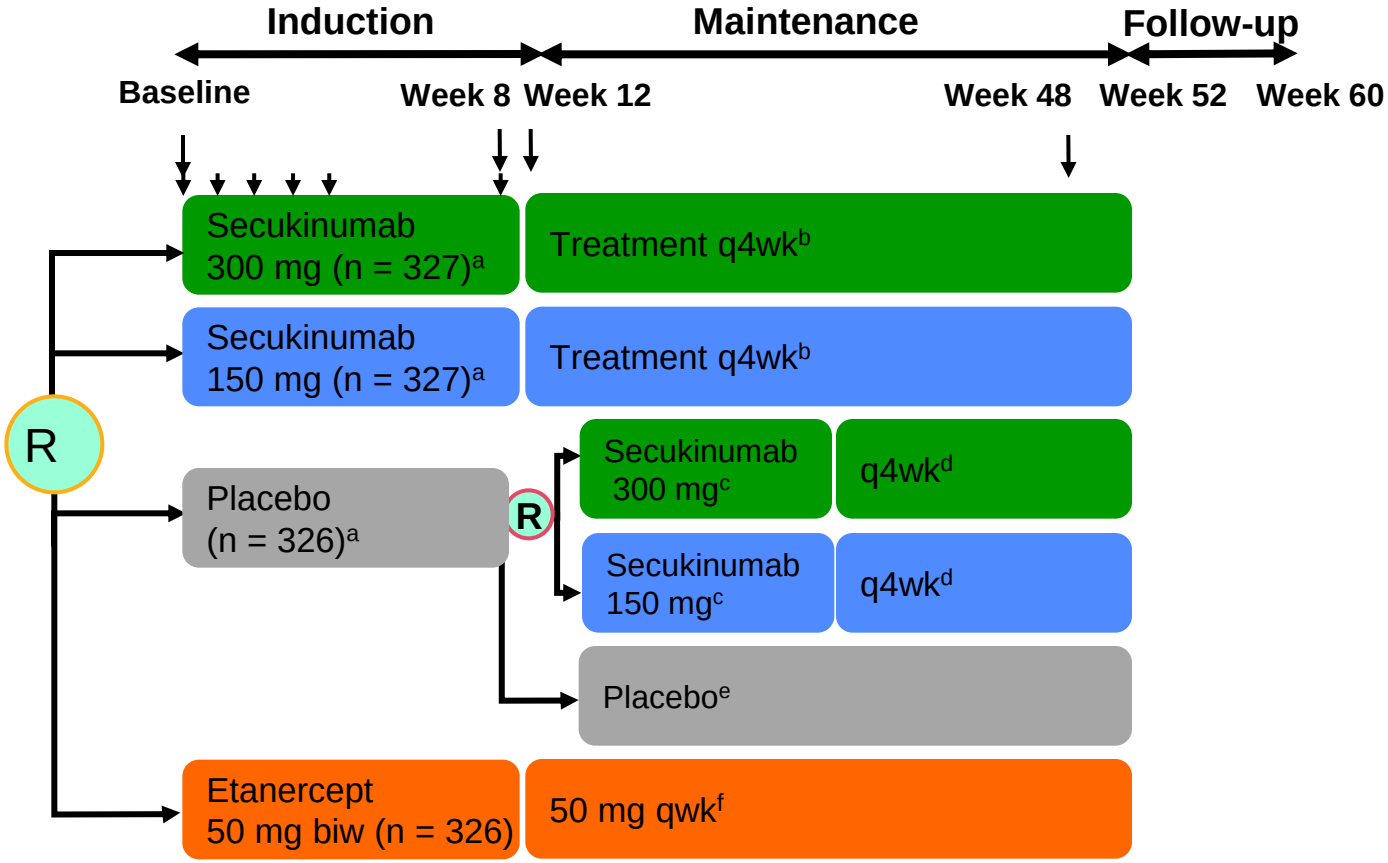


BSL, baseline; q4wk, every 4 weeks; R, randomization.

[a]Treatment starts at Week 12 (+ placebo for blinding) and continues q4wk to Week 48;[b]Treatment starts at Week 20, then q4wk to Week 48; [c]Treatment at Weeks 12, 13, 14, 15, 16, and 20, then q4wk to Week 48.

FIXTURE Study Design
Secukinumab vs Etanercept vs placebo

SEC vs ETN



[a]Treatment or placebo at baseline and Weeks 1, 2, 3, 4, and 8. Short arrows indicate time points doses were given during induction period. [b]Maintenance treatment starts at Week 12 and continues q4wk until Week 48. [c]Treatment at Weeks 12, 13, 14, and 15. [d]Treatment q4wk from Week 16 until Week 48. [e]Placebo at Weeks 12, 13, 14, and 15, then q4wk from Week 16 until Week 48. [f]Treatment qwk from Week 12 until Week 51. biw, twice weekly; qwk, every week; q4wk, every 4 weeks; R, randomization.

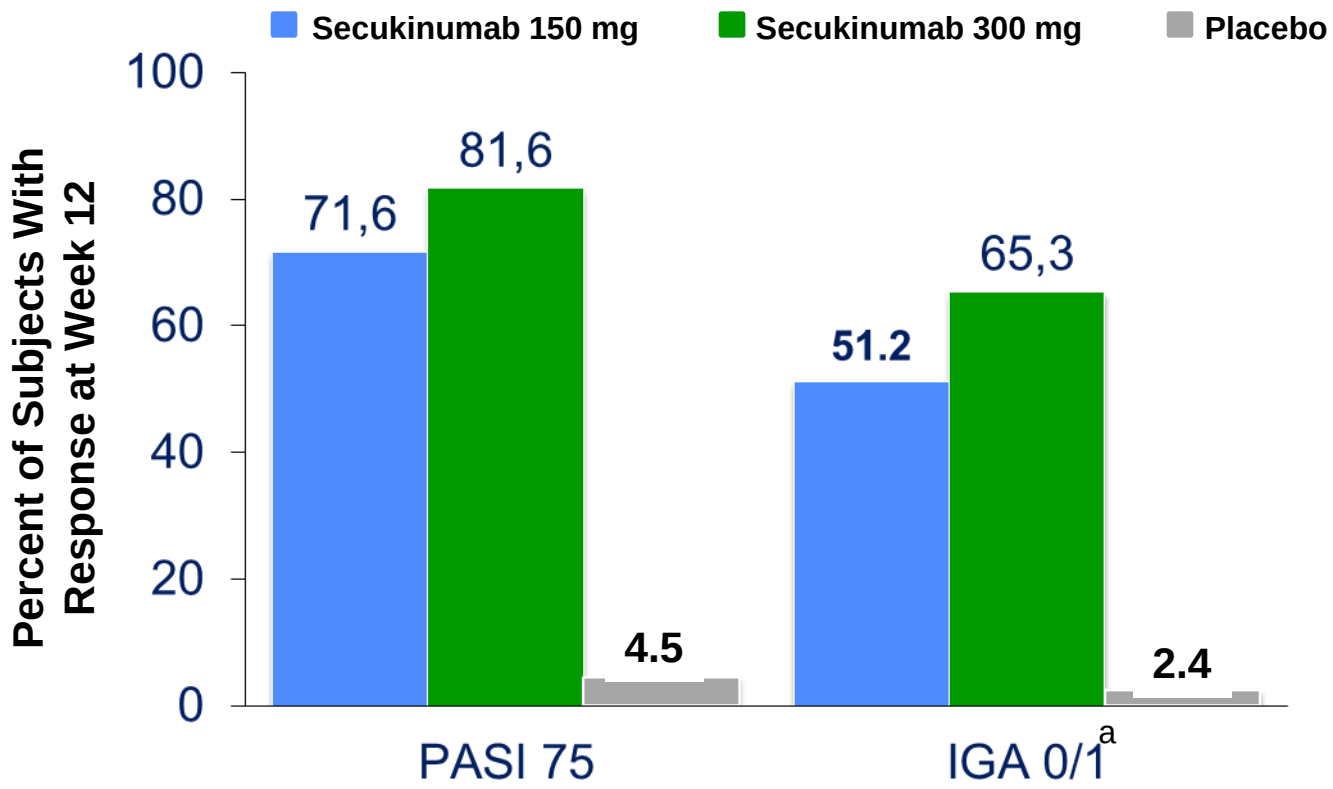
Baseline Characteristics Were Well Balanced Across Treatment Arms and Comparable to Recent Trials in Moderate-to-Severe Psoriasis

	ERASURE			FIXTURE			
Characteristic	Secukinumab 300 mg (n = 245)	Secukinumab 150 mg (n = 245)	Placebo (n = 248)	Secukinumab 300 mg (n = 327)	Secukinumab 150 mg (n = 327)	Etanercept (n = 326)	Placebo (n = 326)
Age — yr[a]	44.9 ± 13.46	44.9 ± 13.33	45.4 ± 12.63	44.5 ± 13.19	45.4 ± 12.92	43.8 ± 12.95	44.1 ± 12.64
Male gender — n (%)	169 (69.0)	168 (68.6)	172 (69.4)	224 (68.5)	236 (72.2)	232 (71.2)	237 (72.7)
Race — n (%)							
Caucasian	171 (69.8)	171 (69.8)	176 (71.0)	224 (68.5)	219 (67.0)	219 (67.2)	218 (66.9)
Asian	52 (21.2)	54 (22.0)	46 (18.5)	73 (22.3)	72 (22.0)	74 (22.7)	72 (22.1)
Weight — kg[a]	88.8 ± 23.99	87.1 ± 22.34	89.7 ± 25.02	83.0 ± 21.59	83.6 ± 20.80	84.6 ± 20.51	82.0 ± 20.39
BMI — kg/m^2,[a]	30.3 ± 7.16	29.8 ± 6.84	30.3 ± 7.83	28.4 ± 6.44	28.4 ± 5.90	28.7 ± 5.92	27.9 ± 6.08
Time since psoriasis diagnosis — yr[a]	17.4 ± 11.09	17.5 ± 12.02	17.3 ± 12.36	15.8 ± 12.29	17.3 ± 12.22	16.4 ± 12.01	16.6 ± 11.63
PASI score[a]	22.5 ± 9.23	22.3 ± 9.83	21.4 ± 9.08	23.9 ± 9.95	23.7 ± 10.50	23.2 ± 9.81	24.1 ± 10.47
BSA involved — %[a]	32.8 ± 19.30	33.3 ± 19.17	29.7 ± 15.89	34.3 ± 19.21	34.5 ± 19.42	33.6 ± 17.97	35.2 ± 19.13
IGA mod 2011 score — n (%)							
3 (moderate disease)	154 (62.9)	161 (65.7)	151 (60.9)	203 (62.1)	206 (63.0)	195 (59.8)	202 (62.0)
4 (severe disease)	91 (37.1)	84 (34.3)	97 (39.1)	124 (37.9)	121 (37.0)	131 (40.2)	124 (38.0)
Psoriatic arthritis reported — n (%)	57 (23.3)	46 (18.8)	68 (27.4)	50 (15.3)	49 (15.0)	44 (13.5)	49 (15.0)
Previous systemic treatment — n (%)							
Any	163 (66.5)	156 (63.7)	146 (58.9)	206 (63.0)	212 (64.8)	214 (65.6)	204 (62.6)
Conventional agent[b]	128 (52.2)	125 (51.0)	108 (43.5)	195 (59.6)	198 (60.6)	204 (62.6)	199 (61.0)
Biologic agent	70 (28.6)	73 (29.8)	73 (29.4)	38 (11.6)	45 (13.8)	45 (13.8)	35 (10.7)
Anti-TNF	48 (19.6)	44 (18.0)	51 (20.6)	12 (3.7)	15 (4.6)	21 (6.4)	12 (3.7)
Failed TNF inhibitor	17 (6.9)	18 (7.3)	21 (8.5)	10 (3.1)	9 (2.8)	10 (3.1)	3 (0.9)
Anti–IL-12/IL-23	32 (13.1)	37 (15.1)	31 (12.5)	23 (7.0)	23 (7.0)	22 (6.7)	21 (6.4)

ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΤΗΤΑ

ERASURE
Σημαντική διαφορά στην αποτελεσματικότητα PASI 75 και IGA 0/1 μεταξύ secukinumab και placebo στην εβδομάδα 12

SEC vs PB



[a]IGA score of 0 (clear) or 1 (almost clear) and an improvement of at least 2 points on the IGA scale compared with baseline.
P < 0.0001 for all comparisons of secukinumab vs. placebo.

Κλίμακα των 5 σημείων (IGA)

5-point IGA mod 2011 scale used in phase 3 trials (39)		
Score	Short descriptor	Detailed descriptor
0	Clear	No signs of psoriasis; postinflammatory hyperpigmentation may be present
1	Almost clear	No thickening; normal to pink coloration; no to minimal focal scaling
2	Mild	Just detectable to mild thickening; pink to light red coloration; predominantly fine scaling
3	Moderate	Clearly distinguishable to moderate thickening; dull bright red, clearly distinguishable to moderate thickening; moderate scaling
4	Severe	Severe thickening with hard edges; bright to deep dark red coloration; severe/coarse scaling covering almost all or all lesions

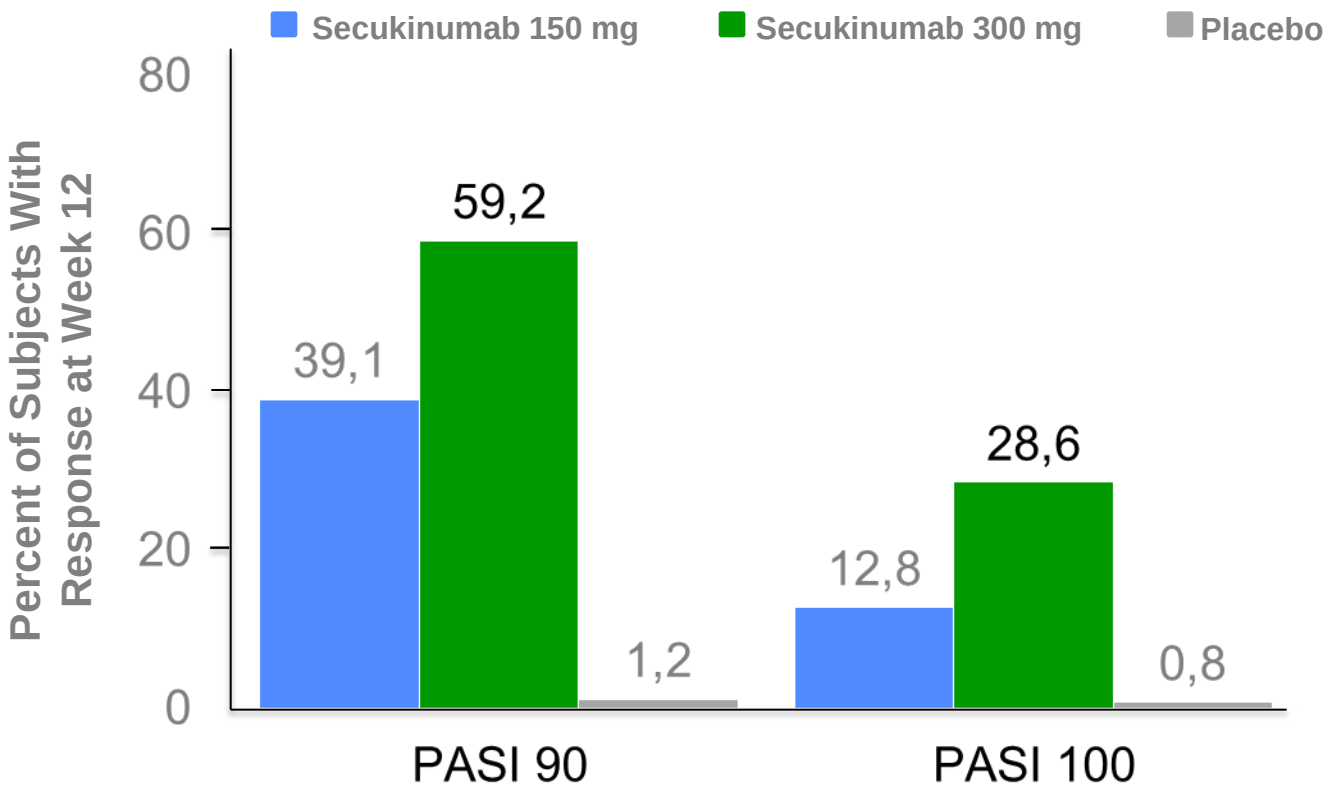
IGA, investigator's global assessment; mod, modified.

- Η κλίμακα IGA είναι περισσότερο αυστηρή για το score 1 ("almost clear")
- Η κλίμακα PGA που χρησιμοποιείται έως σήμερα στις περισσότερες μελέτες, σχετίζεται με το PASI75, ενώ η **IGA με το PASI90**

Langley R et al. The 5-point investigator's global assessment (IGA) scale: a modified tool for evaluating plaque psoriasis severity in clinical trials. J Derm Treat. 2013

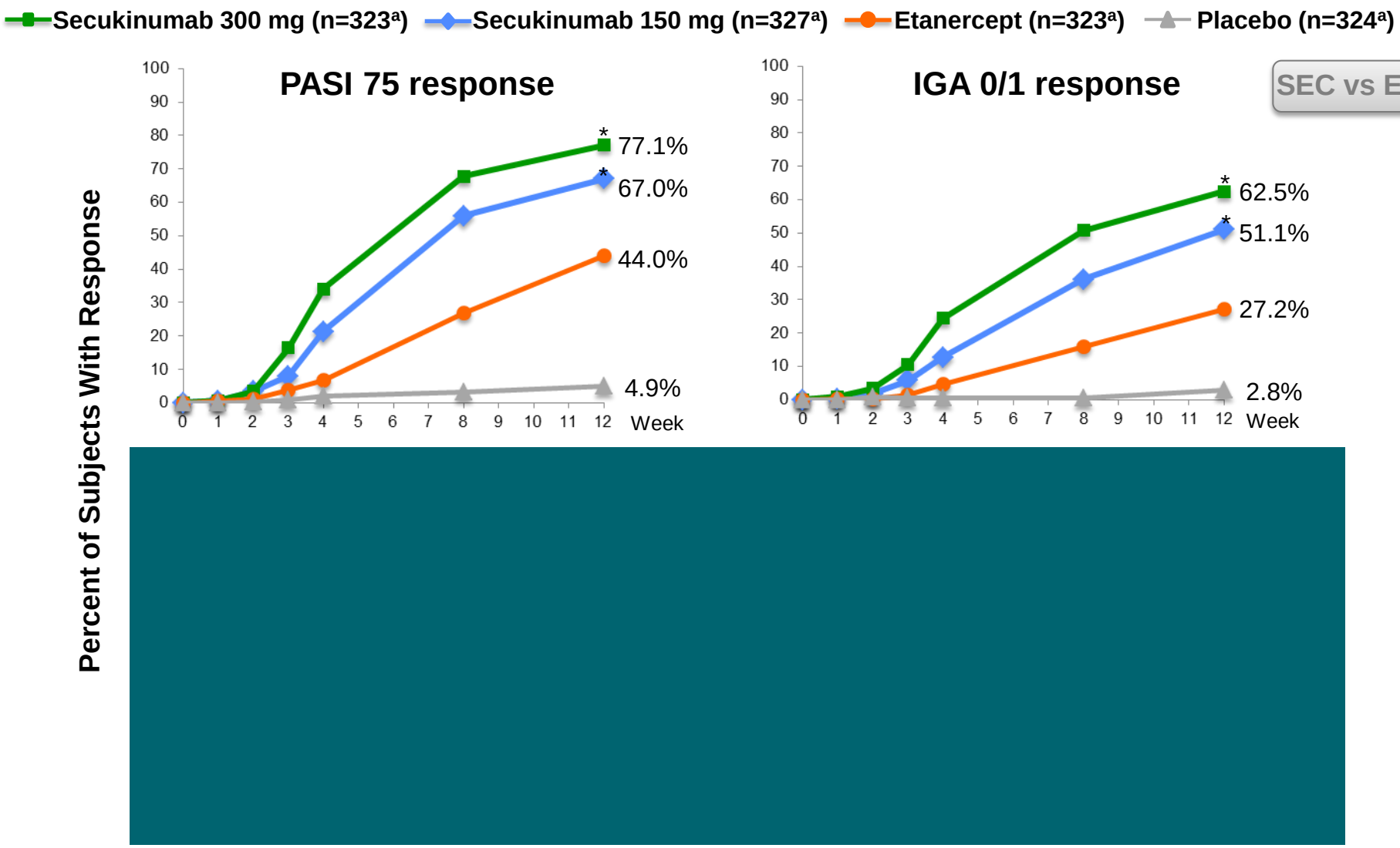
ERASURE:
Υψηλή επίτευξη PASI 90 και PASI 100 με το Secukinumab, στην εβδομάδα 12, συγκριτικά με το placebo)

SEC vs PB



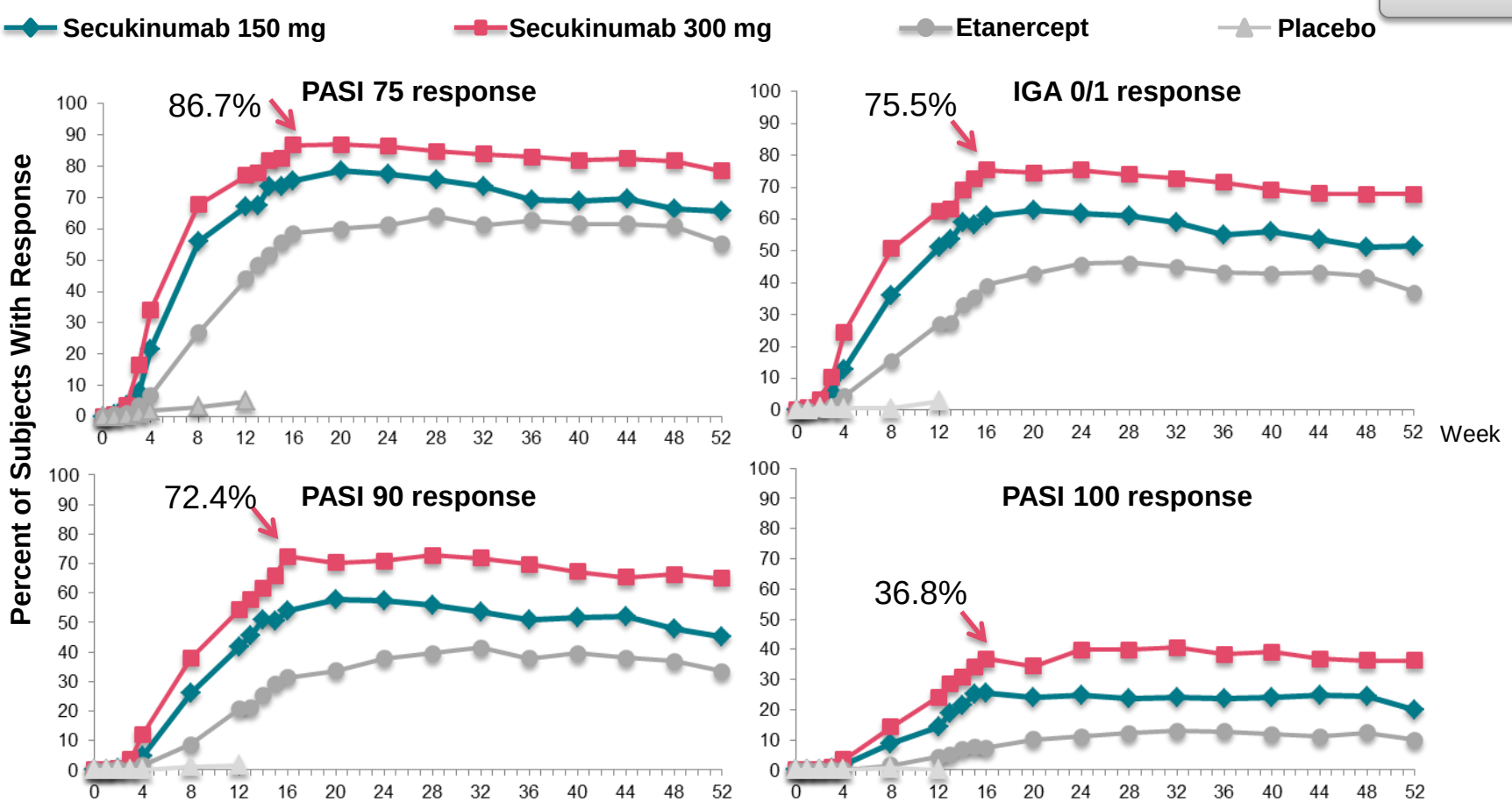
P < 0.0001 for all comparisons of secukinumab vs. placebo. *P*-values were obtained for PASI 90 by the multiple testing strategy and for PASI 100 by Cochran-Mantel-Haenszel test.

FIXTURE- Ανώτερη αποτελεσματικότητα του Secukinumab έναντι του Etanercept την εβδομάδα 12



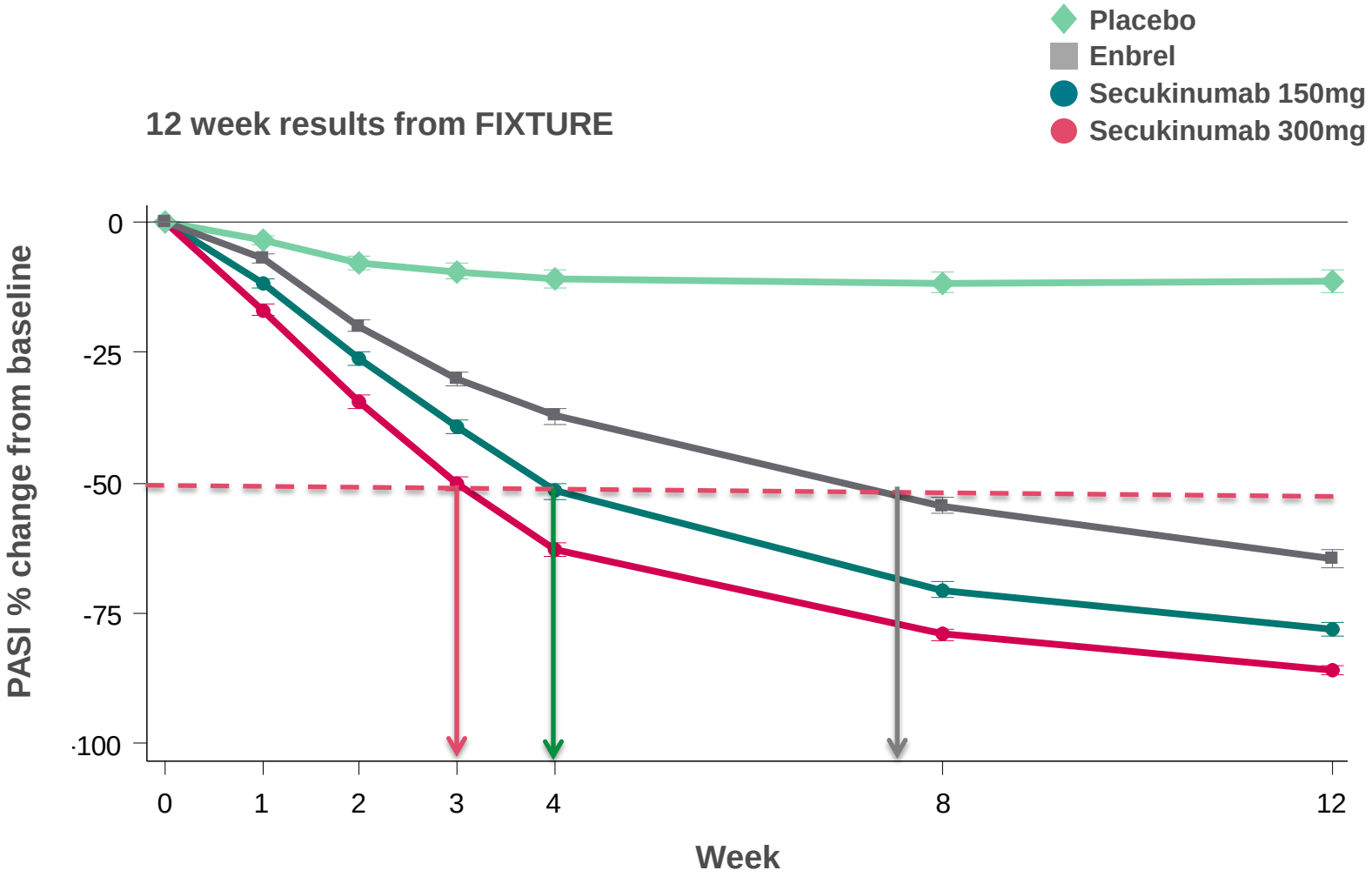
FIXTURE
Ανώτερη αποτελεσματικότητα του Secukinumab έναντι του Etanercept στα PASI75, PASI 90, PASI 100 και IGA μετά από 52 εβδομάδες

SEC vs ETN



ΤΑΧΥΤΗΤΑ ΕΠΙΤΕΥΞΗΣ ΑΠΟΤΕΛΕΣΜΑΤΟΣ

ΤΑΧΥΤΗΤΑ – 50% μείωση στο PASI μετά από 3 εβδομάδες θεραπείας με secukinumab



ΙΣΧΥΡΟ ΑΠΟΤΕΛΕΣΜΑ

Secukinumab: 81,6% των ασθενών πετυχαίνουν PASI75 την εβδομάδα 12 (ERASURE)

Αποτελεσματικότητα των θεραπειών

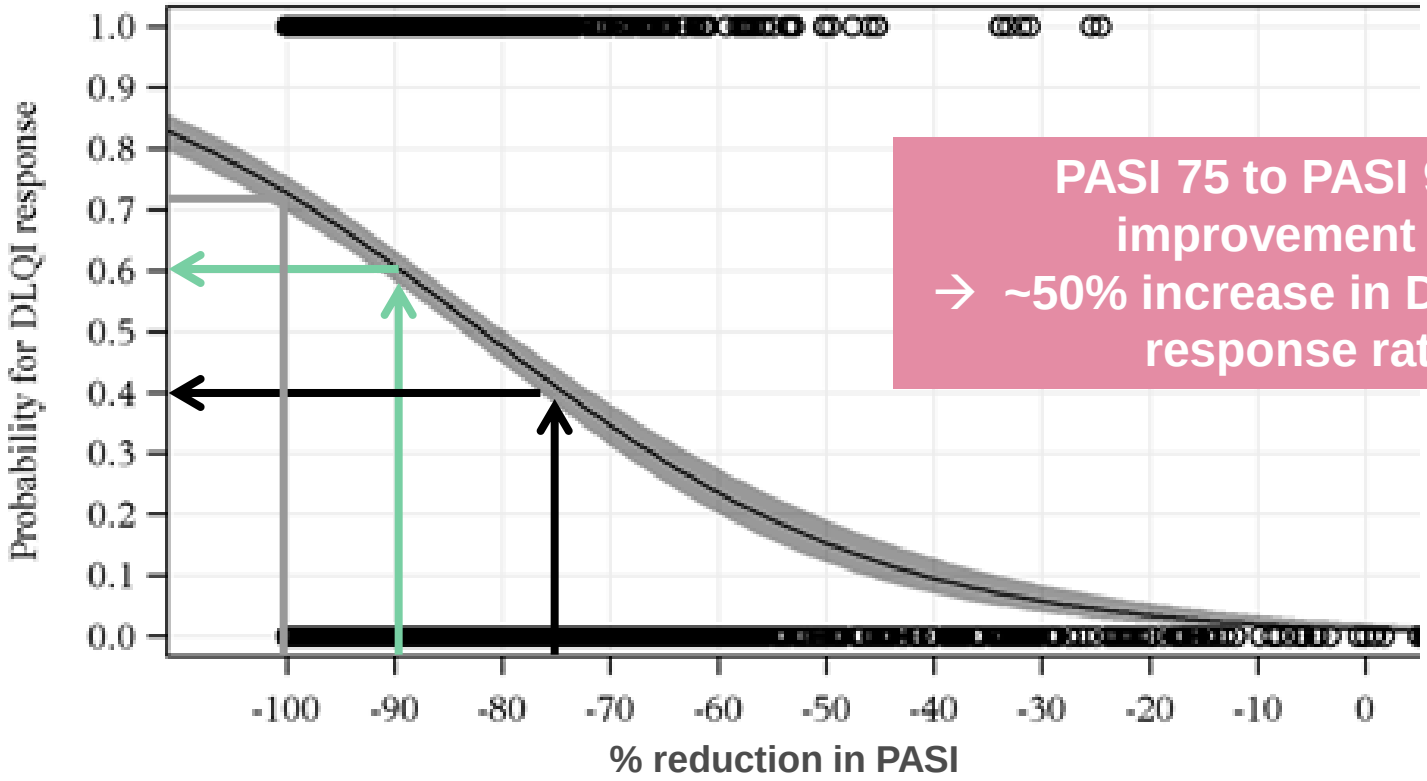
Παράγοντας	Δοσολογία	PASI 75 μετά από 12εβδ
Etanercept	2 x 25 mg/week	34%
Etanercept	**2 x 50 mg/week**	**49%**
Ustekinumab Ustekinumab	45 mg/12 weeks (<100kg ΒΣ) 90mg/12 weeks (>100kg ΒΣ)	**67%** **68-71%**
Adalimumab	40mg eow	**71-80%**
Infliximab	5 mg/kg	**≥80%**
Acitretin	0.5 mg/kg/d	20–30%
Methotrexate	5–15 mg/week	25–50%
Ciclosporin	**3 mg/kg/d**	**50–70%**

Τα δεδομένα δεν προκύπτουν από συγκριτικές μελέτες

Nast A *et al Arch Dermatol, Res* 2007; 299: 111-38; Saurat J-H *et al BJD* 2008; 158 (3): 558-66; Papp KA *et al Lancet* 2008; 371: 1675-84; Leonardi CL *et al Lancet* 2008; 371: 1665-74

Είναι το PASI 75 αρκετό για τους ασθενείς?

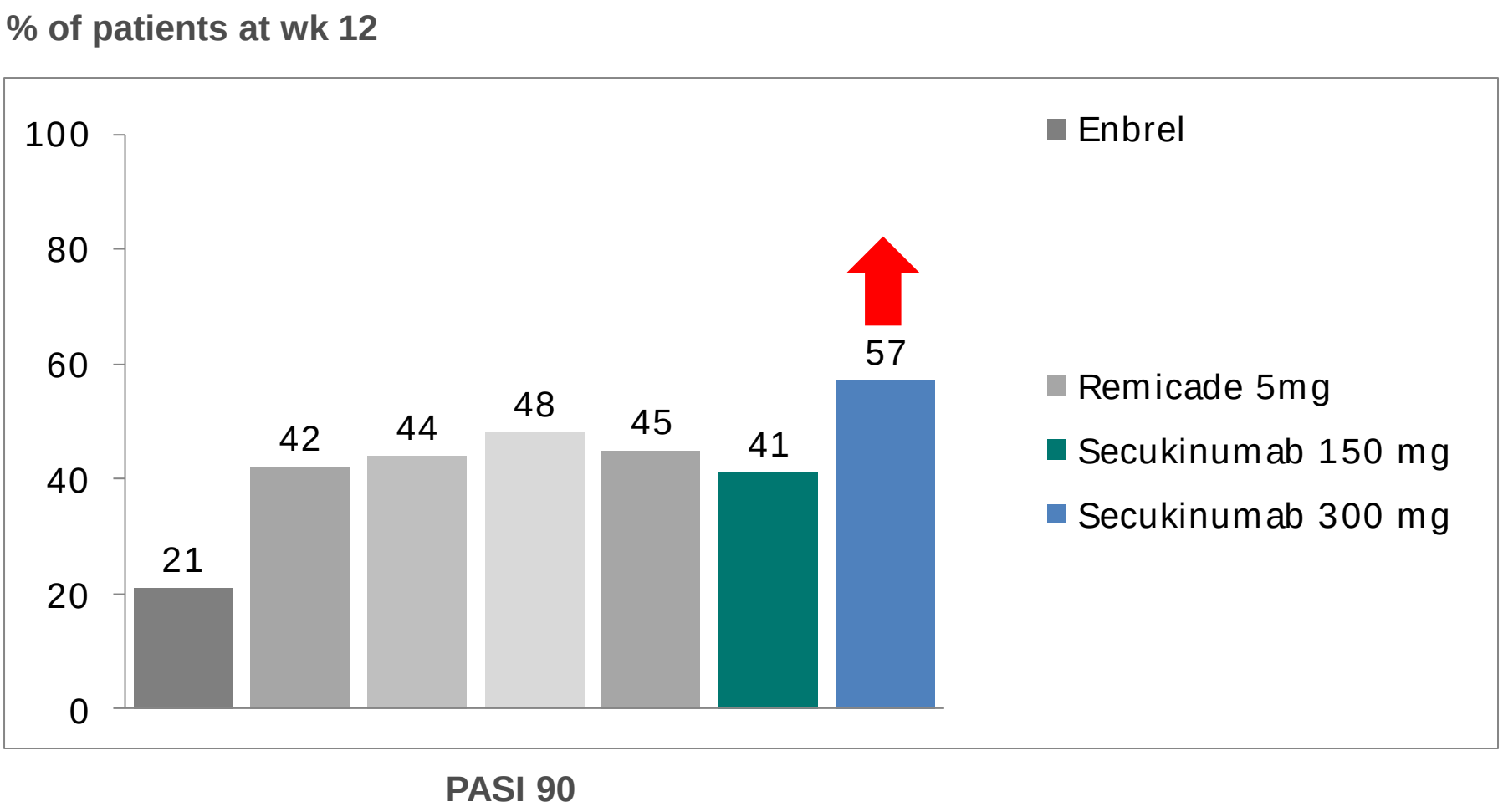
Η επίτευξη σχεδόν πλήρους κάθαρσης, (PASI 90), σχετίζεται με καλύτερο QoL από ότι η επίτευξη PASI 75



PASI 75 to PASI 90 improvement
→ ~50% increase in DLQI 0/1 response rate

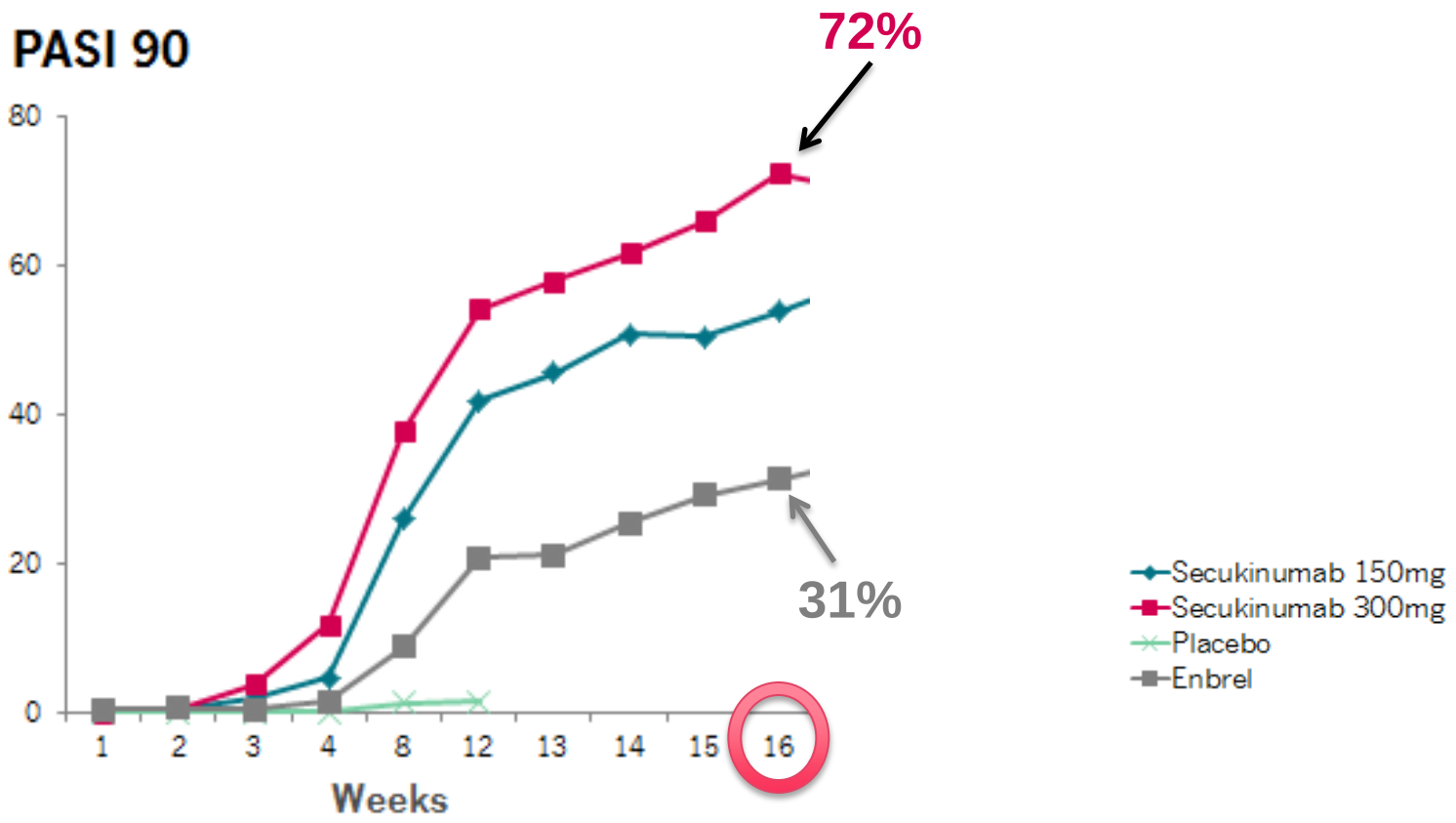
Dermatology Life Quality Index (DLQI 0/1) response means psoriasis has **no effect on a patient's life*
Source: Data on file from Secukinumab phase 3 program at week 12

Το Secukinumab (300 mg) επαναπροσδιορίζει την αποτελεσματικότητα



Week 12 and week 16 pooled data (A2302/3)
Enbrel® A2303 vs competitor historical data
Cross study comparison for illustrative purposes only

Το 72% των ασθενών πετυχαίνει PASI 90 έως την εβδομάδα 16

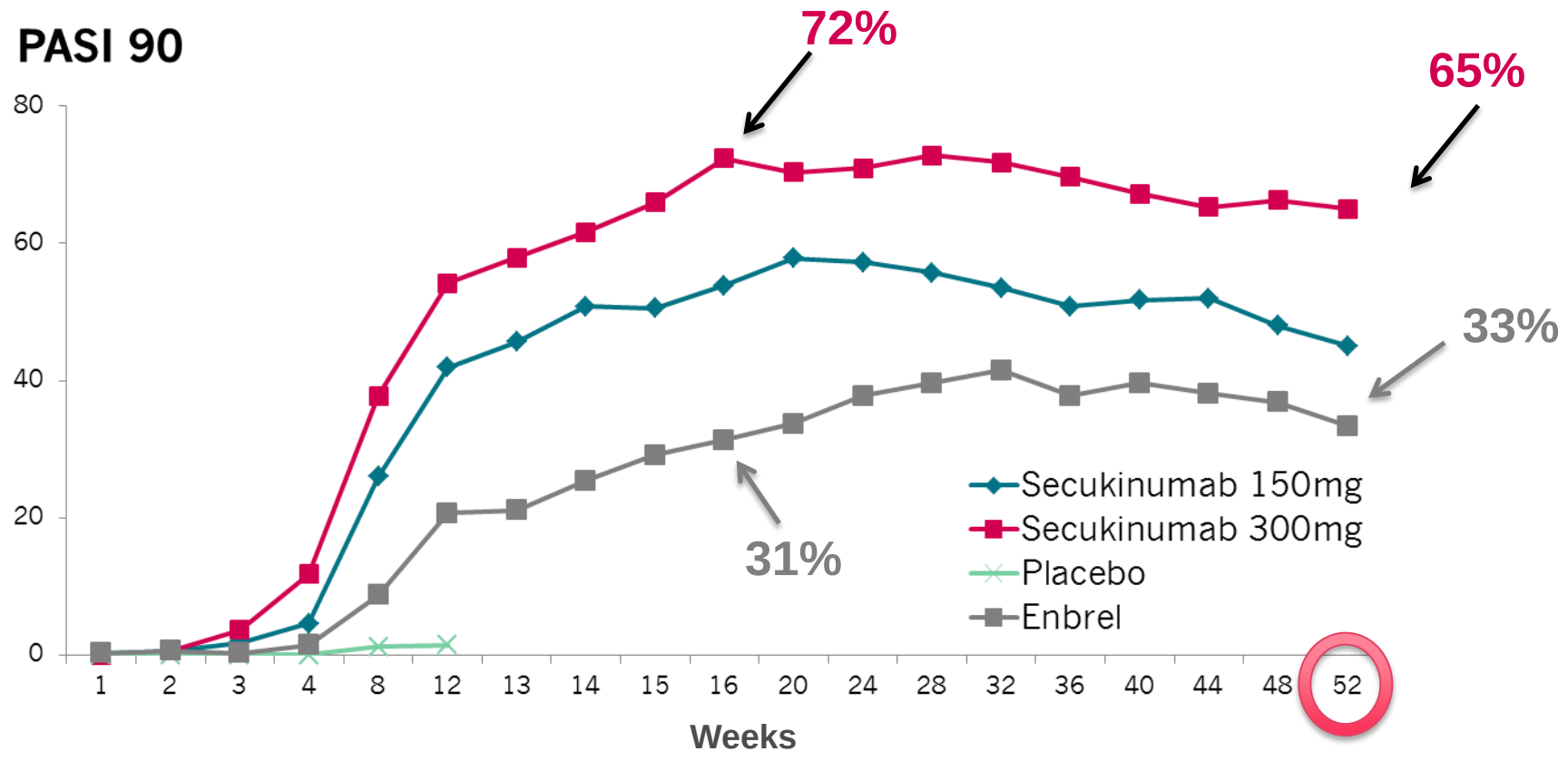


FIXTURE: PASI 90 response over time up to Week 16

ΔΙΑΤΗΡΗΣΗ ΑΠΟΤΕΛΕΣΜΑΤΟΣ

65% των ασθενών πέτυχαν PASI 90 έως την εβδομάδα 52 – χωρίς προβλήματα ανοσογονικότητας

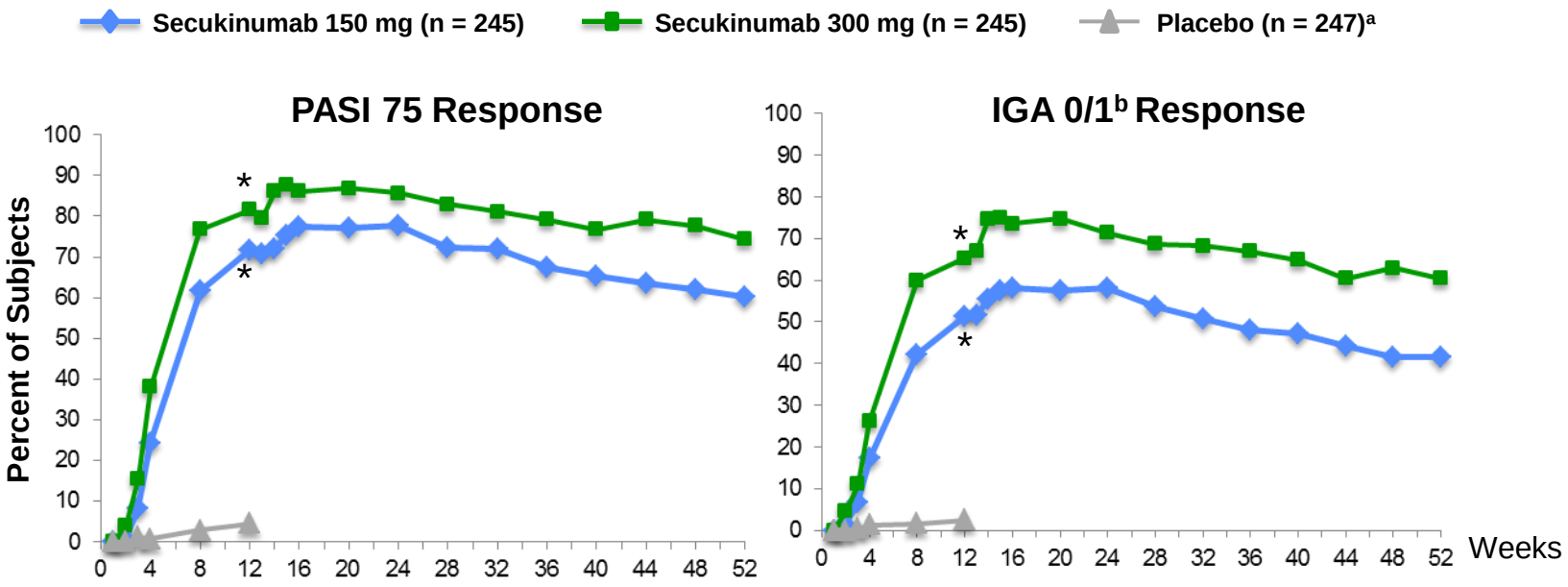
SEC vs ETN



FIXTURE: PASI 90 response over time up to Week 52

Το Secukinumab βελτιώνει ταχύτατα την ψωρίαση και διατηρεί υψηλή αποτελεσματικότητα έως την εβδομάδα 52

SEC vs PB



*P < 0.0001 vs. placebo at Week 12.

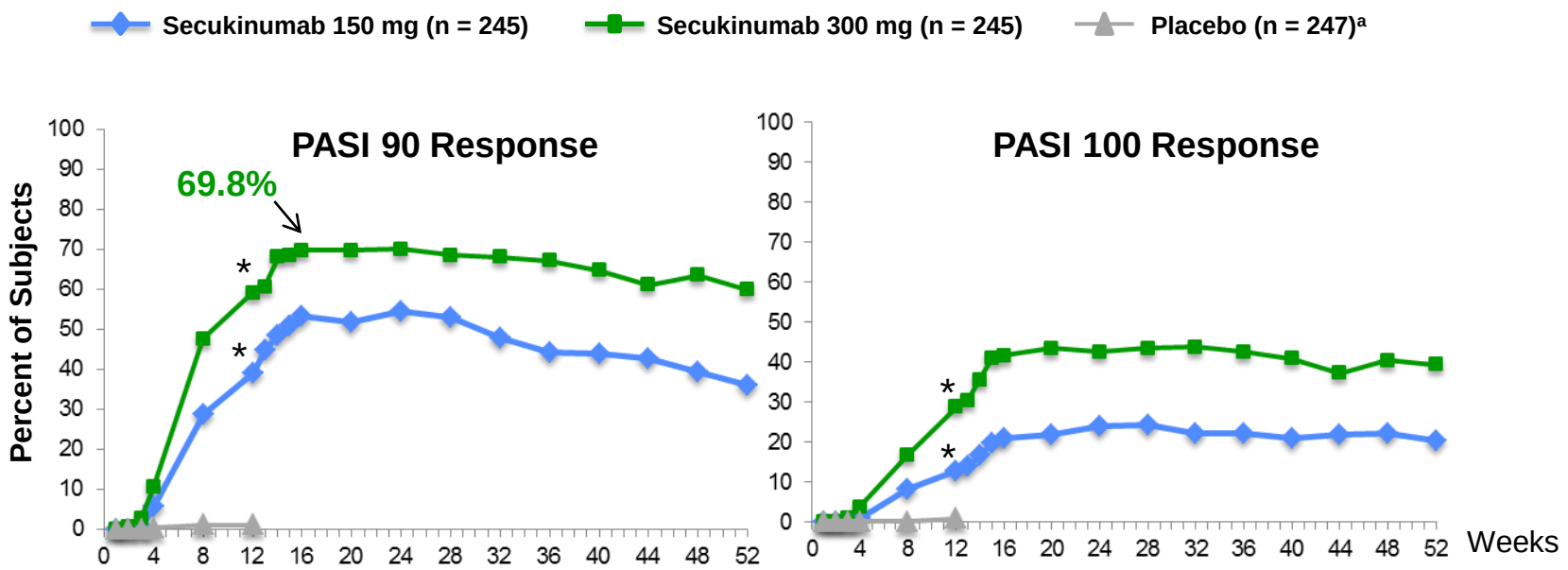
[a]One subject did not sign informed consent before starting study procedures and was excluded from analyses.

[b]IGA score of 0 (clear) or 1 (almost clear) and an improvement of at least 2 points on the IGA scale compared with baseline.

Το Secukinumab βελτιώνει ταχύτατα την ψωρίαση και διατηρεί υψηλή αποτελεσματικότητα έως την εβδομάδα 52

SEC vs PB

- Η ανταπόκριση PASI 90 την εβδομάδα 16 ήταν 69.8% για τους ασθενείς υπό secukinumab 300 mg



**P* < 0.0001 vs. placebo at Week 12.

[a]One subject did not sign informed consent before starting study procedures and was excluded from analyses.

ΑΣΦΑΛΕΙΑ

ERASURE: Σε όλη τη διάρκεια δεν παρατηρήθηκαν νέα ή μη αναμενόμενα AE

SEC vs PB

	Induction Period (Baseline–Week 12)			Entire Treatment Period (Baseline–Week 52)		
	Secukinumab 300 mg (n = 245)	Secukinumab 150 mg (n = 245)	Placebo (n = 247)	Any Secukinumab 300 mg (n = 349)	Any Secukinumab 150 mg (n = 353)	Placebo[a] (n = 247)
Exposure to study treatment, days: mean (SD)	84.1 (7.2)	82.4 (11.4)	82.0 (11.7)	320.7 (74.4)	313.0 (81.2)	101.1 (71.2)
	n (%)			n (Incidence Rate per 100 Subject-Years)		
Subjects with any AE(s)	135 (55.1)	148 (60.4)	116 (47.0)	286 (245.5)	287 (269.5)	124 (323.0)
Death	0	0	0	0	0	0
Non-fatal SAEs	6 (2.4)	4 (1.6)	4 (1.6)	19 (6.3)	19 (6.4)	5 (7.4)
Any AE leading to discontinuation	3 (1.2)	5 (2.0)	4 (1.6)	12 (b)	18 (b)	5 (b)
Infections and infestations	72 (29.4)	66 (26.9)	40 (16.2)	193 (100.0)	185 (95.4)	48 (83.9)
Most common AEs by preferred term[c]						
Nasopharyngitis	22 (9.0)	23 (9.4)	19 (7.7)	57 (20.9)	69 (26.2)	20 (30.8)
Headache	12 (4.9)	13 (5.3)	7 (2.8)	31 (10.9)	24 (8.4)	10 (15.1)
Upper respiratory tract infection	9 (3.7)	10 (4.1)	0	32 (11.1)	36 (12.7)	2 (3.0)
Pruritus	9 (3.7)	8 (3.3)	5 (2.0)	15 (5.1)	14 (4.8)	5 (7.4)
Oropharyngeal pain	4 (1.6)	10 (4.1)	3 (1.2)	12 (4.0)	12 (4.1)	3 (4.4)
Fatigue	2 (0.8)	8 (3.3)	2 (0.8)	3 (1.0)	10 (3.4)	2 (2.9)
Hypertension	0	9 (3.7)	3 (1.2)	16 (5.3)	21 (7.3)	3 (4.4)
Influenza-like illness	5 (2.0)	3 (1.2)	3 (1.2)	14 (4.7)	17 (5.8)	3 (4.5)

*Placebo administered for 3 months only.

†Occurring at an incidence rate (IR) ≥10 per 100 patient-years in any treatment group; listed in descending order of frequency for both secukinumab groups combined.

FIXTURE: Δεν παρατηρήθηκε διαφορά στα AE και SAE μεταξύ secukinumab και etanercept

	Induction Period (Baseline–Week 12)				Entire Treatment Period (Baseline–Week 52)			
	Secukinumab 300 mg (n = 326)	Secukinumab 150 mg (n = 327)	Etanercept (n = 323)	Placebo (n = 327)	Any Secukinumab 300 mg (n = 467)	Any Secukinumab 150 mg (n = 469)	Etanercept (n = 323)	Placebo — Induction and Responders[a] (n = 327)
Exposure to study treatment, days: mean (SD)	82.8 (9.79)	83.3 (11.56)	82.6 (9.45)	81.7 (11.45)	320.7 (75.28)	317.5 (75.35)	331.9 (89.70)	95.3 (61.01)
	n (%)				n (Incidence Rate per 100 Subject-Years)			
Subjects with any AEs	181 (55.5)	191 (58.4)	186 (57.6)	163 (49.8)	376 (252.0)	364 (236.4)	253 (243.4)	168 (329.7)
Death	0	0	0	0	0	0	0	0
Non-fatal serious AEs	4 (1.2)	7 (2.1)	3 (0.9)	6 (1.8)	27 (6.8)	24 (6.0)	20 (7.0)	7 (8.3)
Discontinuations due to AEs	4 (1.2)	2 (0.6)	6 (1.9)	3 (0.9)	14[b]	10[b]	12[b]	3[b]
Infections and infestations	87 (26.7)	101 (30.9)	79 (24.5)	63 (19.3)	269 (105.4)	240 (91.9)	170 (91.4)	65 (89.5)
Most common AEs[c]								
Nasopharyngitis	35 (10.7)	45 (13.8)	36 (11.1)	26 (8.0)	122 (35.2)	108 (31.4)	86 (35.7)	26 (32.8)
Headache	30 (9.2)	16 (4.9)	23 (7.1)	23 (7.0)	58 (15.7)	47 (12.4)	40 (15.2)	24 (29.6)
Diarrhea	17 (5.2)	12 (3.7)	11 (3.4)	6 (1.8)	38 (9.9)	36 (9.3)	22 (7.9)	7 (8.4)
Pruritus	8 (2.5)	12 (3.7)	8 (2.5)	11 (3.4)	16 (4.0)	21 (5.3)	16 (5.7)	11 (13.2)
Arthralgia	5 (1.5)	14 (4.3)	12 (3.7)	10 (3.1)	24 (6.0)	33 (8.5)	23 (8.2)	10 (12.1)
Upper respiratory tract infections	7 (2.1)	10 (3.1)	7 (2.2)	3 (0.9)	26 (6.6)	26 (6.6)	18 (6.4)	3 (3.5)
Back pain	8 (2.5)	8 (2.4)	9 (2.8)	6 (1.8)	31 (7.9)	20 (5.1)	26 (9.3)	6 (7.1)
Cough	11 (3.4)	5 (1.5)	4 (1.2)	4 (1.2)	30 (7.6)	15 (3.7)	12 (4.2)	4 (4.8)
Hypertension	5 (1.5)	10 (3.1)	5 (1.5)	4 (1.2)	20 (5.0)	22 (5.6)	14 (4.9)	4 (4.7)
Nausea	8 (2.5)	6 (1.8)	4 (1.2)	7 (2.1)	11 (2.7)	10 (2.5)	7 (2.4)	7 (8.3)
Oropharyngeal pain	9 (2.8)	5 (1.5)	4 (1.2)	7 (2.1)	25 (6.3)	20 (5.0)	10 (3.5)	7 (8.3)

Σταθερό και ισχυρό προφίλ ασφάλειας με το secukinumab

- Το προφίλ ασφάλειας του Secukinumab στα **150 & 300 mg είναι παρόμοιο**
- Αυξημένη επίπτωση λοιμώξεων στους ασθενείς υπό **secukinumab** σε σύγκριση με το placebo, στην πλειοψηφία ήπιες λοιμώξεις ανωτέρου αναπνευστικού
- Καμία αναφορά για **σοβαρές ευκαιριακές λοιμώξεις** προς το παρόν
- Αυξημένη εμφάνιση λοιμώξεων Candida στους ασθενείς υπό Secukinumab, ήπιες, χωρίς να χρειαστεί να γίνει διακοπή της θεραπείας
- Δεν προκύπτουν στοιχεία για:
  - Κακοήθειες
  - MACE
  - Ανοσογονικότητα

Σε σύγκριση με το Enbrel® λιγότερες αντιδράσεις στο σημείο της ένεσης

Το Secukinumab (fully human IL17A inhibitor) προσφέρει:

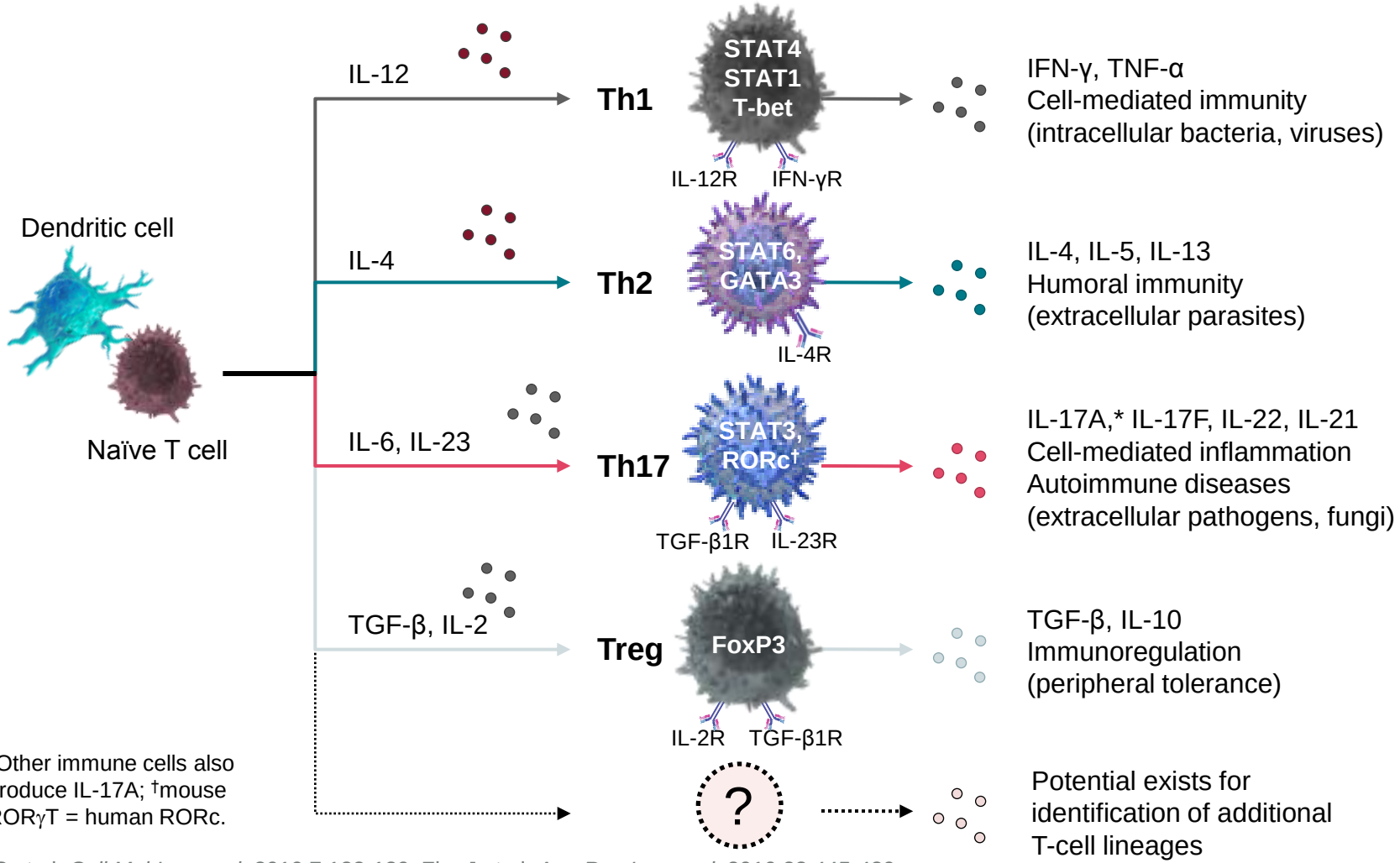
ΤΑΧΥΤΗΤΑ	**~50% μείωση των συμπτωμάτων την εβδομάδα 3**
ΙΣΧΥΡΟ ΑΠΟΤΕΛΕΣΜΑ	**72% των ασθενών πετυχαίνουν PASI 90 την εβδομάδα 16**
ΔΙΑΡΚΕΙΑ	**~65% των ασθενών διατηρούν PASI 90 την εβδομάδα 52**

Source: FIXTURE (A2303)
Wk 12 pooled data (A2302/3/8/9)

Σας ευχαριστώ για την προσοχή σας!

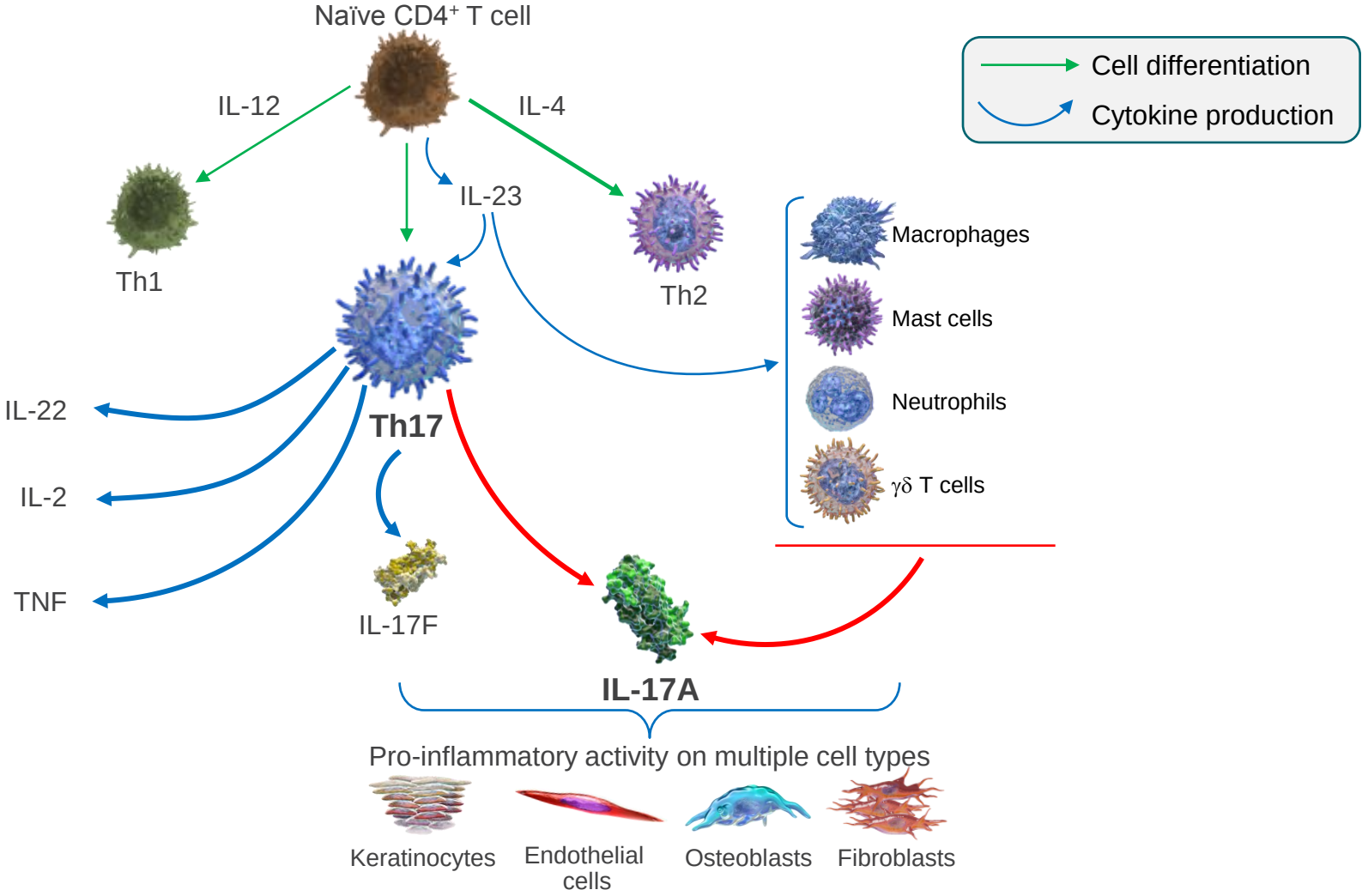
BACK-UP slides

IL-23 Produced by Dendritic Cells Plays a Role in Differentiation and Maintenance of Th-17 Cells



Leung S et al. *Cell Mol Immunol.* 2010;7:182-189; Zhu J et al. *Ann Rev Immunol.* 2010;28:445-489; Marwaha A et al. *Front Immunol.* 2012;3:1-8; Hemdan N et al. *Immunol Lett*. 2012:148:97-109; Annunziato F, Romagnani S. *Blood.* 2009;114:2213-2219.

IL-23 Stimulates Th17 Cells (and Other Immune Cells) to Produce IL-17A



Iwakura Y et al. *J Clin Invest*. 2006;116:1218-1222; Ouyang W et al. *Eur J Immunol*. 2009;39:670-675; Vignali DA, Kuchroo VK. *Nat Immunol.* 2012;13:722-728.

A New Framework for Understanding T-Cell Differentiation

The discovery of Th17 cells:[1,2]

- Provided a new understanding of immune defense against extracellular pathogens such as Gram-negative bacteria and fungi[3,4]
- Reconciled long-standing discrepancies of the Th1/Th2 model[4]
- Explained immune responses in chronic inflammatory diseases inconsistent with the Th1-Th2 paradigm[5,6]

1. Park H et al. *Nat Immunol*. 2005;6:1113-1141; 2. Harrington LE et al. *Nat Immunol.* 2005;6:1123-1132; 3. Korn T et al. *Annu Rev Immunol*. 2009;27:485-517; 4. Gaffen S. *Curr Opin Immunol.* 2011;23:613-619; 5. Weaver CT et al. *Annu Rev Immunol.* 2007;25:821-852; 6. Miossec P et al. *N Engl J Med*. 2009;361: 888-898.

Th17 Cells ≠ IL-17[1-3]

- Th17 cells are a separate lineage of $CD4^+$ T cells characterized by secretion of IL-17[1,2]
- IL-17 is a superfamily of cytokines with unique structural features that distinguish these family members from other cytokine families[2]
- IL-17A is one member cytokine of the IL-17 family[1]
- Th17 cells produce many molecules other than IL-17A[1,3]
- Th17 cells are not the only source for IL-17A[1,2]

NK, natural killer.

1. Kim J et al. *Cell Mol Life Sci.* 2013;70:2271-2290; 2. Jones S et al. *Nat Immunol.* 2012;11:1022-1025;
3. Miossec P et al. *Nat Reviews.* 2012;11:763-776.

IL-17 in Normal Immune Defense and Autoimmunity

What is IL-17?
IL-17 Is a Family of Interleukins*[1]

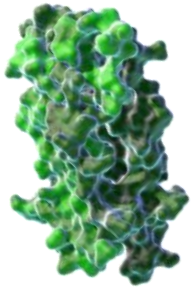
IL-1 Family	IL-2 Family	IL-6 Family	IL-12 Family[2]	IL-17 Family
IL-1β	IL-2	IL-6	IL-12	**IL-17A**
IL-1α	IL-15	IL-11	IL-23	IL-17F
IL-1Ra	IL-21		IL-27	IL-17B
IL-18			IL-35	IL-17D
IL-33				IL-17C
IL-36 α, β, γ				IL-17E (aka IL-25)

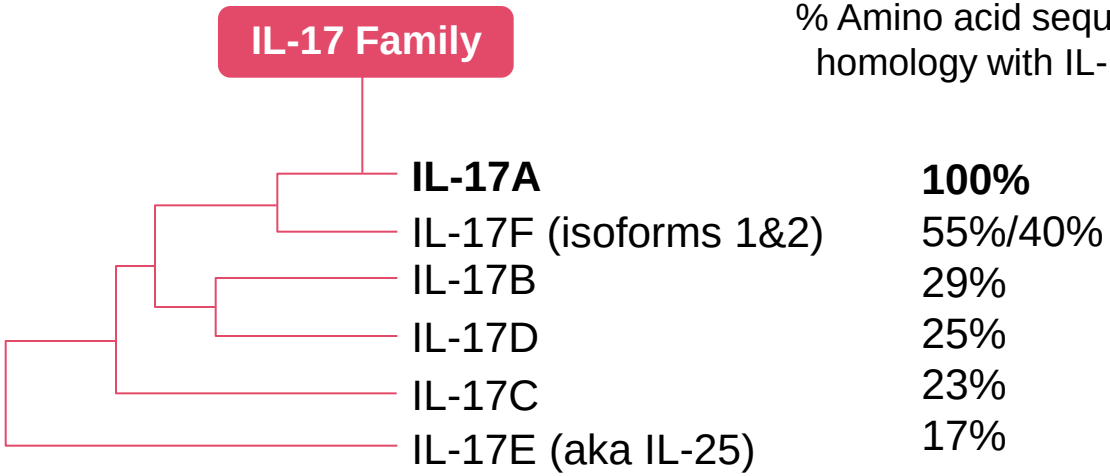
- IL-17 is a superfamily of cytokines with unique structural features that distinguish these family members from other cytokine families
- The IL-17 cytokine family plays an important role in immune responses in
  - Normal physiology[3]
  - Pathologic conditions[3]

*Representative IL families, not a complete list of families or members; IL-17 family list complete.

1. Meager A, Wadhwa M. *Encyclopedia of Life* Sciences. Chichester, England: John Wiley & Sons Ltd; 2007.
2. Vignali DA, Kuchroo VK. *Nat Immunol.* 2012;13:722-728.
3. Miossec P et al. *N Engl J Med*. 2009;361:888-898.

IL-17A Has Emerged as a Critical Pro-inflammatory Cytokine in the IL-17 Cytokine Family



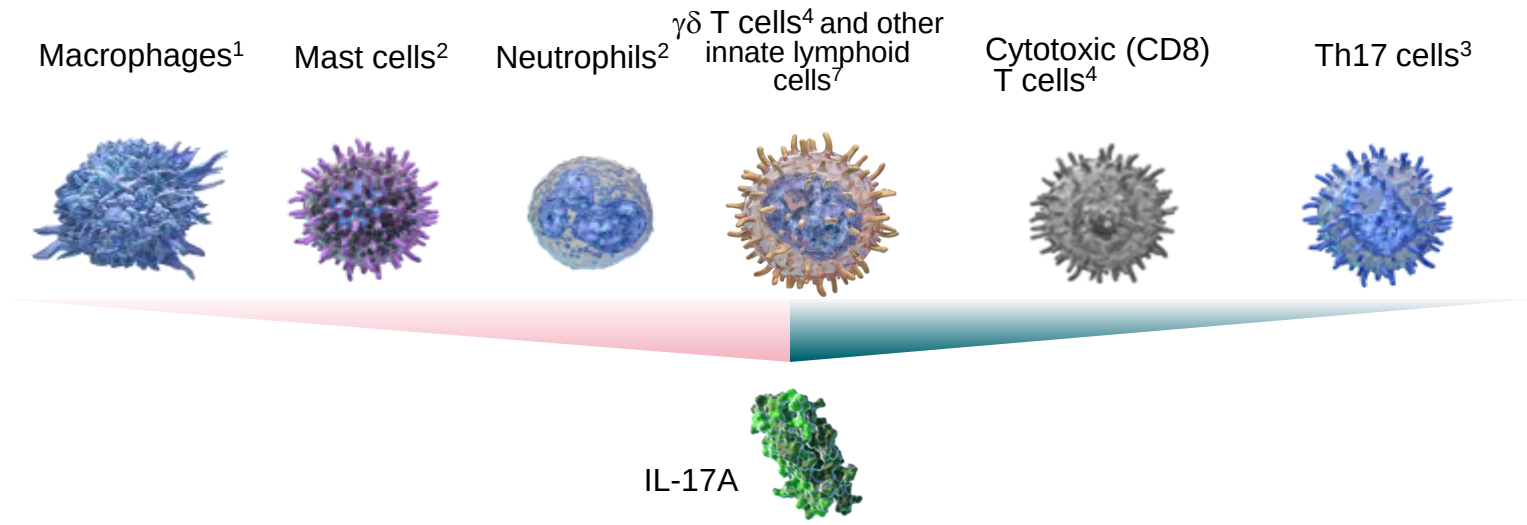


IL-17A

- Is also referred to as IL-17[1]
- Is a homodimeric glycoprotein (35 kDa)[1]
- Bridges innate and adaptive immunity through signaling[2]
- Plays important roles against extracellular pathogens[3]
- Promotes inflammatory pathology[1,4]

1. Ivanov S, Linden A. *Trends Pharmacol Sci.* 2009;30:95-103; 2. Kolls J, Linden A. *Immunity.* 2004;21:467-476; 3. Gaffen S. *Nat Rev Immunology.* 2009;9:556-567; 4. Blanco P et al. *Cytokine Growth Factor Rev.* 2008;19:41-52.

IL-17A Is Expressed by a Variety of Innate and Adaptive Immune Cells

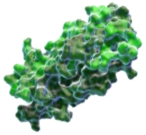


Additional Immune Cells Expressing IL-17A

Innate	Adaptive
Natural killer cells[3]	Natural killer T cells[3,4]
Eosinophils[5]	
$CD4^+$ lymphoid tissue inducer–like cells[6]	

1. Onishi R, Gaffen S. *Immunology.* 2010;129:311-321; *2.* Lin A et al. *J Immunol.* 2011;187:490-500; 3. Miossec P et al. *N Engl J Med*. 2009;361:888-898; 4. Weaver C et al. *Annu Rev Immunol.* 2007;25:821-852; 5. Molet S et al. 2001;108:430-438; 6. Takatori H et al. *J Exp Med.* 2008;206:35-41; 7. Sutton CE et al. *Eur J Immunol.* 2012;42:2221-2231.

IL-17A Has Effector Activity on Cells of Multiple Lineages



IL-17A

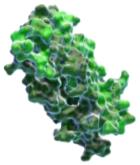
Target-Cell Type

Macrophage, dendritic cell	Endothelial cell	Fibroblast	Osteoblast*	Osteoclast*	Chondrocyte	Keratinocytes
Products						
• IL-1 • TNF • IL-6 • CRP • MMP9	• IL-6 • MMPs	• IL-6 • Chemokines • Growth factors • MMP1, 3, 13	• RANKL • Chemokines • Osteo-clastogenesis	• RANKL • MMP1, 2, 3, 9	• IL-1 • IL-6 • iNOS • Chemokines	• IL-6 • Chemokines • Anti-microbial peptides • Ki67 (proliferation)

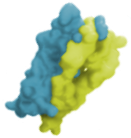
*Effects of IL-17A on osteoblast/osteoclast interactions are not completely understood.
CRP, C-reactive protein; IL, interleukin; MMP, matrix metalloproteinase; RANKL, receptor-activated nuclear factor κB ligand. Adapted from Miossec P et al. *N Engl J Med.* 2009;361:888-898; Onishi R, Gaffen S. *Immunology.* 2010;129:311-321; Kotake S et al. *J Bone Miner Metab.* 2012;30:125-135; Iwakura Y et al. *Immunol Rev.* 2008;226:57-79.

How Are IL-17A and IL-17F Related?

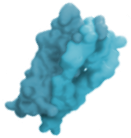
IL-17A



IL-17A/IL-17F



IL-17F



- IL-17A and IL-17F have high (55%/40%) amino acid sequence homology compared with other IL-17 family members[1]
- IL-17A is a homodimeric cytokine composed of two IL-17A subunits[1]
- IL-17A/IL-17F is a heterodimeric cytokine composed of an IL-17A and an IL-17F subunit[2]
- IL-17F is a homodimeric cytokine composed of two IL-17F subunits[1]
- IL-17A, but not IL-17F, is associated with pathogenesis of immune-mediated disease[1]

1. Kolls JK, Linden A. *Immunity.* 2004;21:467-476; 2. Ivanov S, Linden A. *Trends in Pharmacol Sci.* 2009;30:95-103.

Roles of IL-17A and IL-17F in Normal Host Immune Defense

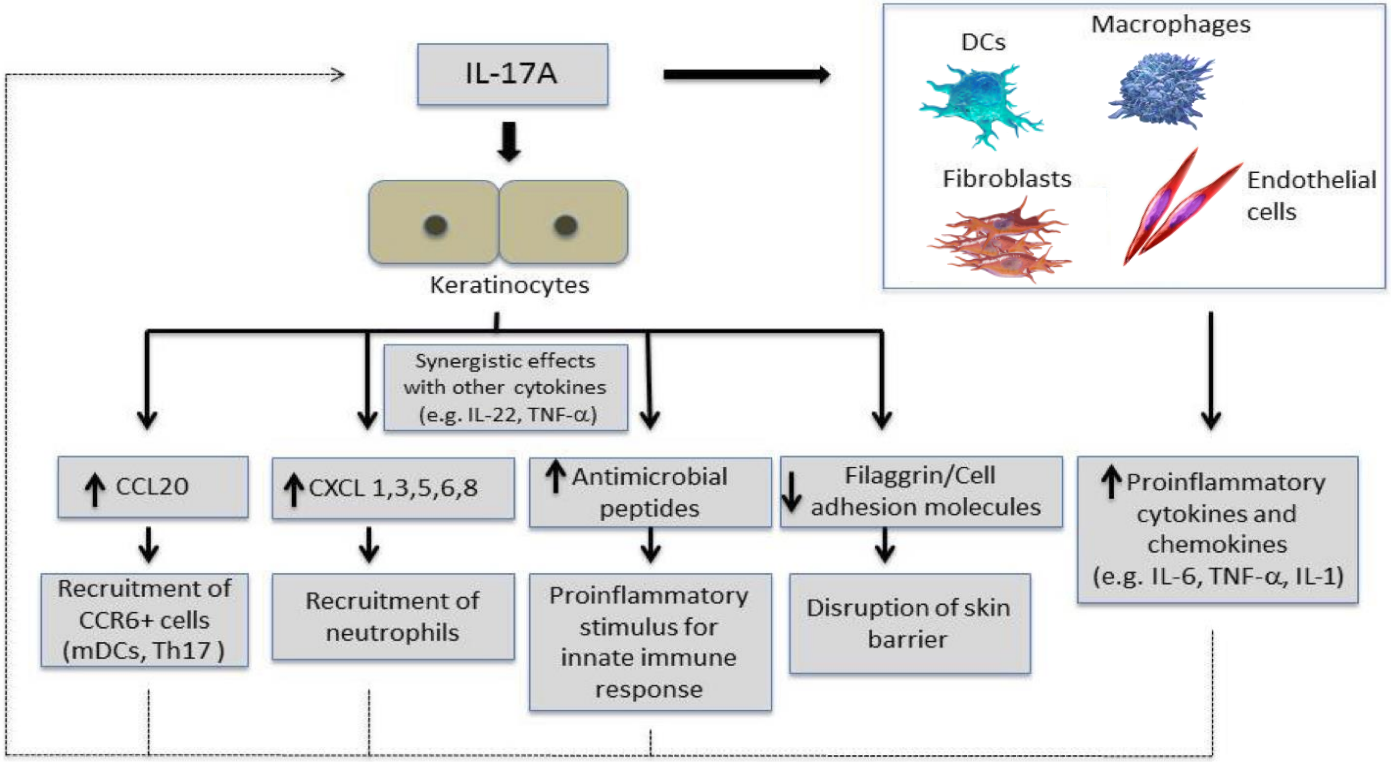
- Neutrophil recruitment[1]
- Induction and expression of inflammatory mediators from multiple cell types:
  - Colony-stimulating (GM-CSF, G-CSF)
  - CXC chemokines[2,3] (CXCL1, CXCL5, IL-8, CCL2, CCL7)
  - Metalloproteinases
  - IL-6
  - Anti-microbial peptides (defensins and S100 proteins)
- Involved in host defense against mucocutaneous candidiasis[4,5]
  - Evidence: Individuals with genetic deficits in IL-17 immunity (or auto-antibodies to IL-17A, IL-17F, and IL-22) are subject to these infections[4,5]

G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor.

1. Gaffen SL. *Nat Rev Immunol.* 2009;9:556-567; 2. Weaver CT et al. *Annu Rev Immunol.* 2007;25:821-852; 3. Iwakura Y et al. *Immunol Rev.* 2008;226:57-79. 4.Puel A et al. *Science.* 2011;332:65-68. 5.Puel A et al. *J Exp Med.* 2010;207:291-297.

IL-17 in Psoriasis

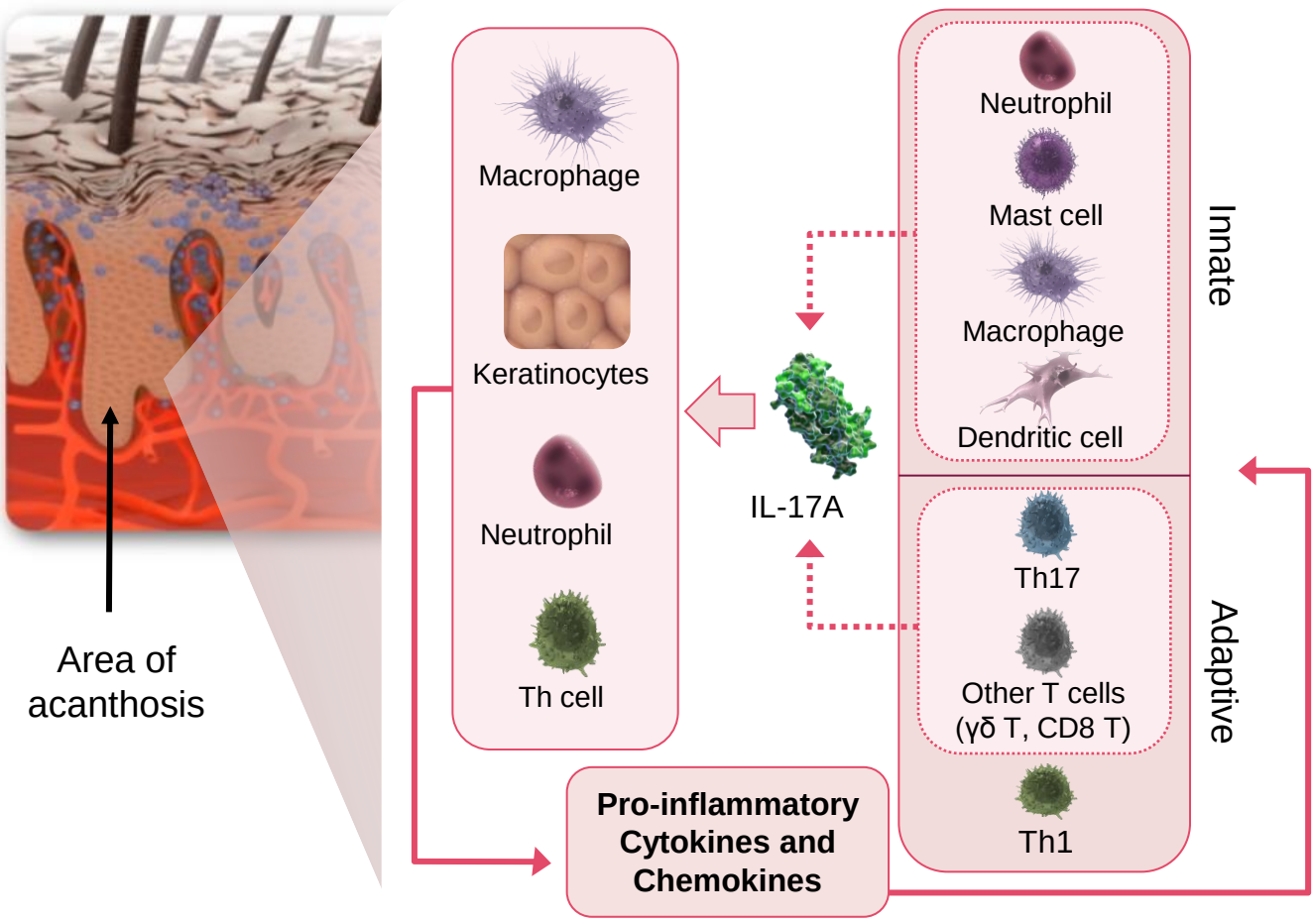
IL-17A as a Key Mediator of Psoriasis



- IL-17A is enriched in psoriatic lesions and is produced by a host of cell types in skin

mDC, myeloid dendritic cell.
Girolomoni G et al. *Br J Dermatol.* 2012;167:717-724.

IL-17A–Induced Keratinocyte Activation and Proliferation Promotes a Cytokine Feedback Loop



Lin AM et al. *J Immunol.* 2011;187:490-500; Nestle FO et al. *N Engl J Med.* 2009;361:496-509; Res PC et al. *PLoS One.* 2010;5:e14108; Cai Y et al. *Immunity.* 2011;35:596-610.

Summary

- **Th17 cells and IL-17 cytokines:** protective in immune defense, but also pathogenic for immune-mediated diseases
- **IL-17A:** associated with development of immune-mediated diseases, including psoriasis
- **IL-17A:** acts on multiple cell types to induce pro-inflammatory feedback loop
- **Human epidermal keratinocytes:** dominant skin cell population expressing IL-17 receptors
- **Psoriatic lesions:** show increased expression of IL-17A
- **Not just Th17 cells:** innate immune cells (mast cells, neutrophils) produce IL-17A in psoriatic lesions, may act in pathophysiology of psoriasis