South Beach Symposium
clinical + aesthetic dermatology
SBS PART I
THE MEDICAL DERMATOLOGY Summit
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The Logic Behind Biologics for Psoriasis

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Dean for Clinical Therapeutics
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Chairman Emeritus
Kimberly and Eric J. Waldman Department of Dermatology

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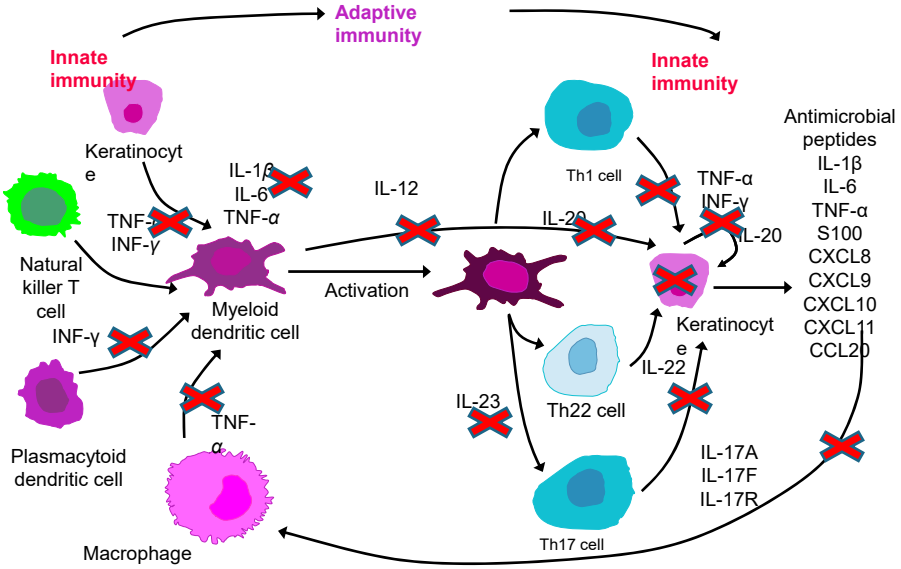
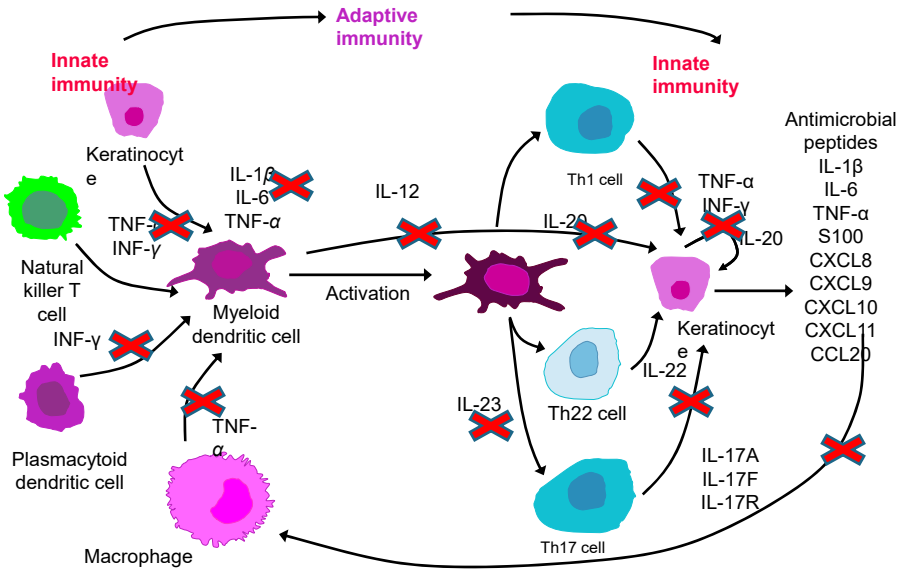
Mechanism of Methotrexate



Adapted from: Nestle F, et al, NEJM 2009; 501.

4

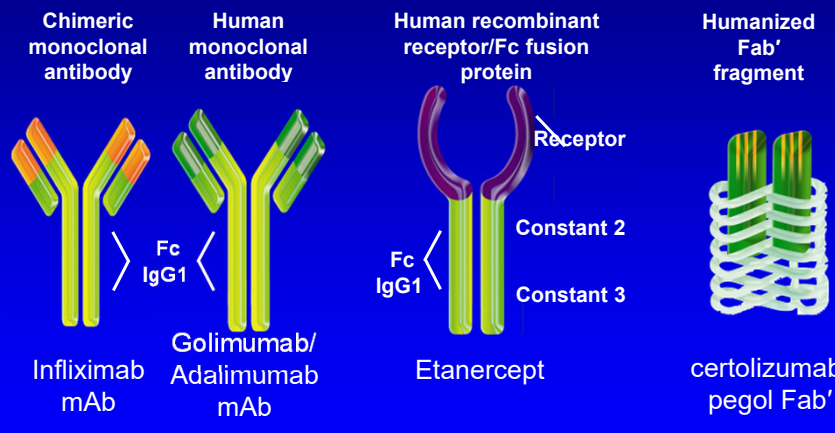
Mechanism of Cyclosporine



Adapted from: Nestle F, et al, NEJM 2009; 501.

5

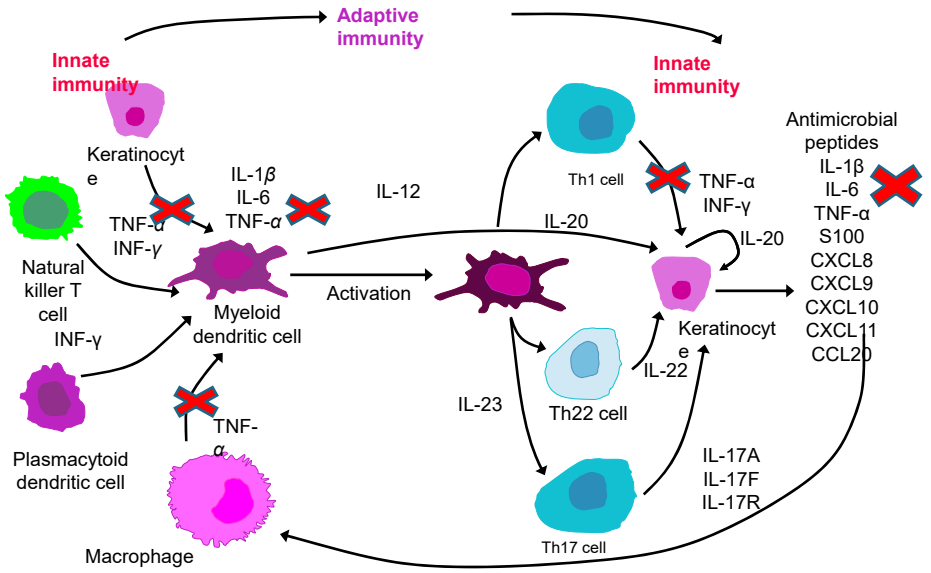
Monoclonal Antibodies, Fusion Proteins and Fab' fragments against TNF: Structure



Adapted from Hanauer SB. Gastroenterol Disord 2004;4(Suppl. 3):S18-24.

6

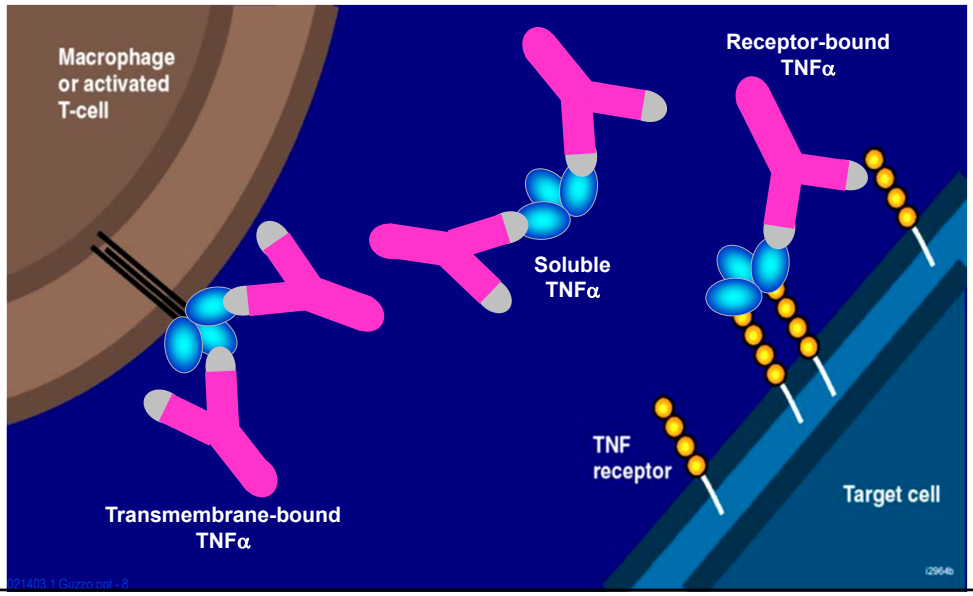
Mechanism of TNF blockers



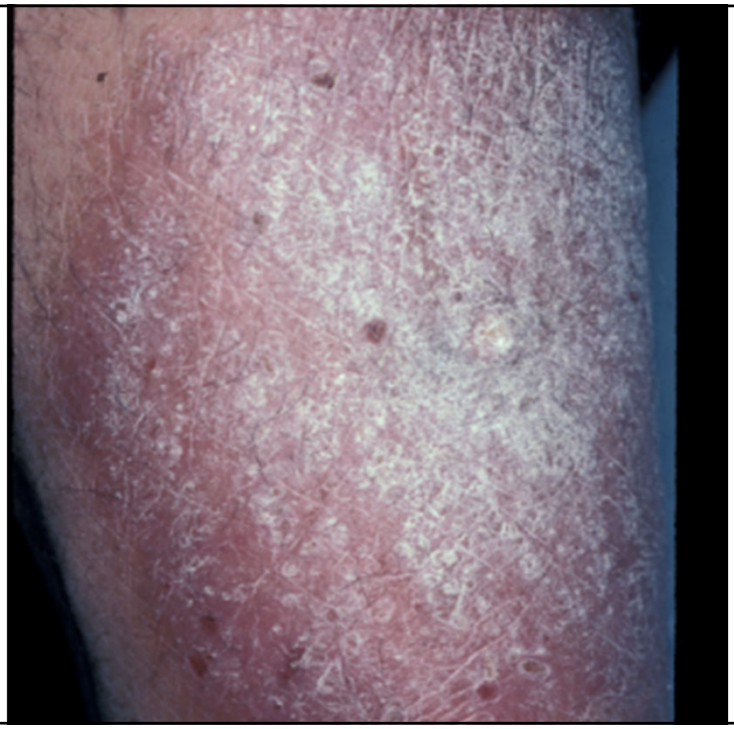
Adapted from: Nestle F, et al, NEJM 2009; 501.

7

Infliximab Neutralization of TNFα



8



9

10

Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial.

Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Lancet. 2001;357(9271):1842-7.

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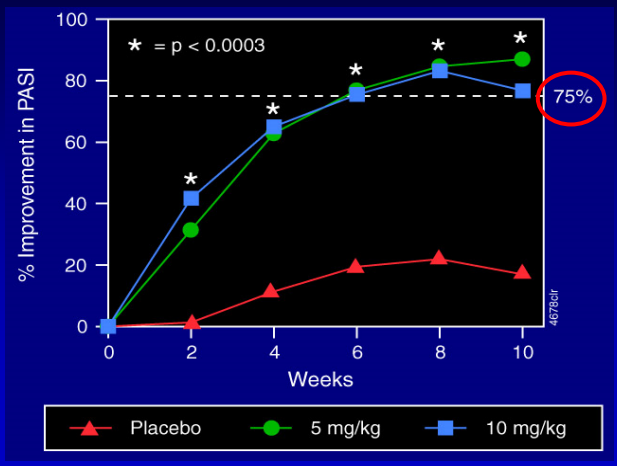
Infliximab in Psoriasis (N=33)

Mean PASI Score Through Week 10



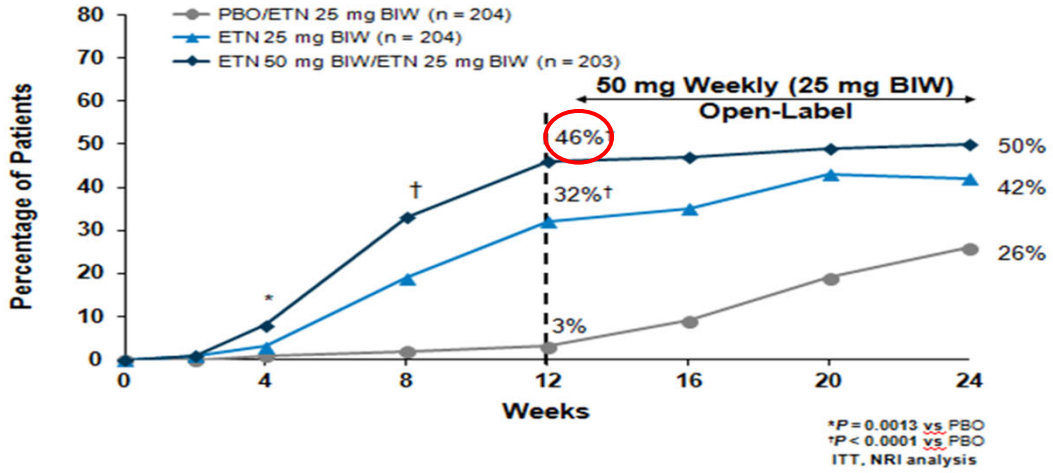
Chaudhari U, et al. *Lancet*. 2001;357:1842-1847.

12

Etanercept Global Psoriasis Trial Part II

ETANERCEPT

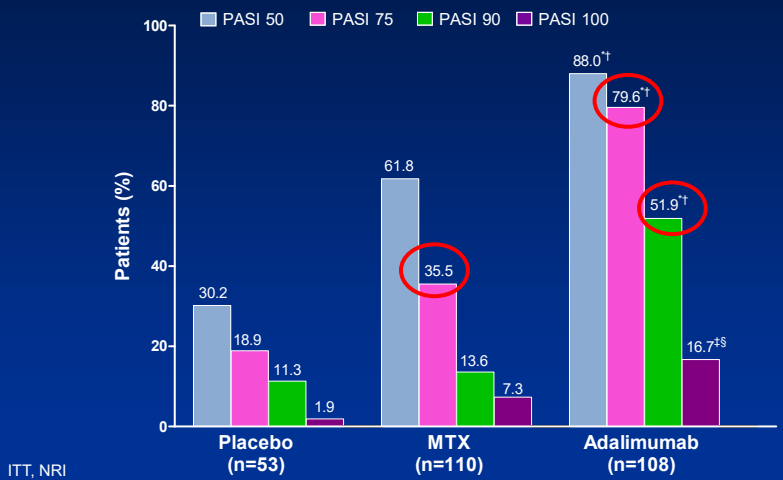
PASI 75 Response Through Week 24



1. Enbrel® (etanercept) Prescribing Information, Immunex Corporation, Thousand Oaks, Calif. 2. Papp KA, et al. *Br J Dermatol.* 2005;152:1304-1312. 3. Data on file, Amgen.

13

PASI response rates at Week 16 of CHAMPION



ITT, NRI
*P<0.001, adalimumab vs. placebo
†P<0.001, adalimumab vs. MTX
‡P<0.01, adalimumab vs. placebo
§P<0.05, adalimumab vs. MTX

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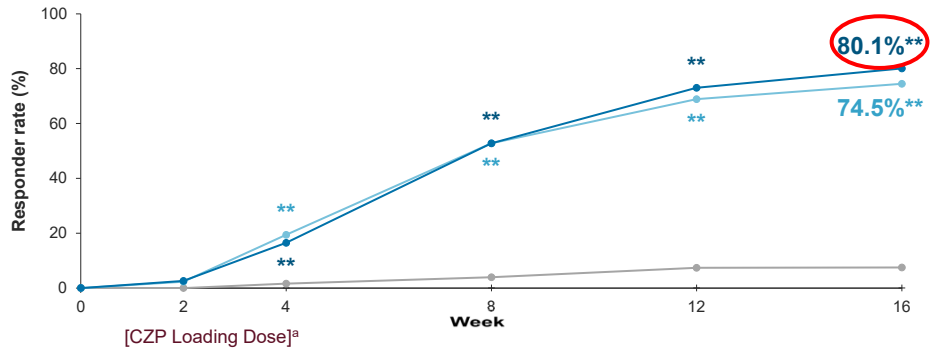
PASI 75 Responder Rates from Baseline to Week 16

Pooled Phase 3 Studies (CIMPASI-1/-2 and CIMPACT)



	[CZP Loading Dose]a				
Placebo (N=157)	0%	1.6%	3.9%	7.4%	7.5%
CZP 200 mg Q2Wa (N=351)	2.3%	19.4%	52.8%	68.9%	74.5%
CZP 400 mg Q2W (N=342)	2.6%	16.5%	52.8%	73.0%	80.1%

**p<0.0001 versus placebo (not adjusted for multiplicity); aCZP 200 mg Q2W patients received loading dose of CZP 400 mg at Weeks 0, 2, and 4; Responder rates are the adjusted predicted probabilities based on logistic regression model with factors for treatment, region, study, prior biologic exposure (yes/no), study*region, and study*prior biologic exposure where missing data were imputed using NRI method (patients missing PASI response are considered to be nonresponders); CZP, certolizumab pegol; LD, loading dose of CZP 400 mg Q2W at Weeks 0, 2, and 4; NRI, nonresponder imputation; PASI 75, ≥75% reduction in psoriasis area and severity index; Q2W, every 2 weeks

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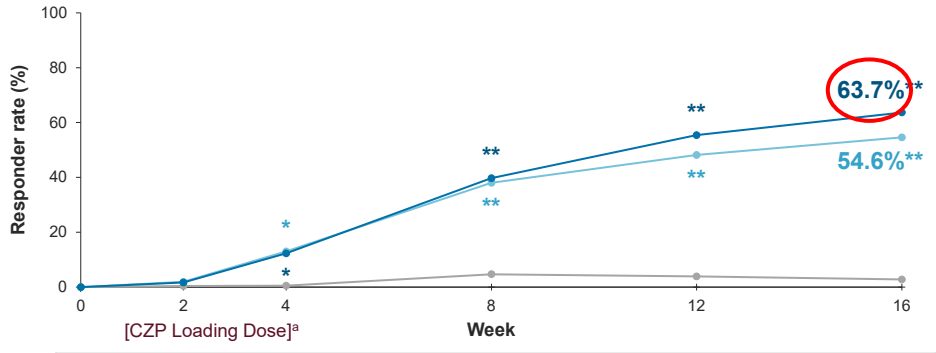
PGA 0/1 Responder Rates from Baseline to Week 16

Pooled Phase 3 Studies (CIMPASI-1/-2 and CIMPACT)



	[CZP Loading Dose]a				
Placebo (N=157)	0.4%	0.5%	4.7%	3.9%	2.8%
CZP 200 mg Q2Wa (N=351)	1.9%	13.0%	38.0%	48.2%	54.6%
CZP 400 mg Q2W (N=342)	1.7%	12.3%	39.7%	55.4%	63.7%

*p<0.05, **p<0.0001 versus placebo (not adjusted for multiplicity); aCZP 200 mg Q2W patients received loading dose of CZP 400 mg at Weeks 0, 2, and 4; Responder rates are the adjusted predicted probabilities based on logistic regression model with factors for treatment, region, study, prior biologic exposure (yes/no), study*region, and study*prior biologic exposure where missing data were imputed using NRI method (patients missing PGA 0/1 response are considered to be nonresponders); CZP, certolizumab pegol; NRI, nonresponder imputation; PGA 0/1, 'clear' or 'almost clear' with ≥2-category improvement in physician's global assessment (5-point scale); Q2W, every 2 weeks

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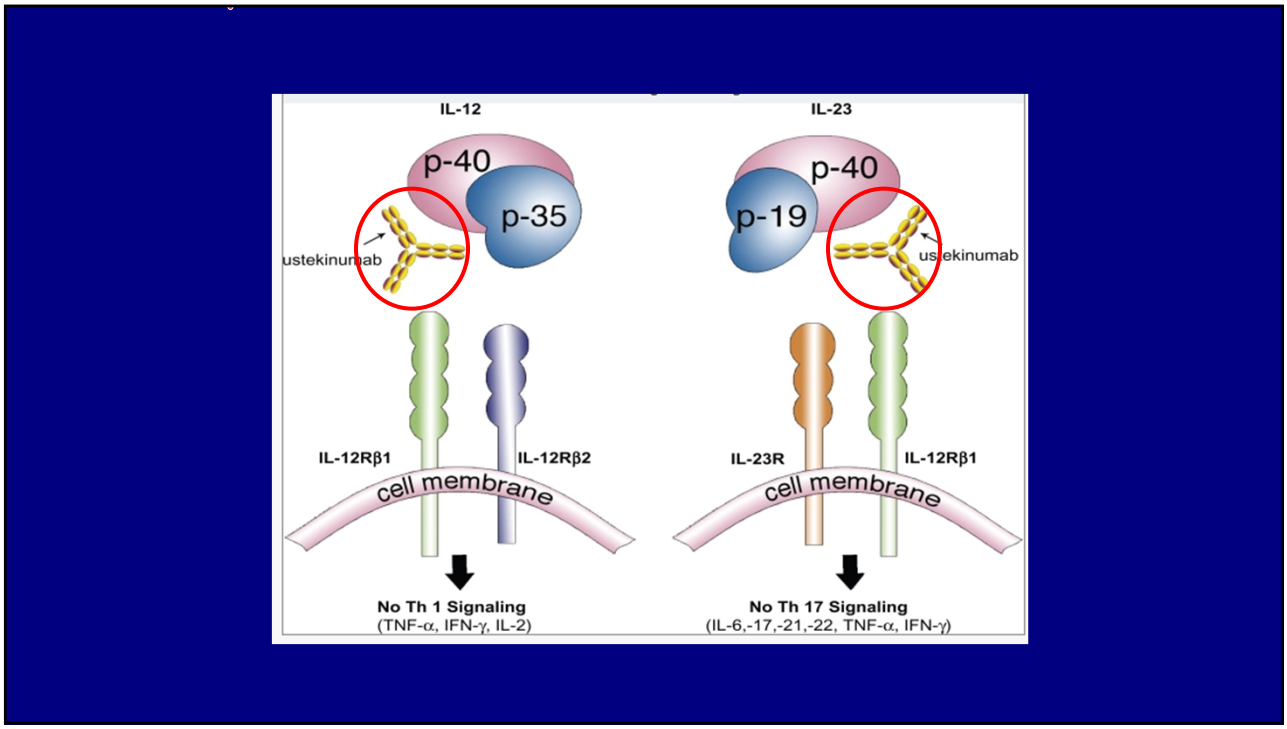

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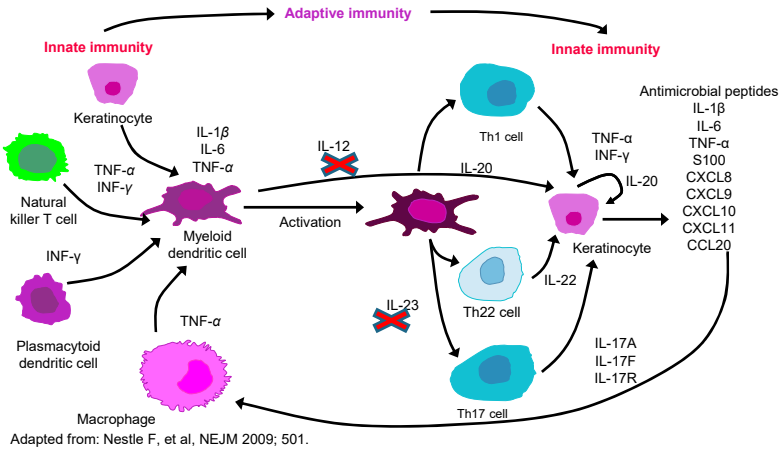
Mechanism of ustekinumab



Adapted from: Nestle F, et al, NEJM 2009; 501.

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Response to CNTO 1275

Baseline

Week 12

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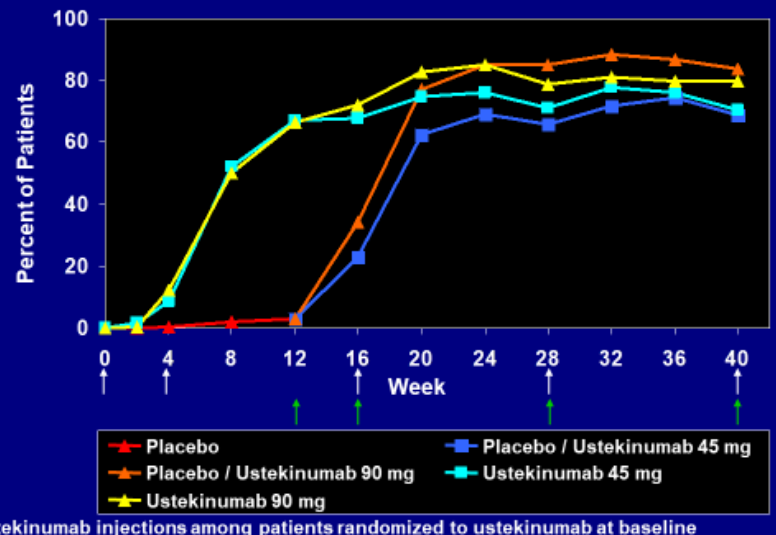
PHOENIX 1

PASI 75 Through Week 40



↑ =Ustekinumab injections among patients randomized to ustekinumab at baseline

↑ =Ustekinumab injections among placebo patients crossed over to ustekinumab at Week 12

Leonardi CL, et al. *Lancet.* 2008;371:1665–1674.

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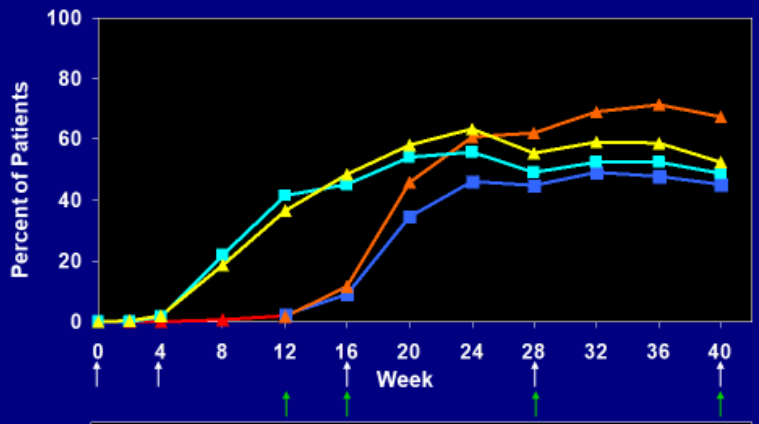
PHOENIX 1

PASI 90 Through Week 40



↑ =Ustekinumab injections among patients randomized to ustekinumab at baseline

↑ =Ustekinumab injections among placebo patients crossed over to ustekinumab at Week 12

Leonardi CL, et al. *Lancet.* 2008;371:1665–1674.

21

Revisiting human IL-12Rβ1 deficiency: a survey of 141 patients from 30 countries.

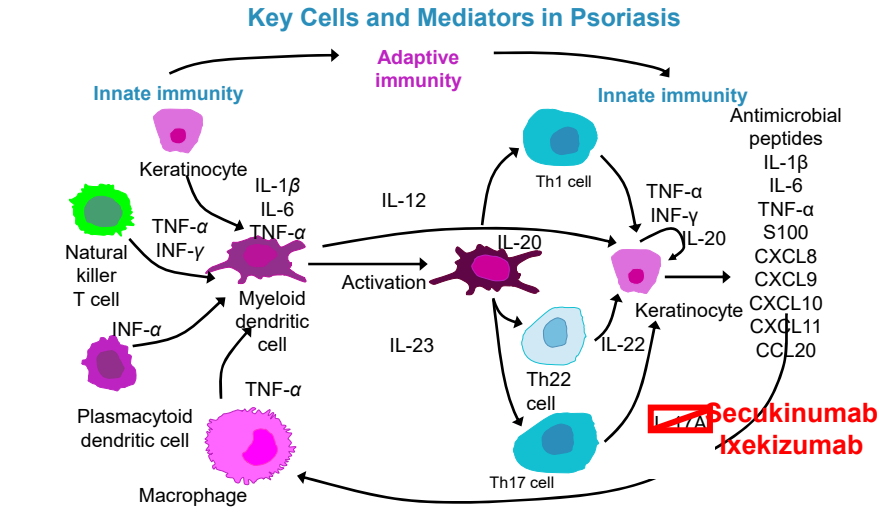
de Beaucoudrey L, et al

Medicine (Baltimore). 2010;89:381-402.

- **141 patients**
- **mycobacterial infections & salmonella**

22

Ixekizumab, Secukinumab,



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

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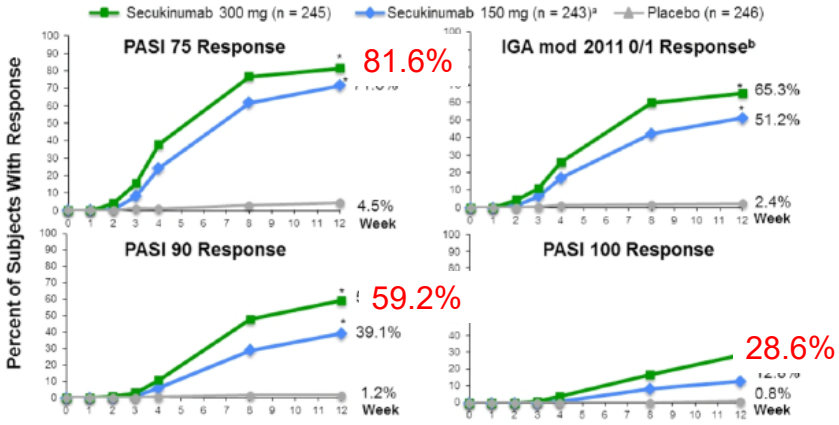
Secukinumab was significantly superior to placebo in achieving clinical efficacy endpoints at Week 12



- Baseline demographic and disease characteristics were well-balanced across treatment groups, including ethnicity, body weight, disease severity, and previous use of biologic therapy for psoriasis

n, number of subjects evaluable for responses. *P < 0.001 vs. placebo.
[a]Number of subjects evaluable for IGA mod 2011 0/1 response in secukinumab 150 mg group was 244; [b]IGA mod 2011 score of 0 (clear) or 1 (almost clear) and an improvement of ≥2 points on the IGA scale compared with baseline.
[1]Langley RG, Elewski BE et al. *N Engl J Med*. 2014;371:326-338.

Lebwohl M, et al. EADV 2014, P1652

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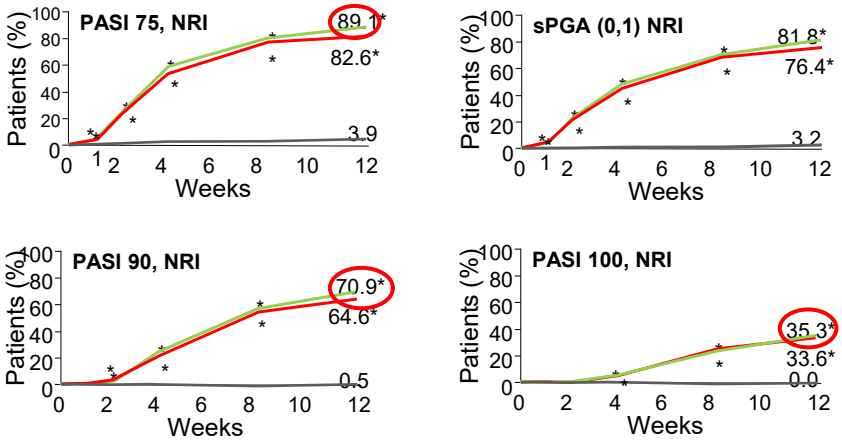
UNCOVER-1: Efficacy outcomes at Week 12

Ixekizumab



*P<0.001 vs PBO based on logistic regression (Fisher's exact test when PBO response was 0%)

Gordon K, et al. WCD 2015 Sponsored by Eli Lilly

NRI, nonresponder imputation

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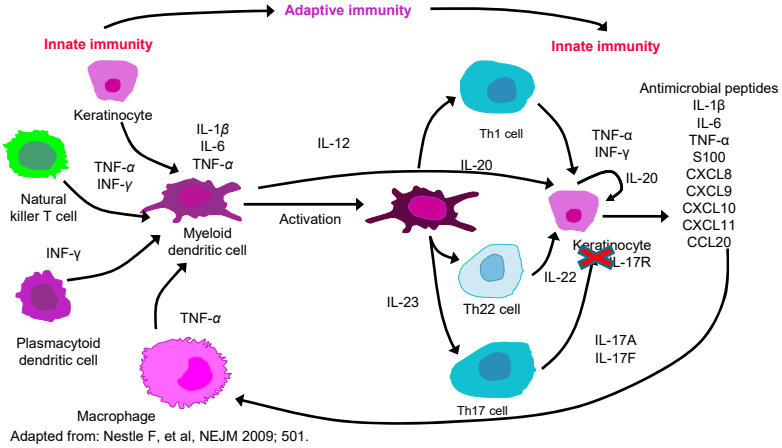
Mechanism of Brodalumab



Adapted from: Nestle F, et al, NEJM 2009; 501.

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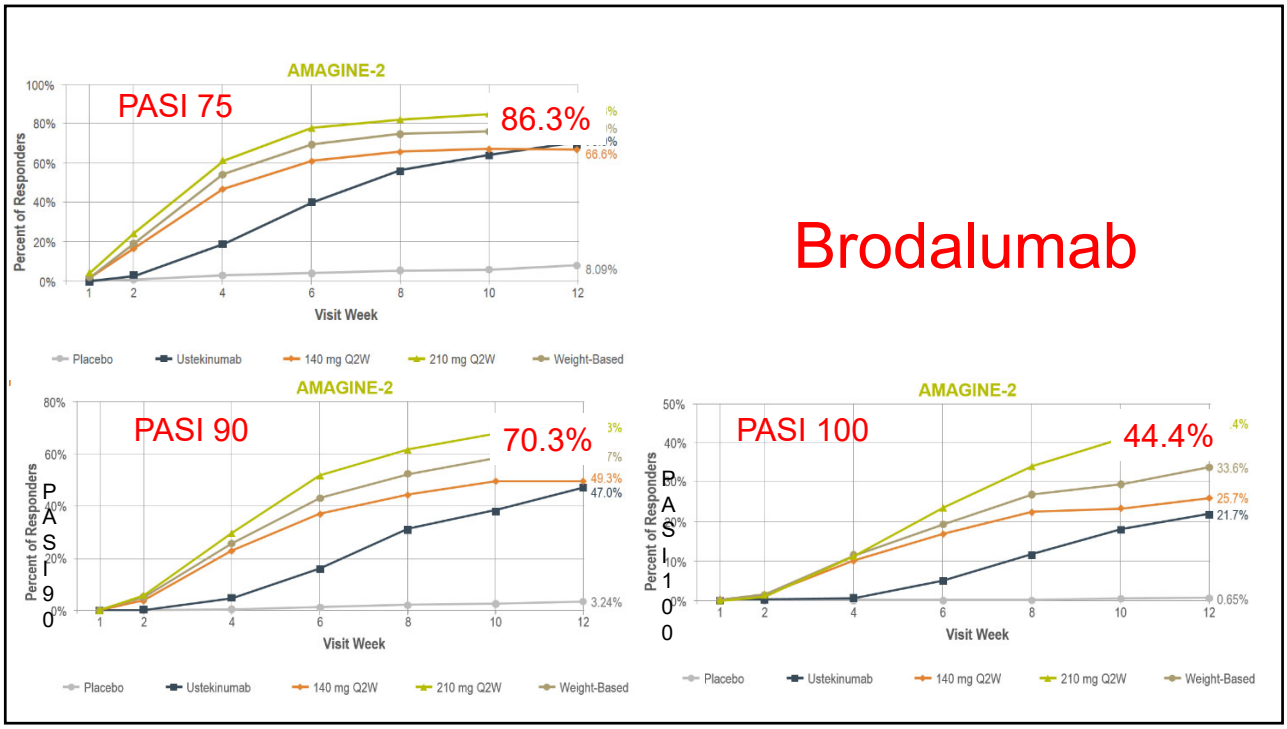
AMAGINE-2
PASI 75
86.3%
66.6%
8.09%
Percent of Responders
Visit Week
Placebo
Ustekinumab
140 mg Q2W
210 mg Q2W
Weight-Based
Brodalumab
AMAGINE-2
PASI 90
70.3%
49.3%
47.0%
3.24%
AMAGINE-2
PASI 100
44.4%
33.6%
25.7%
21.7%
0.65%

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Pearl #1 Anti-IL-17 antibodies are fast

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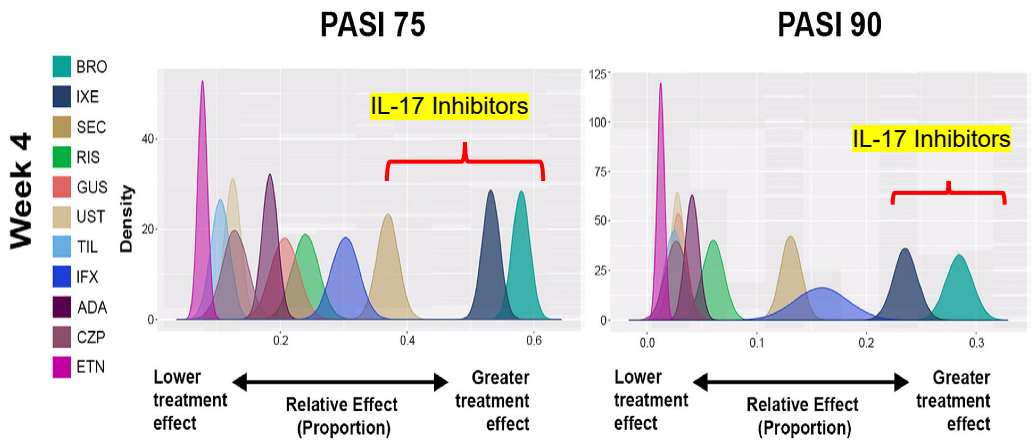
Treatment effects at week 4



Dermatol Ther (Heidelb) (2020) 10:73–86

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Subject #9: Close Up View of Buttocks - Baseline and Week 1

Baseline

Week 1
Ixekizumab Q2W

33

Subject #9: Close Up View of Buttocks - Baseline and Week 2

Baseline

Week 2
Ixekizumab Q2W

34

Subject #9: Close Up View of Buttocks - Baseline and Week 4

Baseline

Week 4
Ixekizumab Q2W
PASI 75 and sPGA 2

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Subject #9: Close Up View of Buttocks - Baseline and Week 8

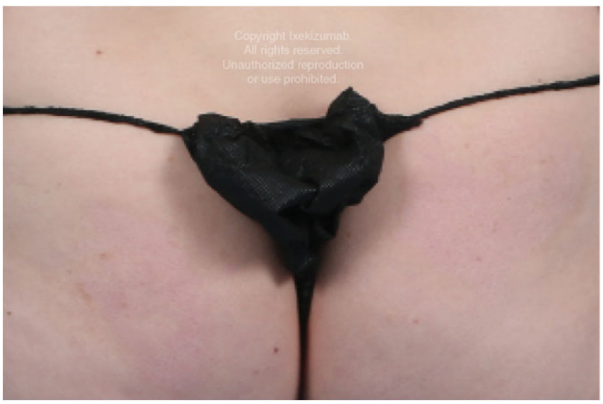
Baseline

Week 8
Ixekizumab Q2W

36

Subject #9: Close Up View of Buttocks - Baseline and Week 12

Baseline



Week 12
Ixekizumab Q2W
PASI 75 and sPGA 1

37

Immunity to infection in IL-17-deficient mice and humans.
Cypowyj S, Picard C, Maródi L, et al
Eur J Immunol. 2012;42:2246-2254.

Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity.
Puel A, Cypowyj S, Bustamante J, et al.
Science. 2011;332(6025):65-68.

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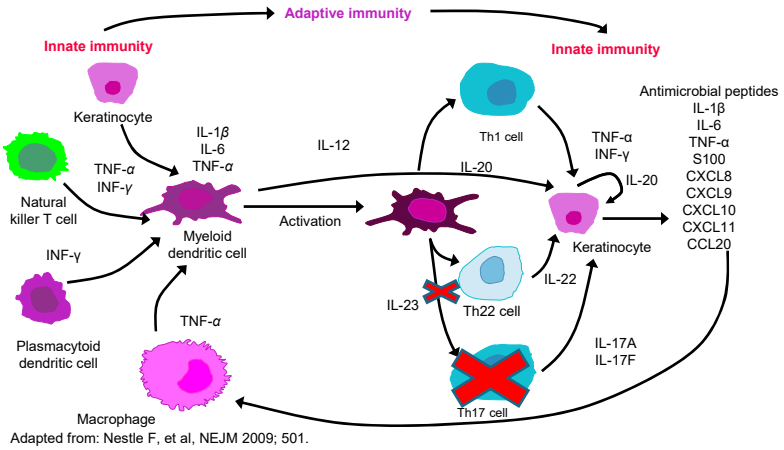
Mechanism of Guselkumab, Tilkdrakizumab, Risankizumab, Mirikizumab



Adapted from: Nestle F, et al, NEJM 2009; 501.

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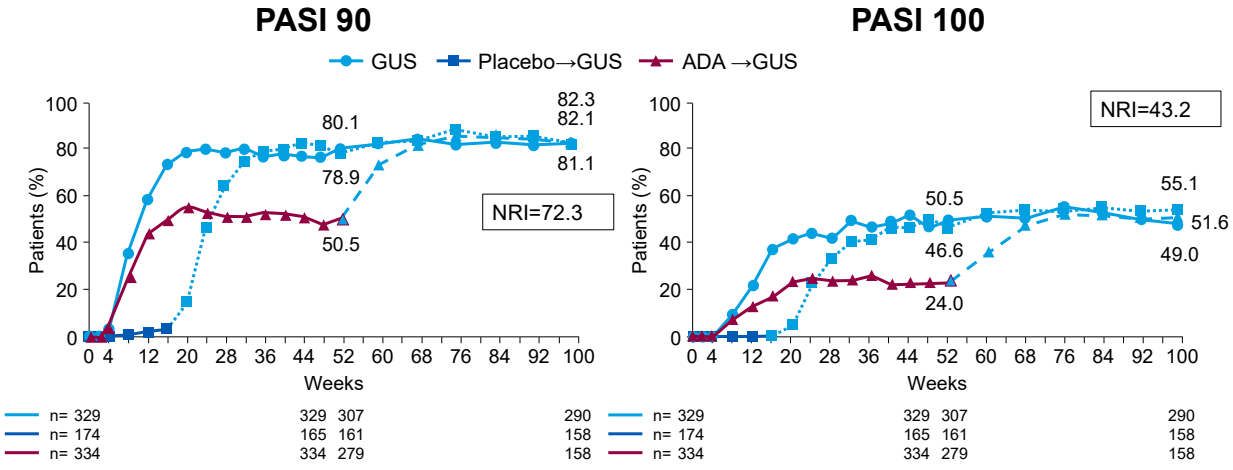
VOYAGE 1: Prespecified endpoints of PASI 90 and PASI 100 response with guselkumab through 2 years



Griffiths CEM, et al. EADV 2017; D3T01.I Sponsored by Janssen Clinical Research and Development LLC

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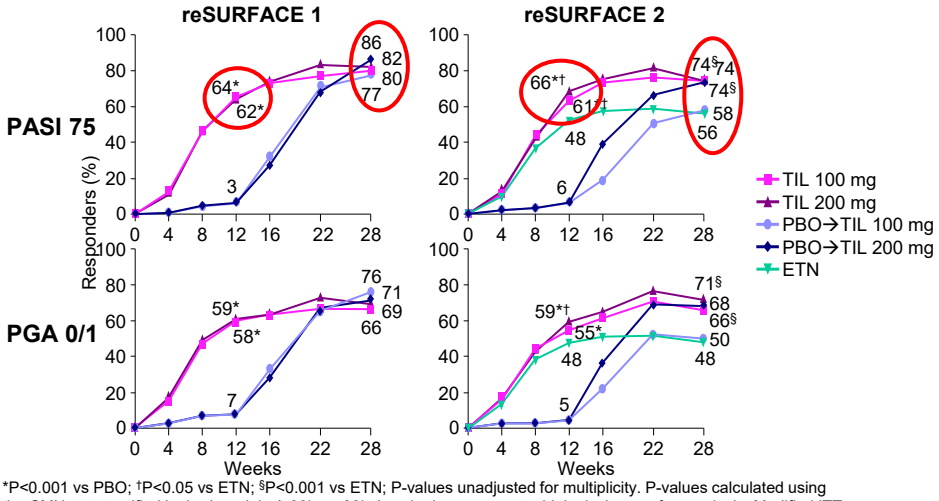
Tildrakizumab-PASI 75; PGA 0/1



*P<0.001 vs PBO; †P<0.05 vs ETN; §P<0.001 vs ETN; P-values unadjusted for multiplicity. P-values calculated using the CMH test stratified by body weight (≤90kg, >90kg) and prior exposure to biologic therapy for psoriasis. Modified ITT population (all randomized patients who received ≥1 dose of study medication). Figure represents observed data only; data shown for Week 12 are based on missing data being imputed as non-responders

Reich K, et al. EADV 2016, D3T01.1l Late Breaker Sponsored by Sun Pharmaceutical

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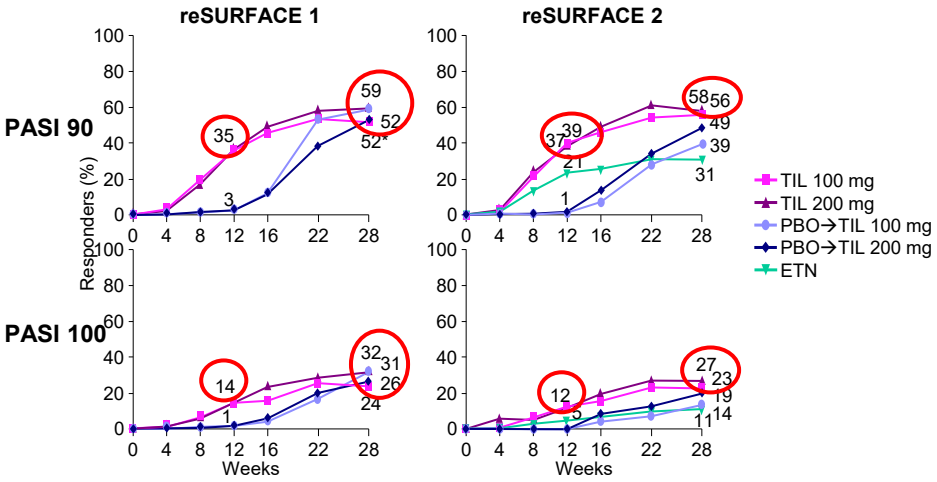
Tildrakizumab-PASI 90 and 100



Modified ITT population (all randomized patients who received ≥1 dose of study medication). Figure represents observed data only; data shown for Week 12 are based on missing data being imputed as non-responders.

Reich K, et al. EADV 2016, D3T01.1l Late Breaker Sponsored by Sun Pharmaceutical

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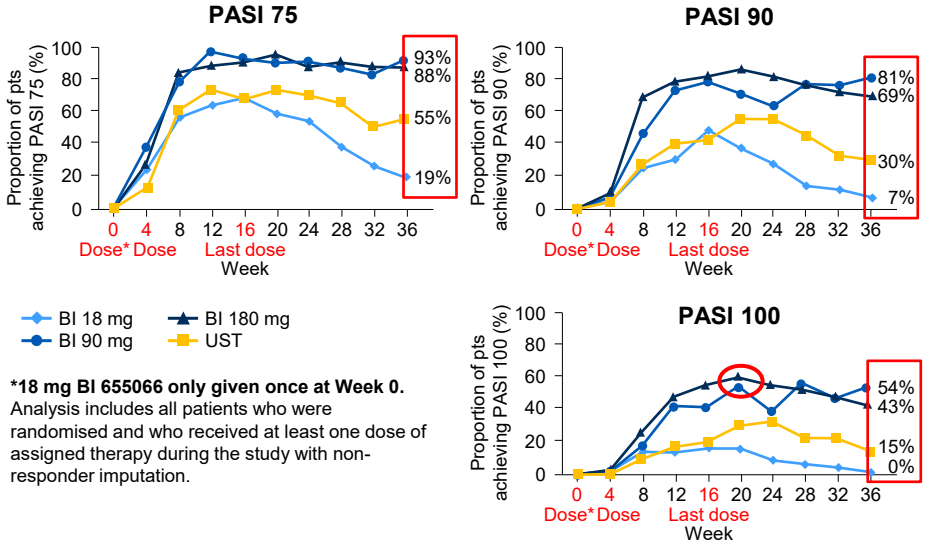
Risankizumab



***18 mg BI 655066 only given once at Week 0.**
Analysis includes all patients who were randomised and who received at least one dose of assigned therapy during the study with non-responder imputation.

Papp K, et al. EADV 2015, FC03.06 Sponsored by Boehringer Ingelheim

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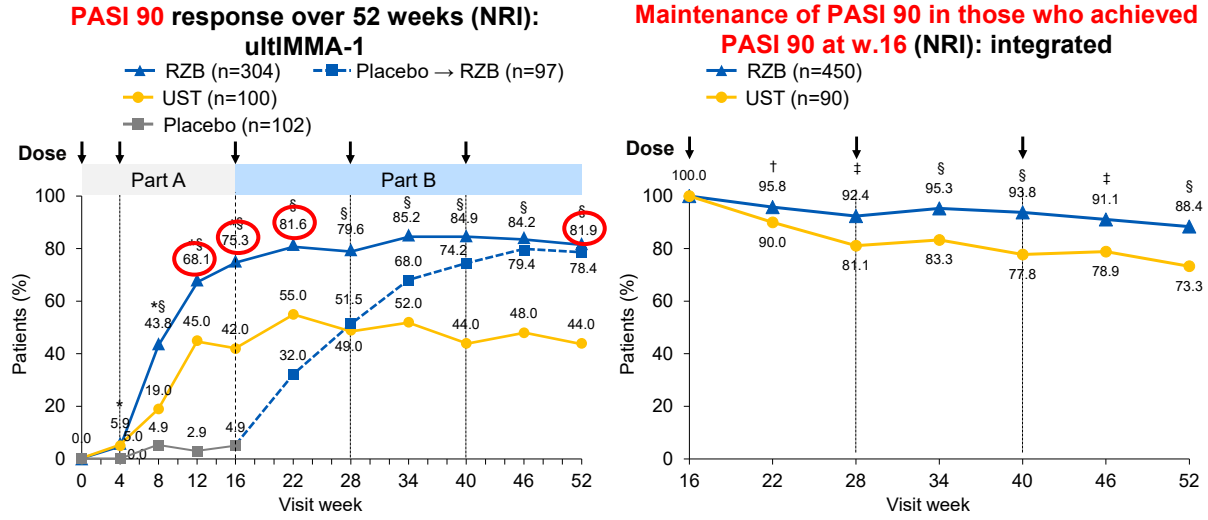
ultIMMa-1 and ultIMMa-2:
PASI 90 responses with risankizumab through Week 52



*P<0.001 vs placebo; †P<0.05, ‡P<0.01, §P<0.001 vs UST

Gordon KB, et al. AAD 2018, Late-breaking Research: Clinical Trials; Sponsored by AbbVie and Boehringer Ingelheim

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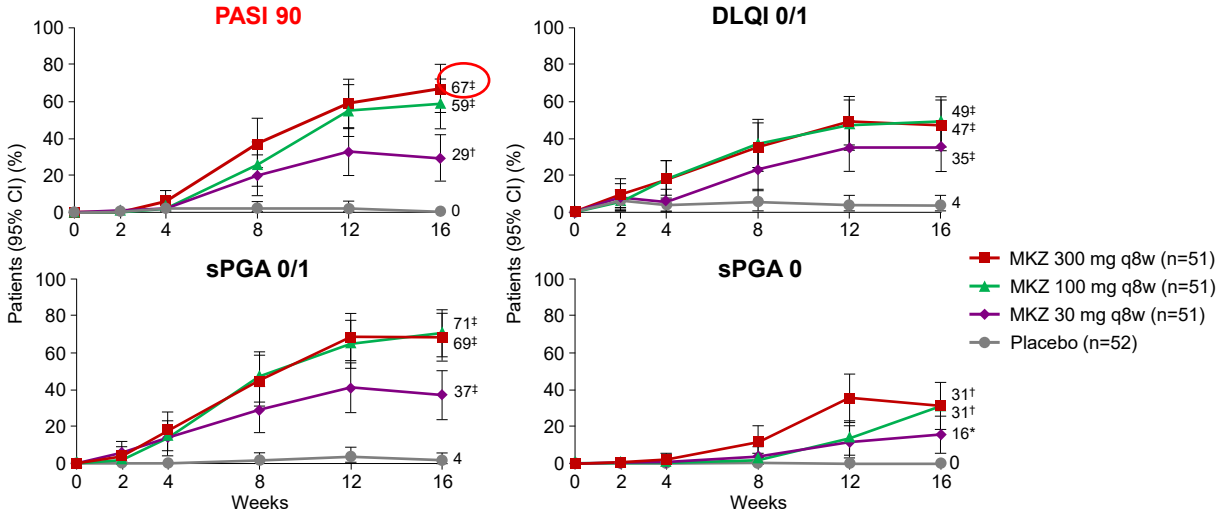
Mirikizumab through Week 16



*P<0.05, †P<0.01, ‡P<0.001 vs placebo. Logistic regression analysis with treatment, geographic region, and previous biologic therapy in the model; NRI

Rich P, et al. AAD 2018, P6131 Sponsored by Eli Lilly and Company

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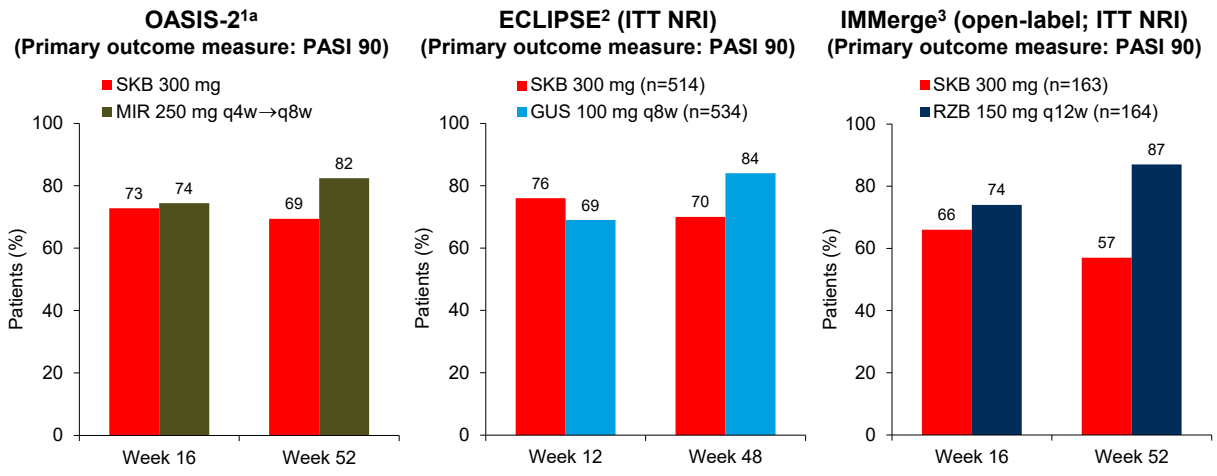
OASIS-2: PASI 90 responses with mirikizumab at Week 16 and Week 52, with reference to the results of ECLIPSE and IMMerge



[a]Data imputation method not available

1. Eli Lilly and Company press release, July 17, 2020, available at: http://lilly.mediaroom.com
2. Reich K, et al. Lancet 2019;394:831–39
3. Warren R, et al. AAD 2020 Late-breaking presentation: Clinical trials

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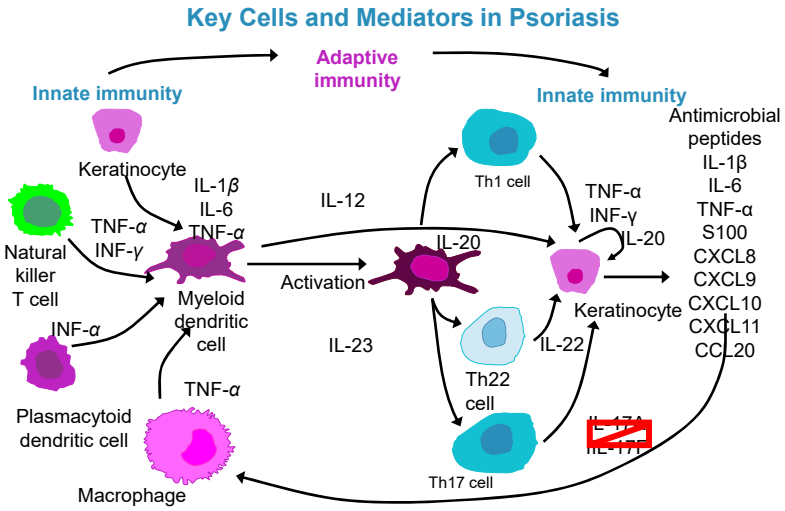
Bimekizumab



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

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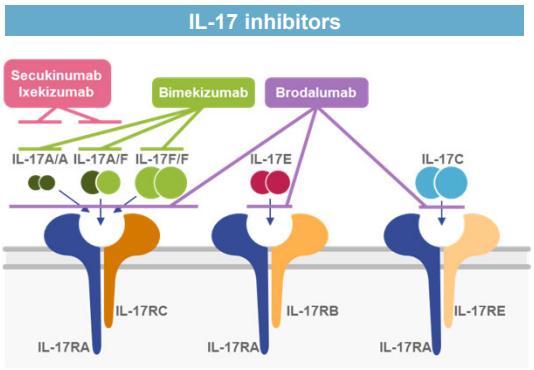
IL-17F and IL-17A are cytokines central to the pathophysiology of PSO



Modifed from: Patel D, Lee D, Kolbinger F, et al. Ann Rheum Dis. 2013;72(Suppl 2):ii116–23.

Role of IL-17 in disease: IL-17A and IL-17F are key cytokines that are central to pathobiology in psoriasis, PsA[1], axSpA[2] and HS.[3]

Role of IL-17F: **IL-17F has overlapping biology with IL-17A. While IL-17A is more potent, IL-17F is more abundant in psoriatic lesions and can drive inflammation independently of IL-17A.**[4-7]

IL-23-independent IL-17 production: IL-17 can be produced independently of IL-23 regulation by some immune cells which can contribute to the pathobiology of IL-17-mediated diseases.[8]

Bimekizumab is an investigational humanized monoclonal IgG1 antibody that selectively inhibits both IL-17F and IL-17A, suppressing inflammation to a greater extent than IL-17A inhibition alone.[7,9]

The safety and efficacy of bimekizumab have not been established and it is not approved by any regulatory authority worldwide.

1. Kolbinger F, Loesche C, Valentin MA, et al. J Allergy Clin Immunol. 2017; 139:923–932; 2. McGonagle D, McInnes I, Kirkham B, et al. Ann Rheum Dis. 2019;78:1167-1178; 3. Matusiak L, Jemec GB and Szepietowski et al. Current Opinion in Pharmacology. 2019; 46:65-72; 4. Yang XO, Chang SH, Park H, et al. J Exp Med. 2008;205(5):1063–1075; 5. Hymowitz SG, Filvaroff EH, Yin JP, et al. Embo J. 2001;20(19):5332–5341; 6. van Baarsen LG, Lebre MC, van der Coelen D, et al. Arthritis Res Ther. 2014;16(4):426; 7. Glatt S, Baeten D, Baker T, et al. Ann Rheum Dis. 2018;77(4):523-532; 8. Cole S, Simpson C, Okoye R, et al. Ann Rheum Dis. 2019; 78(Suppl. 2):232–3 abs. OP0302; 9. Maroof A, Okoye T, Smallie B, et al. Annals of the Rheumatic Diseases. 2017; 76(Suppl 2):213.

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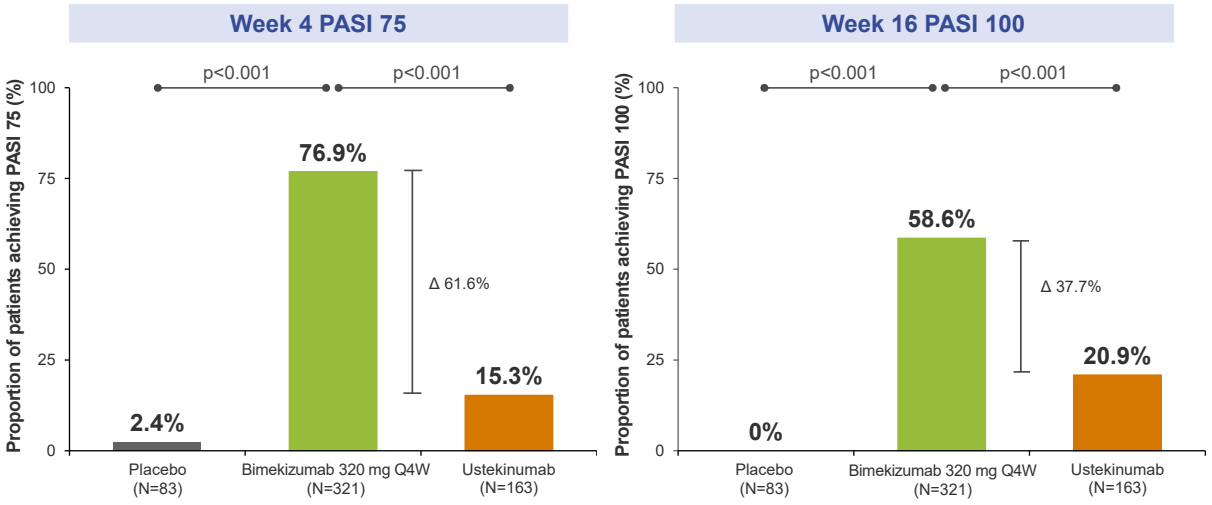
Bimekizumab **BE VIVID** Phase 3 study

Response at week 4 and complete clearance at week 16 (ITT, NRI)

76.9% of bimekizumab-treated patients achieved PASI 75 after one dose, with 58.6% achieving PASI 100 at week 16



For PASI 75 at Week 4 and PASI 100 at Week 16 (versus placebo only), the p value for the comparison of treatment groups was based on the Cochran–Mantel–Haenszel test from the general association; for PASI 100 at Week 16 (versus ustekinumab), the p value for a general association was based on a stratified Cochran–Mantel–Haenszel test where region and prior biologic exposure were used as stratification variables, is considered nominal, and was not controlled for multiplicity. Proportions were calculated using non-responder imputation (NRI). ITT: intent-to-treat; PASI 75/100: ≥75/100% improvement from Baseline in Psoriasis Area and Severity Index; Q4W: every four weeks.

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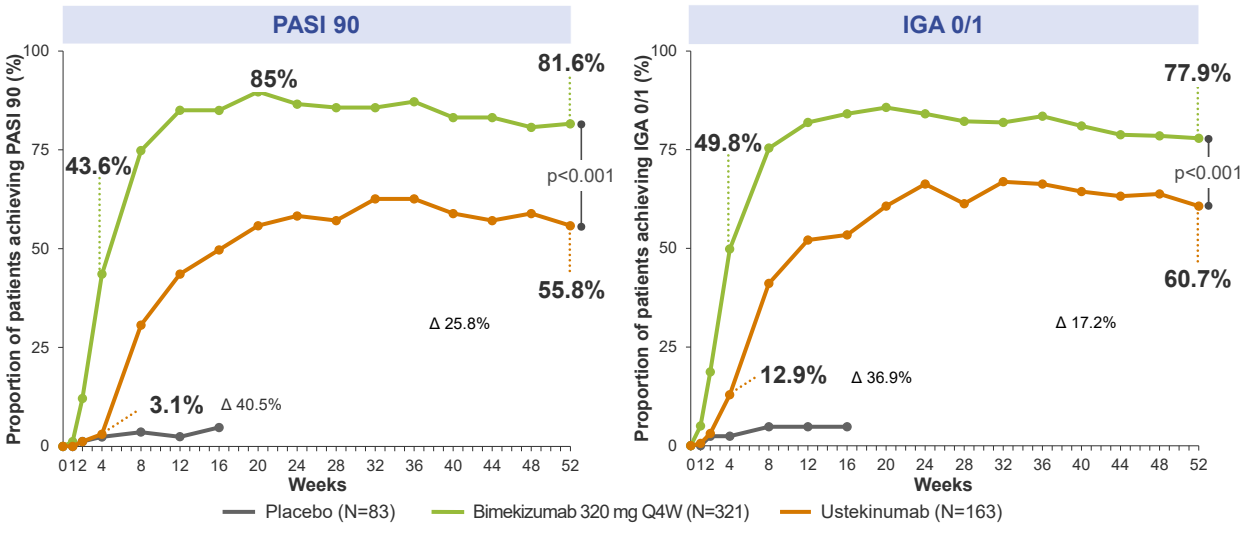
Bimekizumab **BE VIVID** Phase 3 study

Durability at week 52: PASI 90 and IGA 0/1 (ITT, NRI)



p values for the comparison of treatment groups were based on the Cochran–Mantel–Haenszel test from the general association. Proportions were calculated using non-responder imputation (NRI). At Week 16, patients receiving placebo were switched to bimekizumab 320 mg Q4W. IGA 0/1: score of 0 (clear) or 1 (almost clear) with ≥2-category improvement relative to Baseline in Investigator's Global Assessment, scored on a 5-point scale; ITT: intent-to-treat; PASI 90: ≥90% improvement from Baseline in Psoriasis Area and Severity Index; Q4W: every four weeks.

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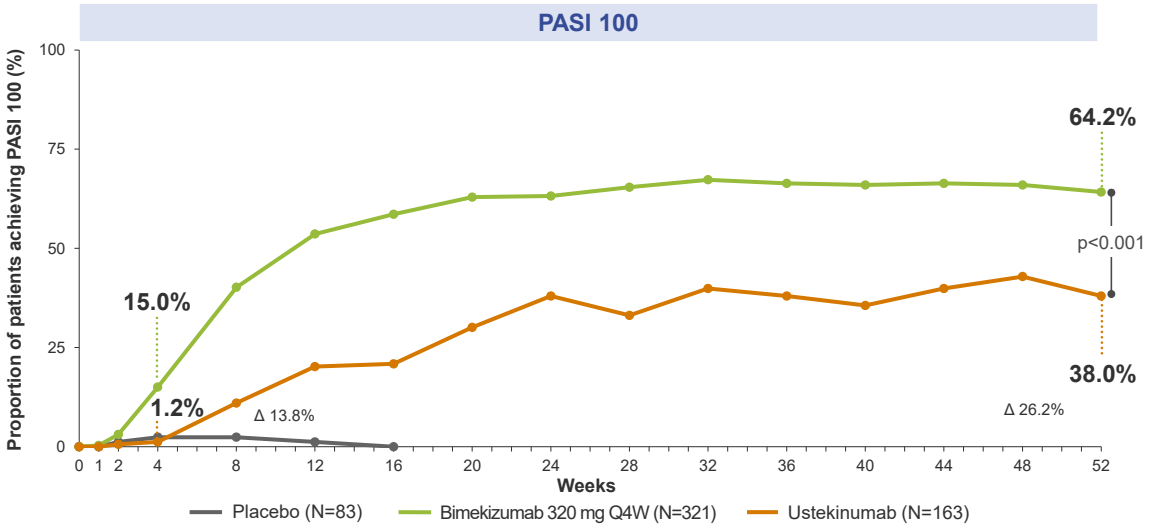
Bimekizumab **BE VIVID** Phase 3 study

Complete clearance: PASI 100 over 52 weeks (ITT, NRI)



The p value for a general association was based on a stratified Cochran–Mantel–Haenszel test where region and prior biologic exposure were used as stratification variables, is considered nominal, and was not controlled for multiplicity. Proportions were calculated using non-responder imputation (NRI). At Week 16, patients receiving placebo were switched to bimekizumab 320 mg Q4W. ITT: intent-to-treat; PASI 100: 100% improvement in psoriasis area severity index (PASI) score; Q4W: every four weeks.

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