Anti IL-4 ve Anti IL-13 Olgu

Rana Işık

Allerji-İmmünoloji Hastalıkları

Amerikan Hastanesi

KOÇ HEALTHCARE

AMERİKAN HASTANESİ

SUNUM PLANI

- Olgu
- Tip 2 inflamasyon ve antagonistleri
- Anti-IL-4 Dupilumab etki mekanizması
- Faz 2 çalışmalar
- Olgunun tedavi sonrası bulguları
- Anti-IL 13 ve çalışmalar

OLGU

- 48 y, k, eh,
- Nefes darlığı, öksürük, hırıltılı solunum
- 10 yıldır astım tanılı
- Son 1 yıldır↑ sık acil başvurusu

OLGU

- Gece semptomları ↑
- Son 1 yılda 3 kez acil başvurusu ve sık sistemik steroid
- Kullandığı İlaçlar:
  - Budesonid/formaterol 800/9 mcg /gün
  - Montelukast 10 mg
  - Mometazon furoat nazal spray
  - Teofilin
  - Salbutamol lüzum halinde

OLGU

- 1 yılda 3 kez sistemik steroid +
- 3 yıldır ex smoker. 5 pak/yıl
- Özgeçmiş: Gastro özefajeal reflü, Allerjik rinit
- Soygeçmiş: Özellik yok
- Fizik muayene
  - Ronküs +

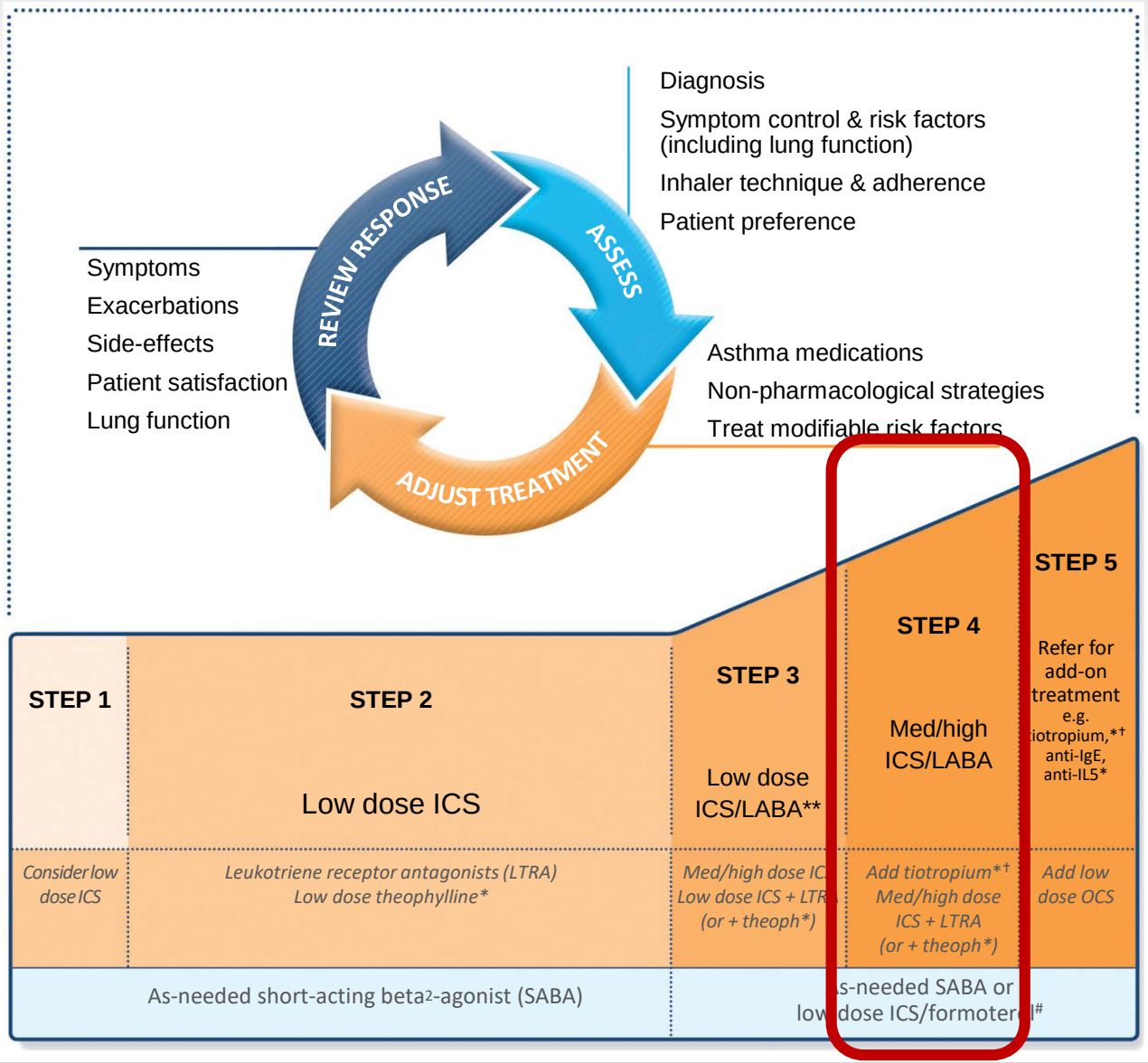
OLGU

- PA ac grafisi: normal
- Hemogram
  - Eozinofil sayısı: 0.75 (10e3/ul) %14.8
- Solunum fonksiyon testi :
  - FEV1:1.93 (%56) rev: %26
  - FVC: 1.36 (% 50)
  - FEV1%: % 70

OLGU

- Deri prik testi : negatif
- AKT: 8
- Total IgE: 160
- ACQ 5:2.73

Stepwise management - pharmacotherapy



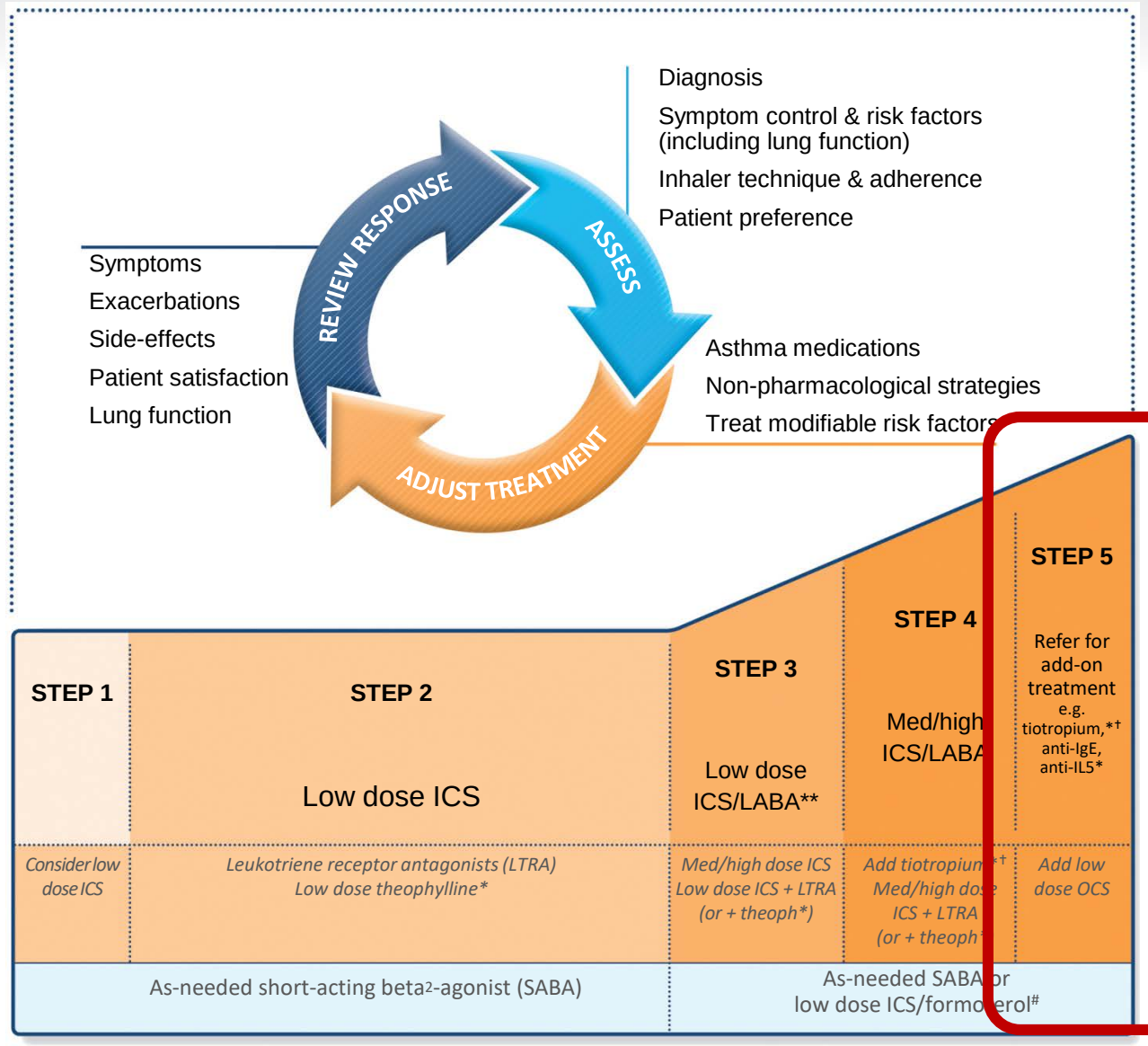
*Not for children <12 years

**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS

#For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy

† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

Stepwise management - pharmacotherapy



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#For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy

† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

OLGU

- Yaygın ronküs
- PA ac grafisi: normal
- Hemogram
  - Eozinofil sayısı: 0.75 (10e3/ul) %14.8
- Solunum fonksiyon testi :
  - FEV1:1.93 (%56) rev: %26
  - FVC: 1.36 (% 50)
  - FEV1%: % 70

Deri prik testi : negatif

AKT:10

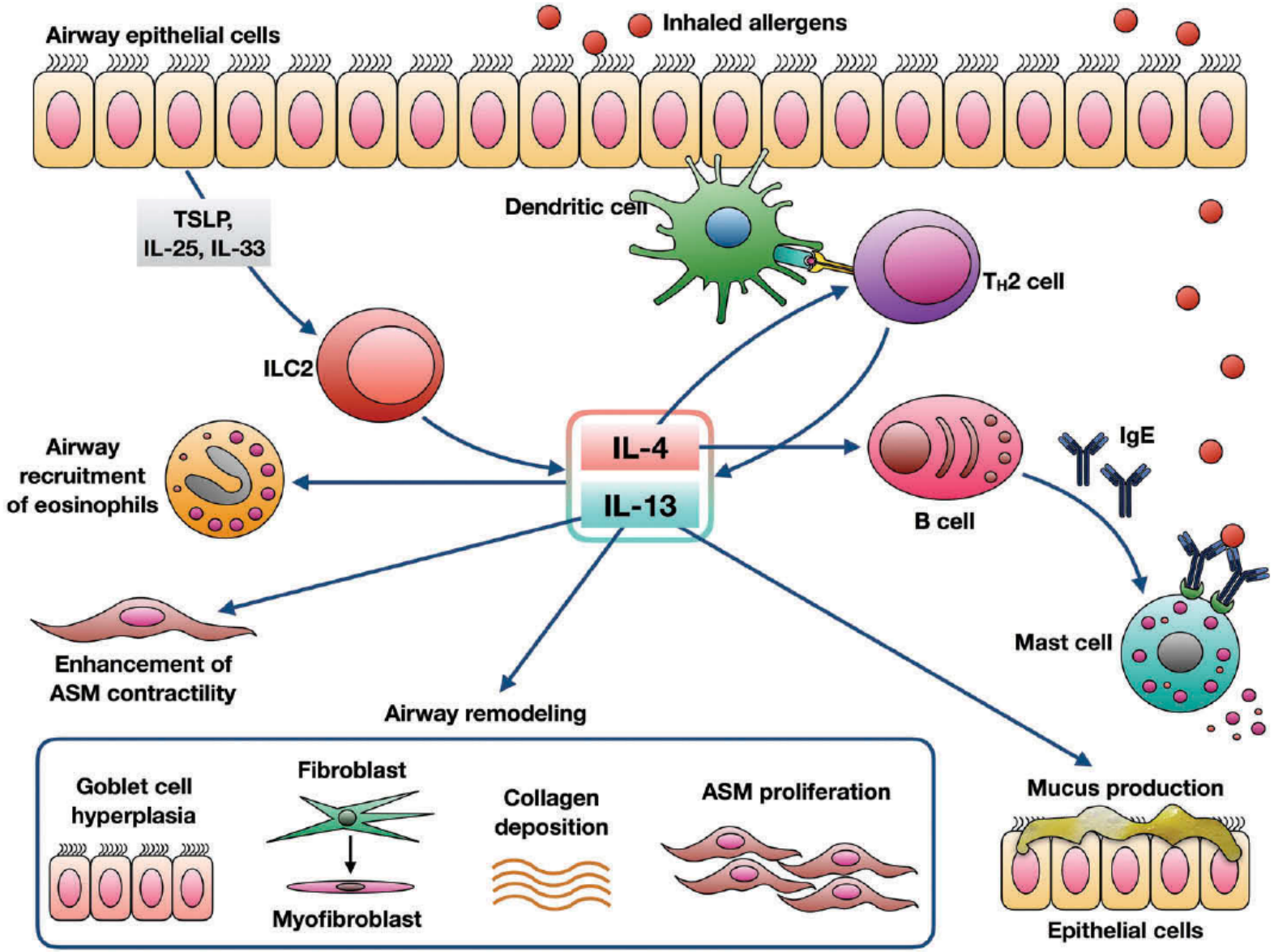
Total IgE: 160

ACQ-5≥1.5

T2 yüksek astım

- Ağır astımlıların % 50'si Tip 2 astım bulgusu
- T2 ile ilişkili interlökinler IL-4, IL-5 ve IL-13
- Ağır astımda anahtar rol
- Aktive Th-2 lenfositler, mast hücreleri, bazofiller ve eozinofiller
- Tip 2 innate lenfoid hücreler

Wenzel SE. Am J Respir Cell Mol Biol 2016;55:1-4
Parulekar AD et al. Curr Opin Pulm Med 2018;24:50-55

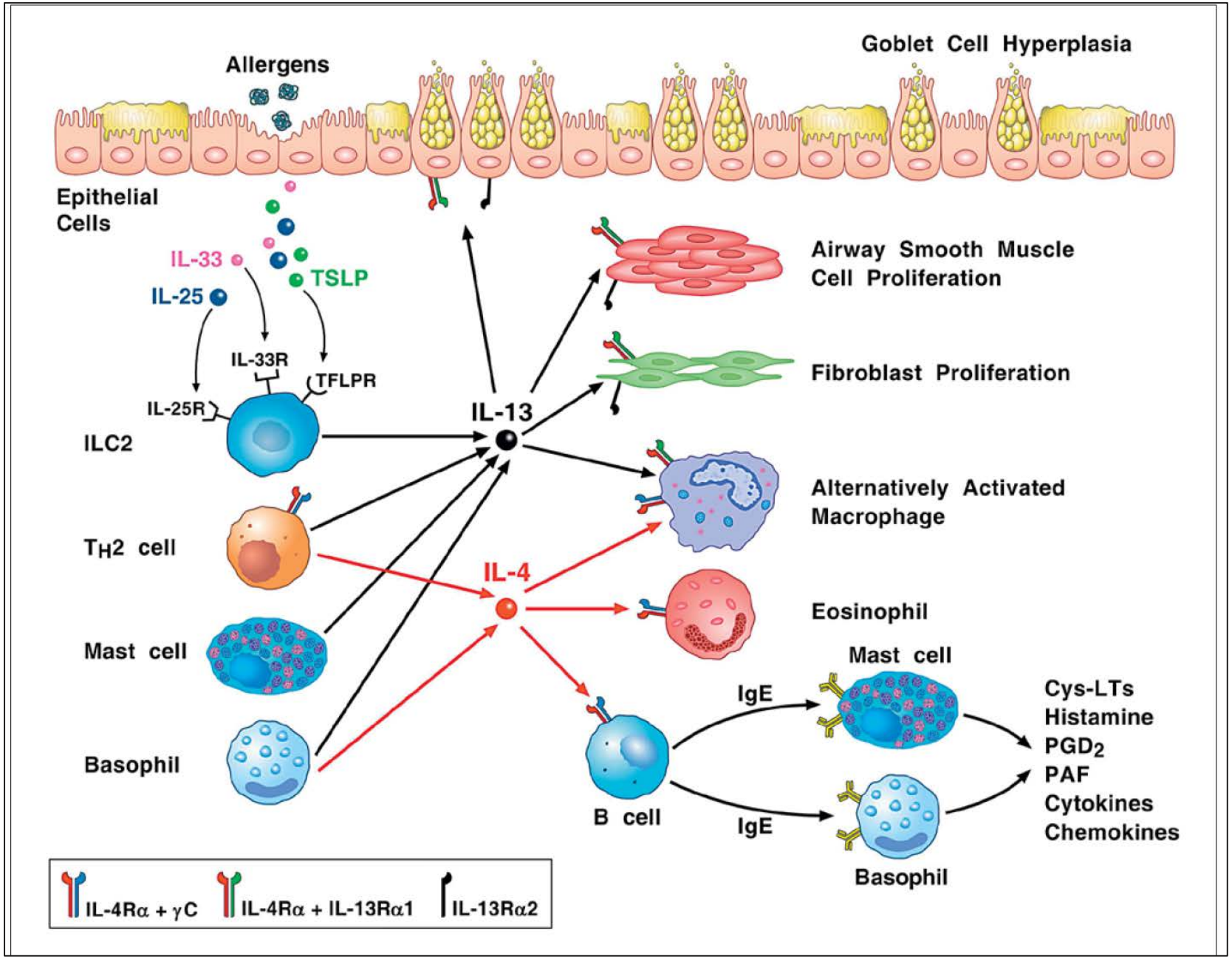


Pelaia C. Expert opinion on biological Therapy 2017;17: 1565

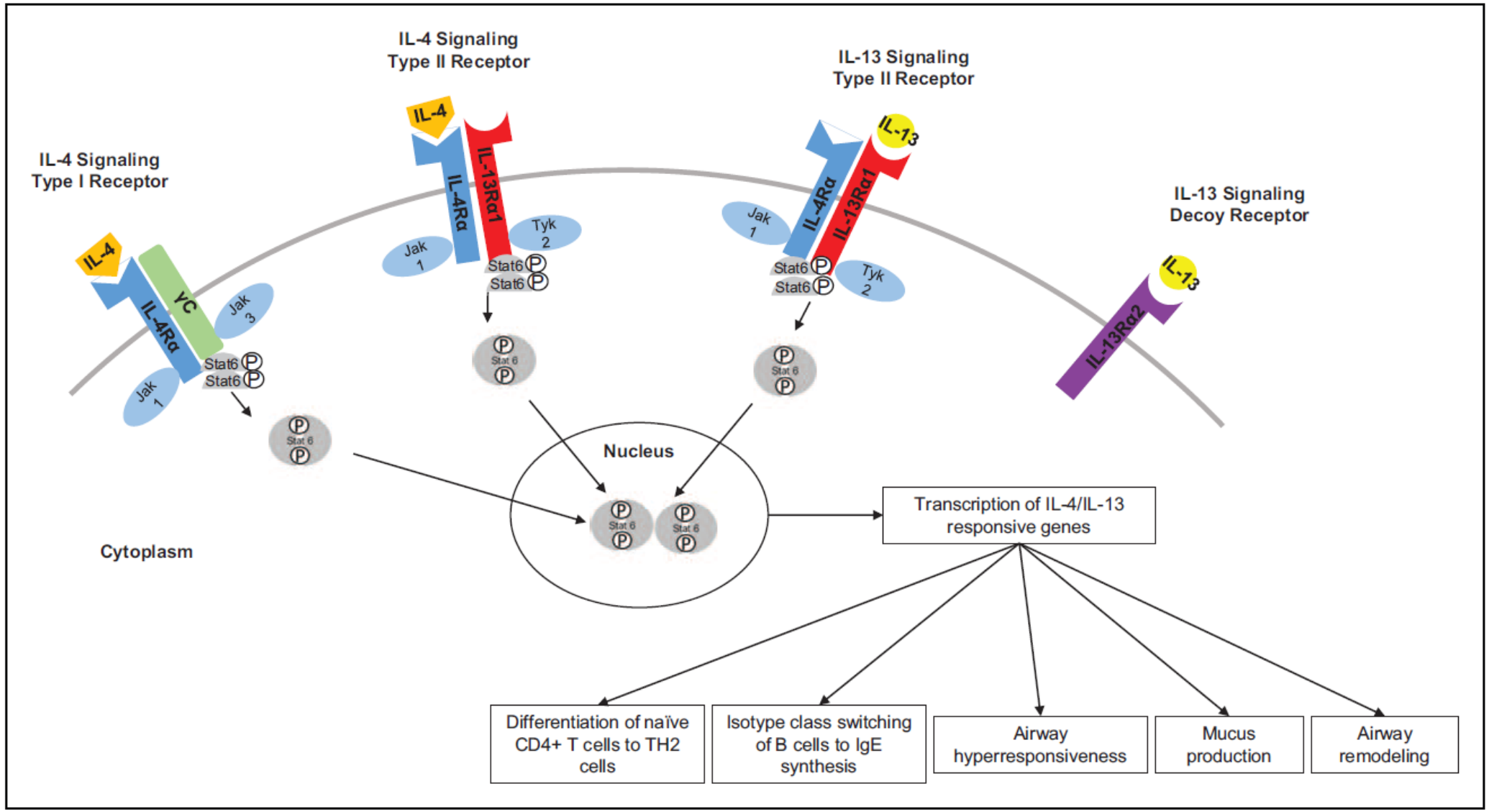
- IL-4 ve 13 IgE sentezini regülasyonu
- IL-4 ve 13 eotaxin sentezini ↑ ve VCAM-1 exp ↑ eozinofil kemotaksisine
- IL-13 NO sentaz aktivitesini ↑ NO oluşumunu ↑ FeNO bronş mukozasında inflamasyon ve IL 13 ↑ göstergesi
- IL-4 ve 13 bronş epitel hücrelerini indükleyerek periostin sekresyonunu

IL-4 ve IL-13

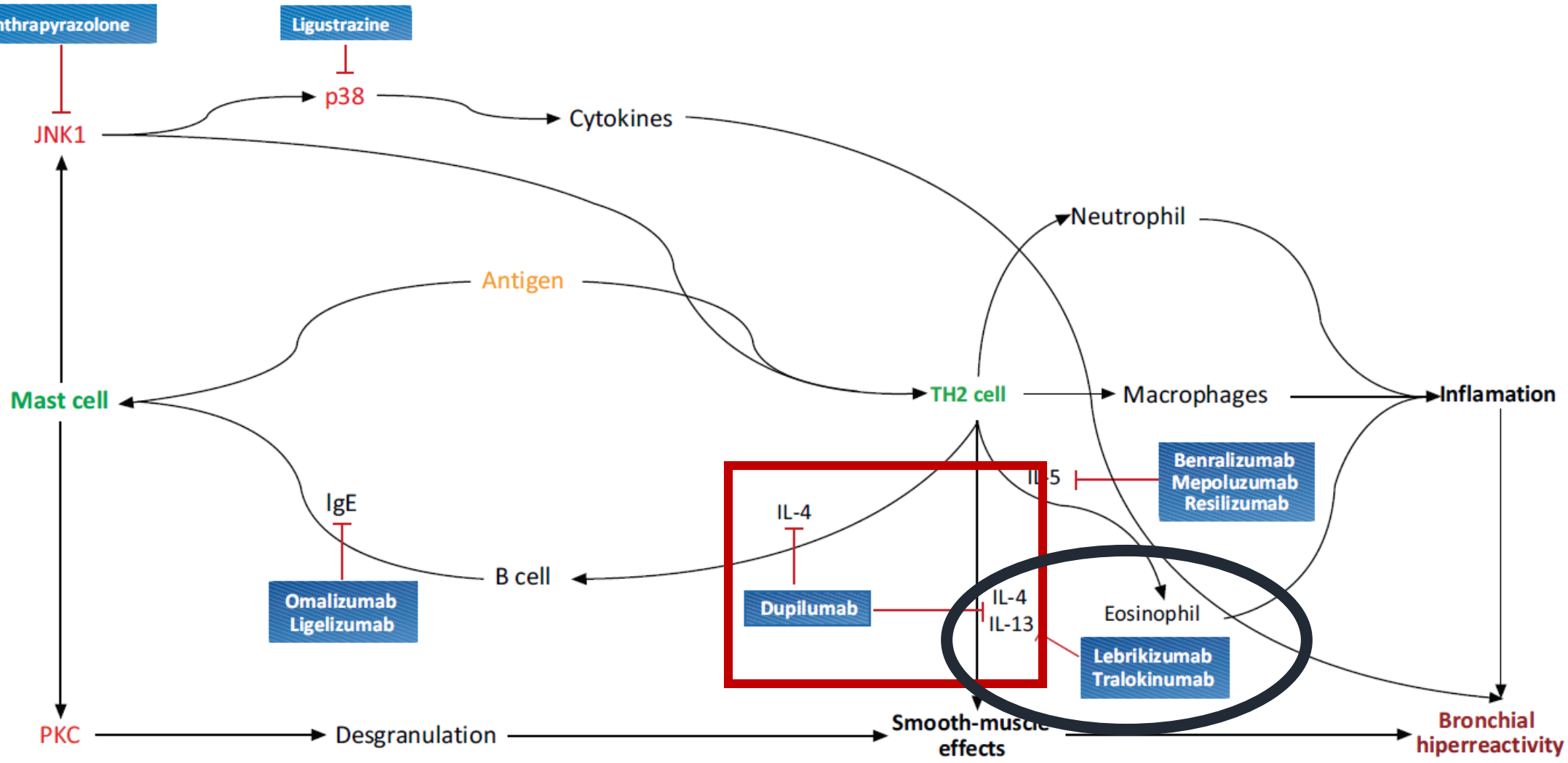
IL-4 ve IL -13	•Th-2 ilişkili sitokinler
IL-4 tip 1 resp	•IL-4Rα ve ɣC
IL-4 tip 2 resp	•IL-4Rα ve IL13Rα1



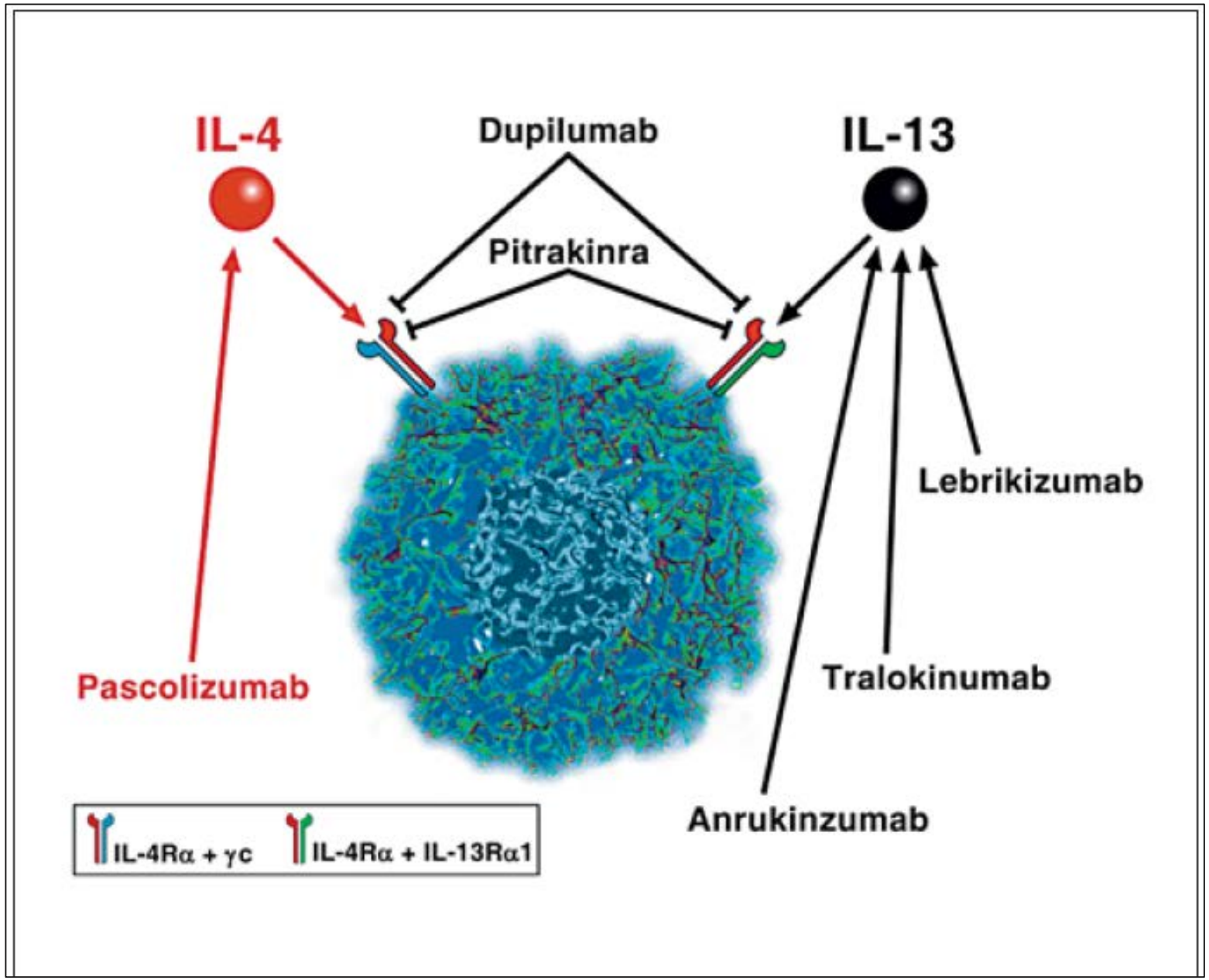
Bagnasco D et al. Int Arch Allergy Immunol 2016;170: 122-131



Parulekar AD et al. Curr Opin Pulm Med 2018;24:50-55



Alves MF, et al. Mini Reviews in Medicinal Chemistry 2018:684-96



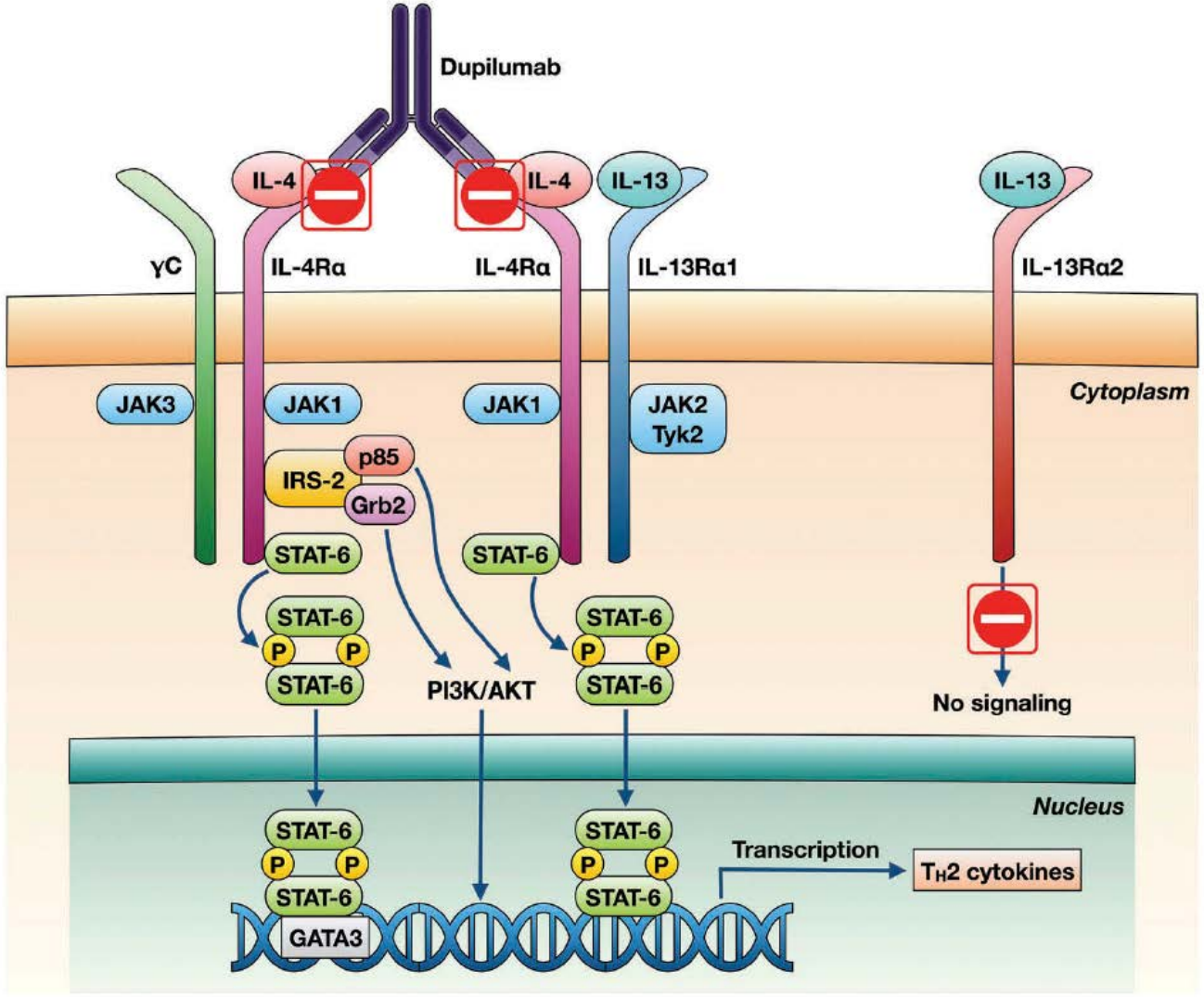
Bagnasco D et al. Int Arch Allergy Immunol 2016;170: 122-131

Table 1. Promising drugs and their target compounds. (Information from the clinical trials was retrieved on the web https://clinicaltrials.gov/).

Drugs	Molecular Target	Mode of Action	Experimental Discoveries	Clinical Trials	Refs.
SP600125 (Anthrapyrazolone)	c-Jun N-terminal kinase (JNK)	JNK inhibitor	Decreased migration of cells to bronchoalveolar lavage and downregulate the expression of TLR9.	-----	[26, 27]
Lebrikizumab	IL-13	Blocks IL-13	Decreased asthma exacerbation in patients. Phase III studies in progress.	NCT01867125 NCT01868061 NCT01875003	[28-34]
Benralizumab	IL-5	Blocks IL-5	Phase I, II and III clinical studies have shown a decrease in eosinophil counts as well as a reduction in the effect of asthma in patients.	NCT00768079 NCT02918071 NCT02821416 NCT02808819	[35-39]
Tralokinumab	IL-13	Blocks IL-13	Tralokinumab inhibited the development of the phenotype in animals. In humans, FEV1 improved. Clinical studies still in progress.	NCT02902809 NCT01592396 NCT02194699 NCT02161757	[40-42]
Ligustrazine	p38 MAPK	Inhibition of p38 MAPK	Activates lymphocyte recruitment and infiltration.	-----	[43, 44]
Dupilumab	Receptor IL-4	Inhibits signaling of IL-4 and IL-13	Effective not only for asthma but also for the treatment of atopic dermatitis, chronic sinusitis and nasal polyps. Phase III clinical study with asthmatic patients in progress.	NCT02134028 NCT03020810 NCT02573233 NCT02414854	[45-50]
Omazilumab	IgE	Binds to immunoglobulin E	Reduces inflammation of the IgE-mediated airways.	-----	[51]
Ligelizumab	IgE	Binds to immunoglobulin E	Greater efficacy than omalizumab in inhibiting the bronchial allergen response.	NCT02075008	[52]
Mepolizumab	IL-5	Blocks IL-5	Decreases exacerbation of asthma. Phase III clinical trials are in progress.	NCT01463644 NCT02105948 NCT02105961	[53, 54]
Reslizumab	IL-5	Blocks IL-5	Decreases recruitment and activation of human eosinophils.	NCT02452190 NCT02293265	[55, 56]
Fervipiprant	Prostaglandin D2	Prostaglandin D2 receptor antagonist	Reduces eosinophilic inflammation of the airways and is well tolerated in patients with moderate to severe persistent asthma.	-----	[57-59]

Table 1. Principal clinical studies with biological drugs anti IL-4 and IL-13 in asthma

Drug	First author [ref.] year	Asthma severity	Patients, n	Dosage	Summary of outcomes
Dupilumab	Wenzel [86] 2013	moderate-to-severe; blood eosinophil count of at least 300 cells/μl	52 on dupilumab 52 on placebo	300 mg weekly placebo	↓ asthma exacerbation (3 in dupilumab group, 23 in placebo group) ↑ FEV_1 change of ACQ5 score ↓ inhalation of albuterol or levalbuterol change in evening asthma score
Tralokinumab	Piper [69] 2013	moderate-to-severe; uncontrolled	194	150 mg 300 mg 600 mg placebo	modified from baseline in mean ACQ score (−0.76 ± 1.04)
	Brightling [70] 2015	severe uncontrolled	452	(1) tralokinumab every 2 weeks (2) tralokinumab every 4 weeks (3) placebo every 2 weeks (4) placebo every 4 weeks	↓ asthma exacerbation vs. placebo in high-periostin and high-DPP-4 groups FEV_1 in high-periostin and high-DPP-4 groups
Lebrikizumab	Hanania [67] 2015	moderate-to-severe	463	37.5 mg 125 mg 250 mg placebo s.c. every 4 weeks	↓ asthma exacerbation in high-periostin group no dose response ↑ FEV_1 in high-periostin group
	Scheerens [66] 2014	mild	29	13 lebrikizumab 16 placebo s.c. every 4 weeks	greater response in high-IgE, high-eosinophil and high-periostin patients
	Noonan [68] 2013	not controlled despite ICS therapy	212	125 mg 250 mg 500 mg placebo s.c. monthly	changes in FEV_1 were higher in patients receiving lebrikizumab but not clinically significant
	Corren [6] 2011	steroid-dependent	219	250 mg placebo	↑ FEV_1 in high-periostin group



IgG4 insan kökenli monoklonal antikor →IL-4R α

IL-4 ve IL-13 sinyalini bloke eden

Pelaia C. Expert opinion on biological Therapy 2017;17: 1565

Dupilumab

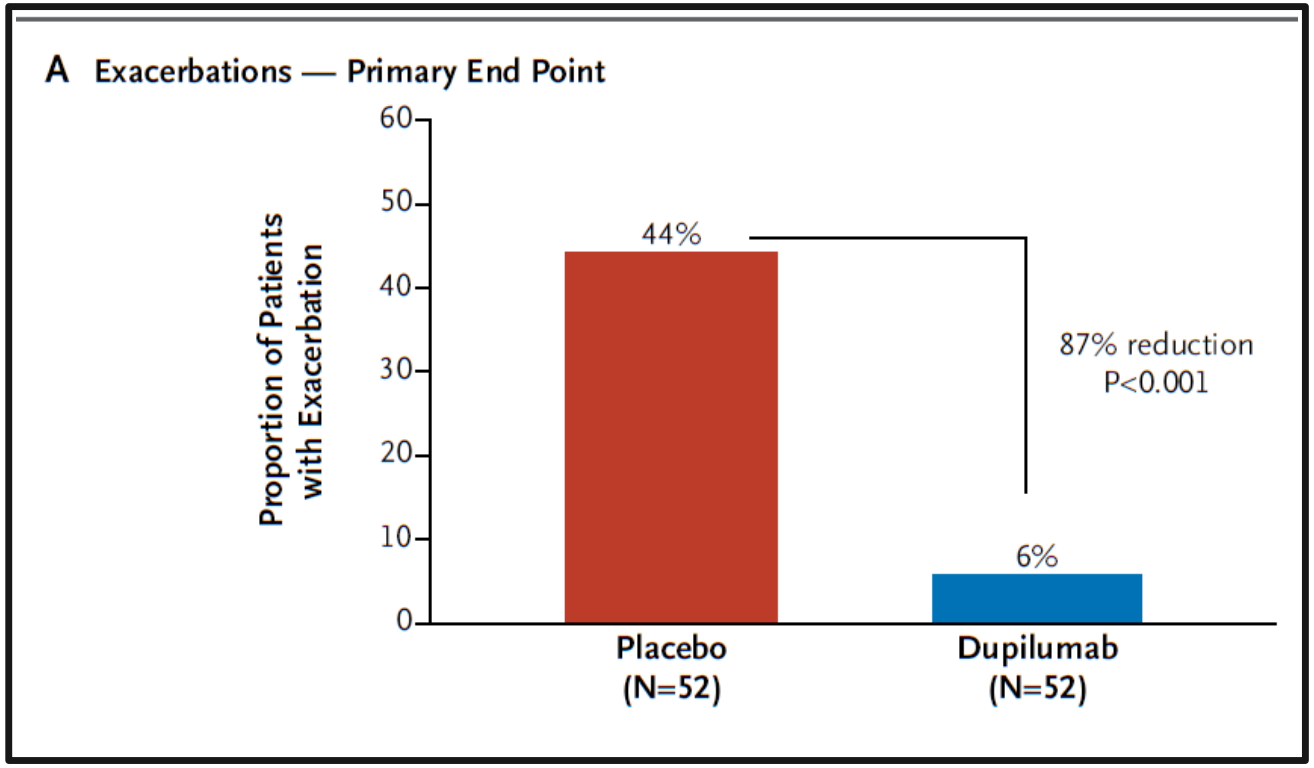
- VCAM gibi adhezyon moleküllerini blokajı
- Eozinofillerin akciğerlere ulaşmasını engelleme
- Mukus sekresyonunu azaltır
- Bazal membran kalınlaşmasını engeller

Dupilumab- Faz 2a

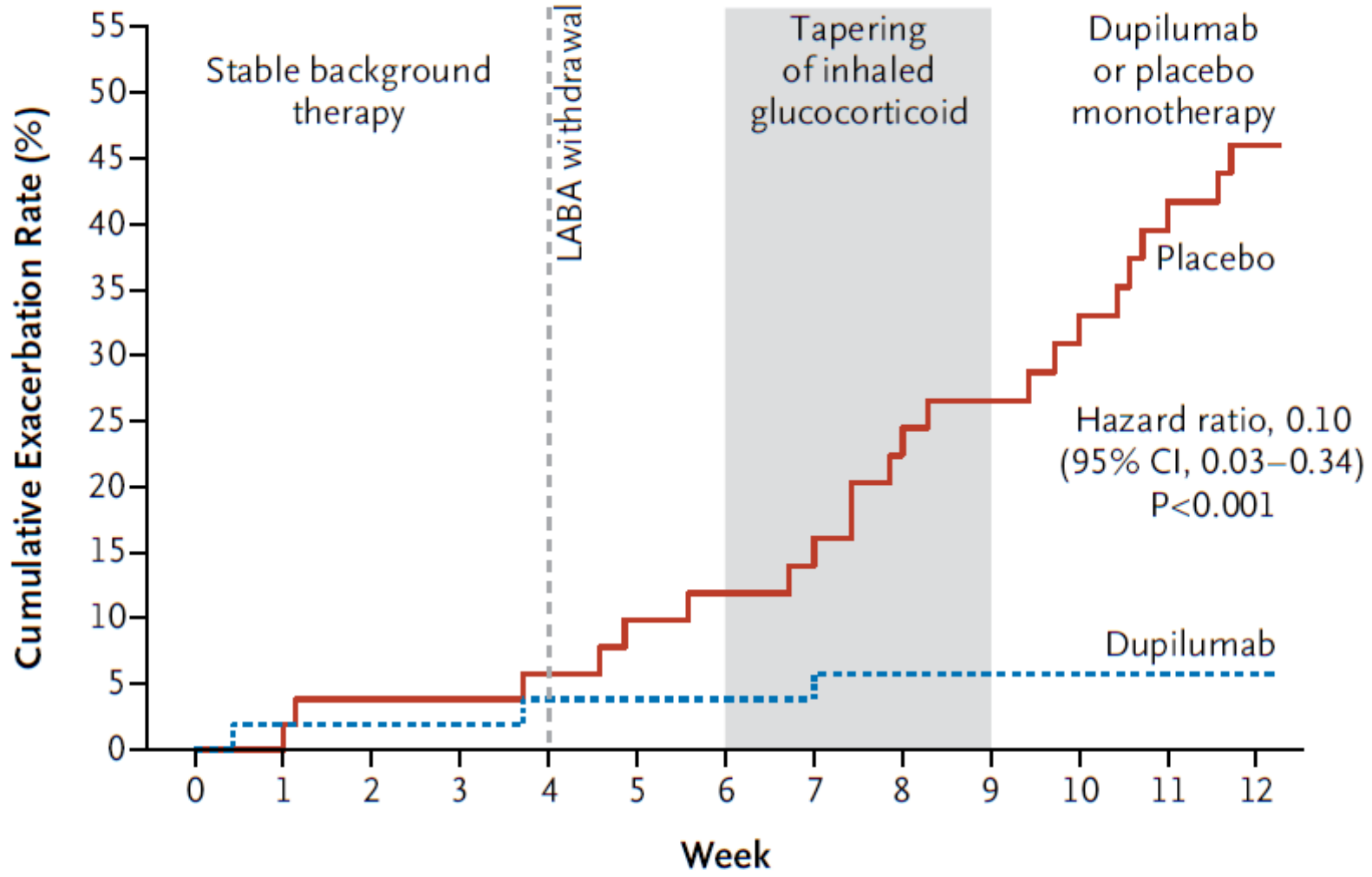
- Randomize, çift kör, plasebo kontrollü paralel grup çalışması
- 18-65 yaş orta-ağır kontrolsüz
- Eozinofil ≥ 300 / µl
- ACQ5>1.5
- Son 2 yılda sistemik steroid gerektiren en az 1 astım atağı geçiren
- Primer sonlanım: 12 haftalık tedavi süresince alevlenme
- Sekonder sonlanım: İlk atağa kadar geçen süre, FEV1 deki, ACQ, PEF ve sabah ve akşam semptomlarındaki değişiklik

Wenzel S, et al. NEJM 2013;368:26

- N: 104
- 1:1
- 300 mg dupilumab haftalık enjeksiyon

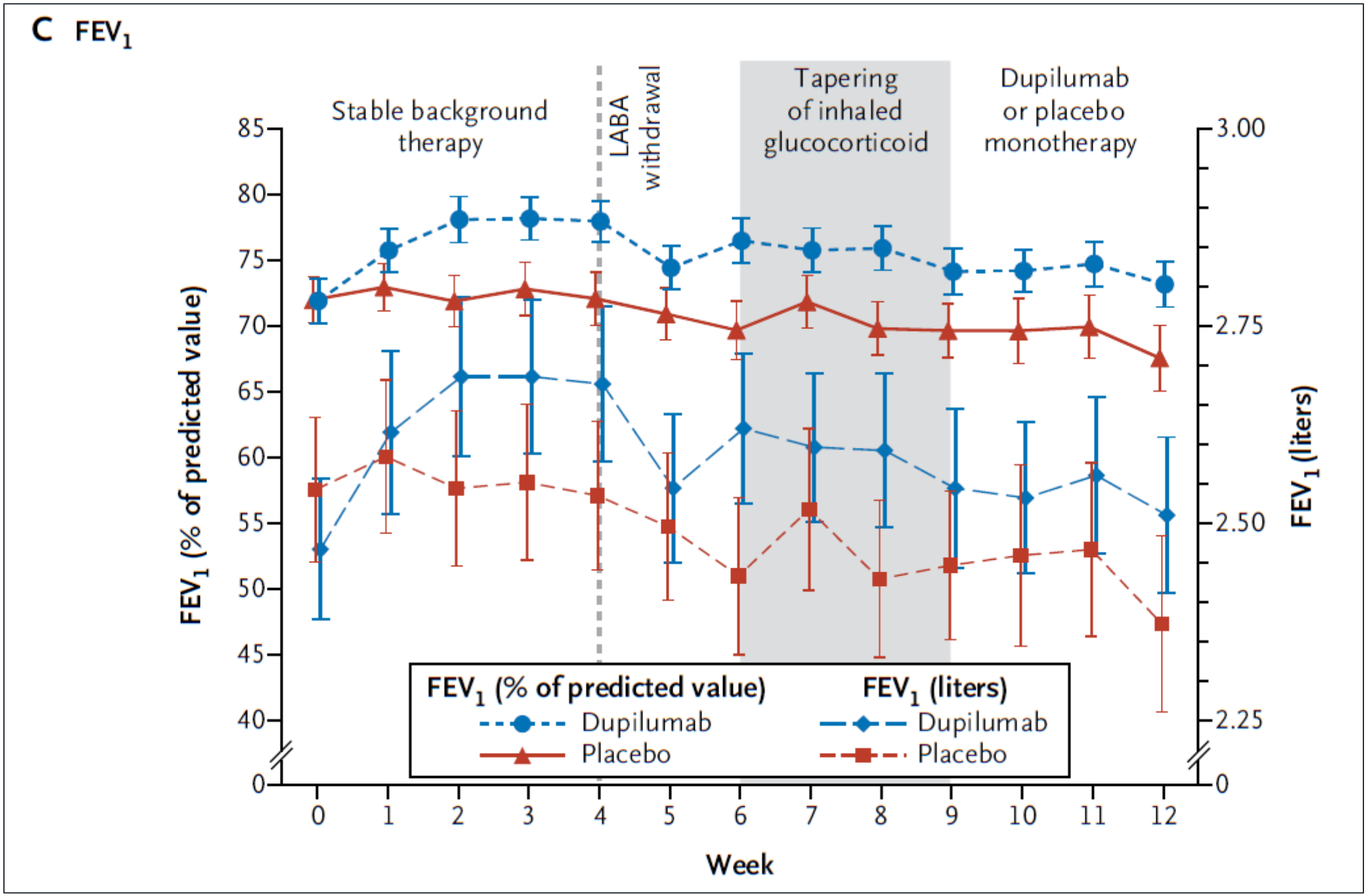


B Time to Exacerbation



No. at Risk

Dupilumab	52	51	51	51	50	50	50	50	47	45	44	43	42
Placebo	52	52	50	50	48	44	43	41	37	35	32	28	24


C FEV1
Stable background therapy
LABA withdrawal
Tapering of inhaled glucocorticoid
Dupilumab or placebo monotherapy
FEV1 (% of predicted value)
FEV1 (liters)
Week
FEV1 (% of predicted value)
Dupilumab
Placebo
FEV1 (liters)
Dupilumab
Placebo

- Gece uyanmalarında ↓
- Salbutamol kullanımı ↓
- FeNO, TARC, Eotaxin ve IgE↓
- Eozinofil düzeyi az değişiklik veya aynı

Dupilumab faz 2b

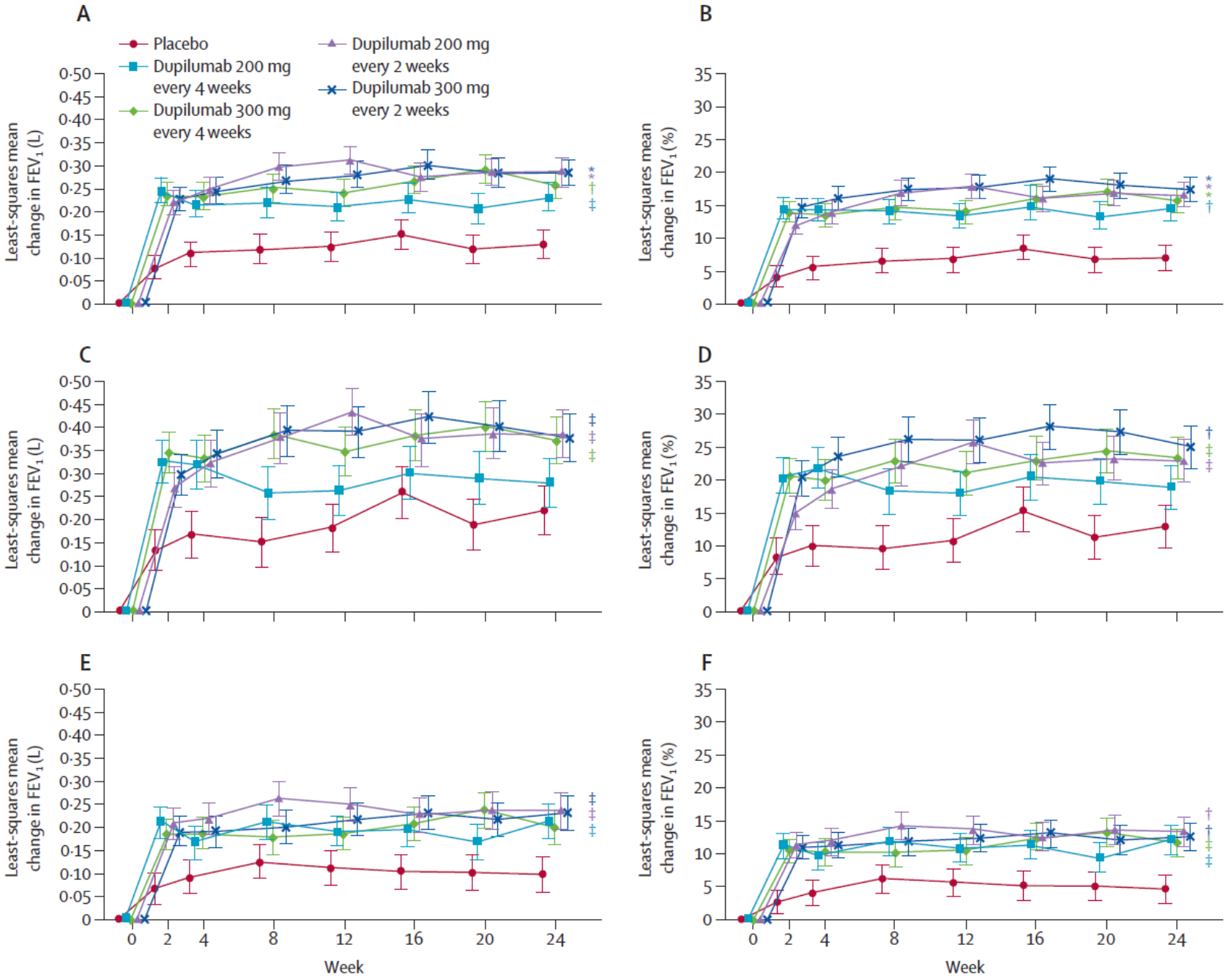
- Çift kör randomize, paralel grup
- 174 merkez 16 ülke
- ≥ 18 yaş
- Orta-yüksek doz İKS+LABA(fluticazone propionate ≥250 mcg veya eş değer)
- ACQ-5 skoru ≥1.5
- Prebronkodilatör FEV1: %40-80 reversibilite :%12 ve 200 ml
- Son 1 yılda sistemik steroid veya acil başvurusu veya hastaneye yatış.
- 14-21 gün tarama dönemi -24 hafta tedavi-16 hafta takip

Wenzel S, et al. Lancet 2016:388:31-44

- Placebo
- 200 mg 4 haftada 1
- 200 mg 2 haftada 1
- 300 mg 4 haftada 1
- 300 mg 2 haftada 1
- Eozinofil 300 veya ↑, 300↓

Sonlanım noktaları

- Primer: 12. haftada FEV-1'deki değişiklik
- Sekonder: 12. ve 24. haftalarda bazale göre
  - FEV1'deki yüzde değişiklik,
  - alevlenme, ağır alevlenmeye kadar geçen süre,
  - sabah ve akşam astım semptom skorları,
  - ACQ-5 ve AQLQ skor,
  - Kurtarıcı ilaç kullanımı



N: 776

Eoz≥ 300 →325

Eoz<300 → 451

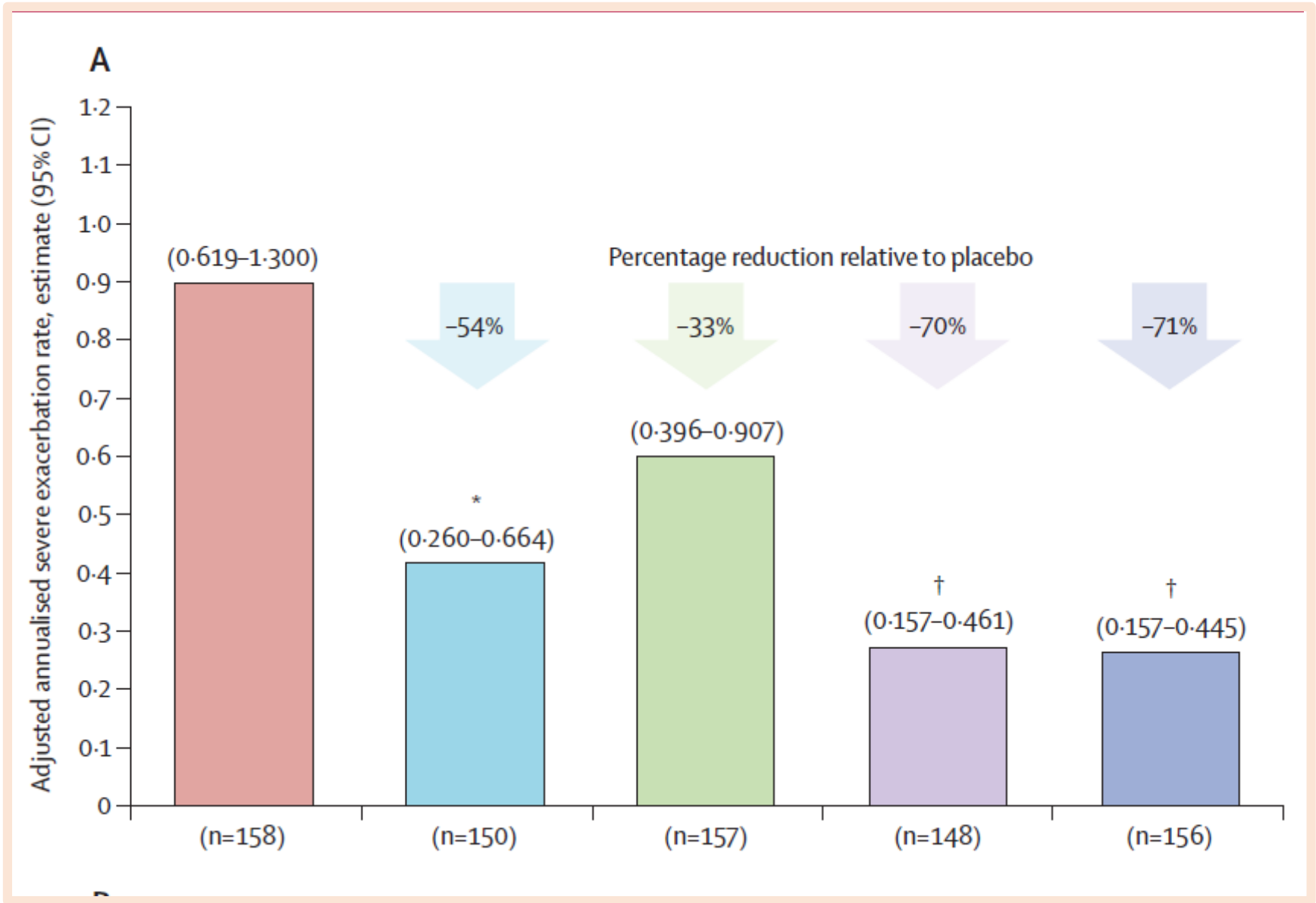
200 mg 2 veya 4 hafta

300 mg 2 veya 4 hafta

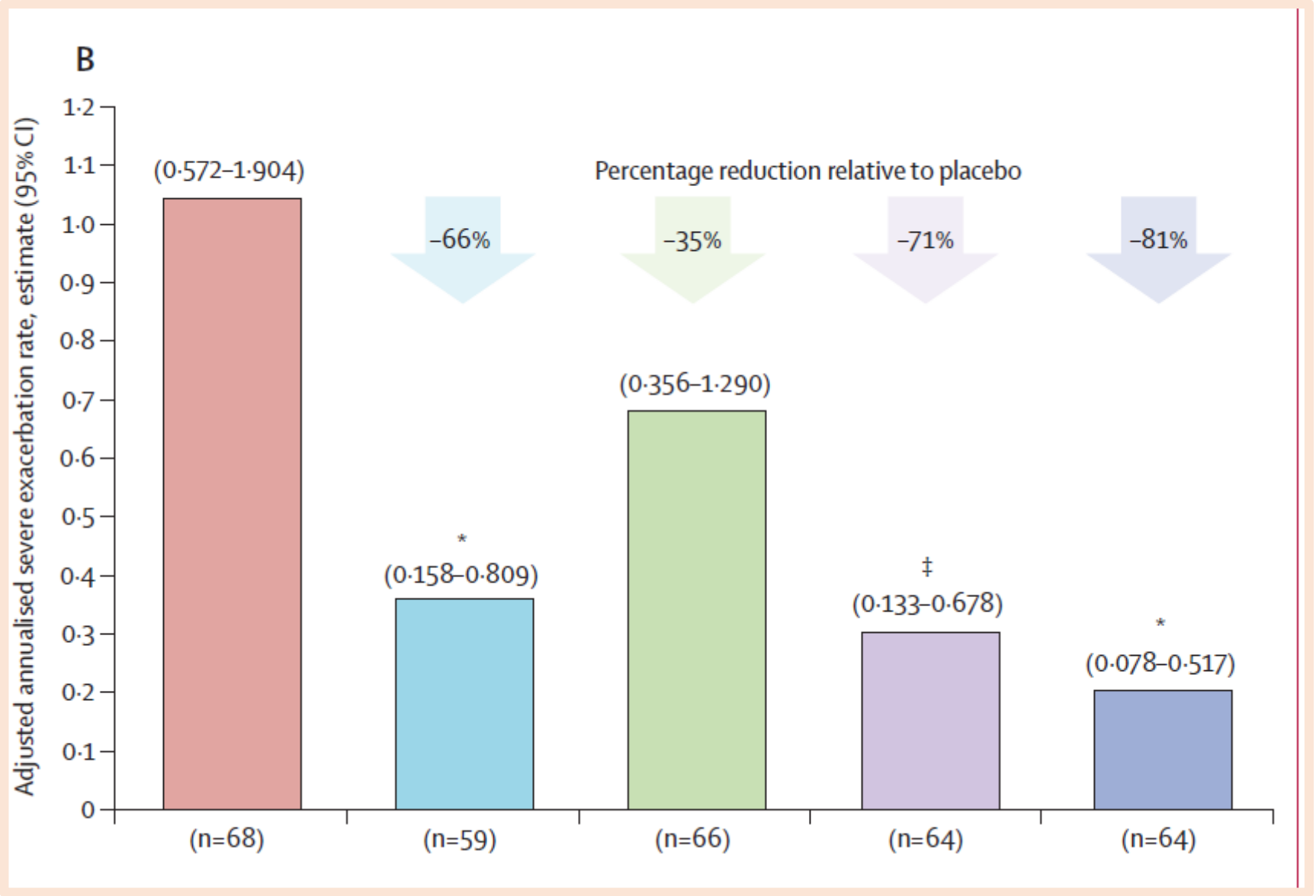
	Placebo	Dupilumab			
		200 mg every 4 weeks	300 mg every 4 weeks	200 mg every 2 weeks	300 mg every 2 weeks
Overall population (n=776)					
Total number of participants	158	154	157	150	157
LS mean change in FEV_1 from baseline at week 12* (L)	0·12 (0·03); 129	0·21 (0·03); 134	0·24 (0·03); 134	0·31 (0·03); 136	0·28 (0·03); 146
LS mean difference *vs* placebo	..	0·10 (0·01–0·18); 134	0·12 (0·04–0·21); 134	0·20 (0·11–0·28); 136	0·16 (0·08–0·25); 146
p value *vs* placebo	..	0·0304	0·0048	<0·0001	0·0002
LS mean change in FEV_1 from baseline at week 12 (%)	6·06% (1·89); 129	13·53% (1·90); 134	14·03% (1·86); 134	18·00% (1·89); 136	17·75% (1·84); 146
LS mean difference *vs* placebo	..	7·47 (2·29–12·65); 134	7·97 (2·85–13·09); 134	11·94 (6·77–17·11); 136	11·69 (6·59–16·80); 146
p value *vs* placebo	..	0·0047	0·0023	<0·0001	<0·0001
LS mean change in FEV_1 from baseline at week 24 (L)	0·13 (0·03); 125	0·23 (0·03); 126	0·26 (0·03); 132	0·29 (0·03); 135	0·28 (0·03); 143
LS mean difference *vs* placebo	..	0·10 (0·01–0·19)	0·13 (0·04–0·21)	0·16 (0·07–0·24)	0·16 (0·07–0·24)
p value *vs* placebo	..	0·0218	0·0037	0·0005	0·0004
LS mean change in FEV_1 from baseline at week 24 (%)	7·01% (1·87); 125	14·52% (1·90); 126	15·68% (1·86); 132	16·62% (1·88); 135	17·34% (1·83); 143
LS mean difference *vs* placebo	..	7·51 (2·35–12·67)	8·67 (3·58–13·77)	9·60 (4·47–14·74)	10·33 (5·26–15·40)
p value *vs* placebo	..	0·0044	0·0009	0·0003	<0·0001
≥1 severe exacerbation event in the 24-week treatment period	41/158 (26%)	23/150 (15%)	29/157 (18%)	13/148 (9%)	17/156 (11%)
Adjusted annualised severe exacerbation event rate estimate	0·897 (0·619–1·300)	0·415 (0·260–0·664)	0·599 (0·396–0·907)	0·269 (0·157–0·461)	0·265 (0·157–0·445)
Risk reduction *vs* placebo (%)	..	53·7% (17·3–74·1)	33·2% (–13·8 to 74·1)	70·0% (43·5–84·1)	70·5% (45·4–84·1)
p value *vs* placebo	..	0·0093	0·1380	0·0002	0·0001

≥300 eosinophils per µL (n=325)					
Total number of participants	68	62	66	65	64
LS mean change in FEV_1 from baseline at week 12* (L)	0·18 (0·05); 58	0·26 (0·06); 53	0·35 (0·05); 55	0·43 (0·05); 57	0·39 (0·05); 59
LS mean difference *vs* placebo	..	0·08 (–0·07 to 0·23)	0·17 (0·03–0·32)	0·26 (0·11–0·40)	0·21 (0·06–0·36)
p value *vs* placebo	..	0·2774	0·0212	0·0008	0·0063
LS mean change in FEV_1 from baseline at week 12 (%)	10·17% (3·32); 58	17·93% (3·43); 53	21·57% (3·32); 55	25·91% (3·32); 57	25·80% (3·35); 59
LS mean difference *vs* placebo	..	7·76 (–1·55 to 17·07)	11·40 (2·28–20·52)	15·74 (6·61–24·87)	15·63 (6·47–24·80)
p value *vs* placebo	..	0·1018	0·0145	0·0008	0·0009
LS mean change in FEV_1 from baseline at week 24 (L)	0·22 (0·05); 52	0·28 (0·06); 50	0·37 (0·05); 57	0·38 (0·05); 59	0·38 (0·05); 58
LS mean difference *vs* placebo	..	0·06 (–0·09 to 0·21)	0·15 (0·01–0·30)	0·16 (0·02–0·31)	0·16 (0·01–0·30)
p value *vs* placebo	..	0·4349	0·0401	0·0264	0·0345
LS mean change in FEV_1 from baseline at week 24 (%)	12·83% (3·22); 52	18·87% (3·36); 50	23·31% (3·20); 57	22·89% (3·21); 59	24·92% (3·25); 58
LS mean difference *vs* placebo	..	6·04 (–3·04 to 15·12)	10·48 (1·66–19·31)	10·07 (1·23–18·90)	12·09 (3·20–20·97)
p value *vs* placebo	..	0·1913	0·02	0·0257	0·0078
≥1 severe exacerbation event in the 24-week treatment period	19/68 (28%)	7/59 (12%)	11/66 (17%)	5/64 (8%)	7/64 (11%)
Adjusted annualised severe exacerbation event rate estimate	1·044 (0·572–1·904)	0·358 (0·158–0·809)	0·678 (0·356–1·290)	0·300 (0·133–0·678)	0·201 (0·078–0·517)
Risk reduction *vs* placebo (%)	..	65·7% (8·3–87·2)	35·1% (–49·9 to 71·9)	71·2% (24·3–89·1)	80·7% (44·1–93·3)
p value *vs* placebo	..	0·0329	0·3119	0·0116	0·0024

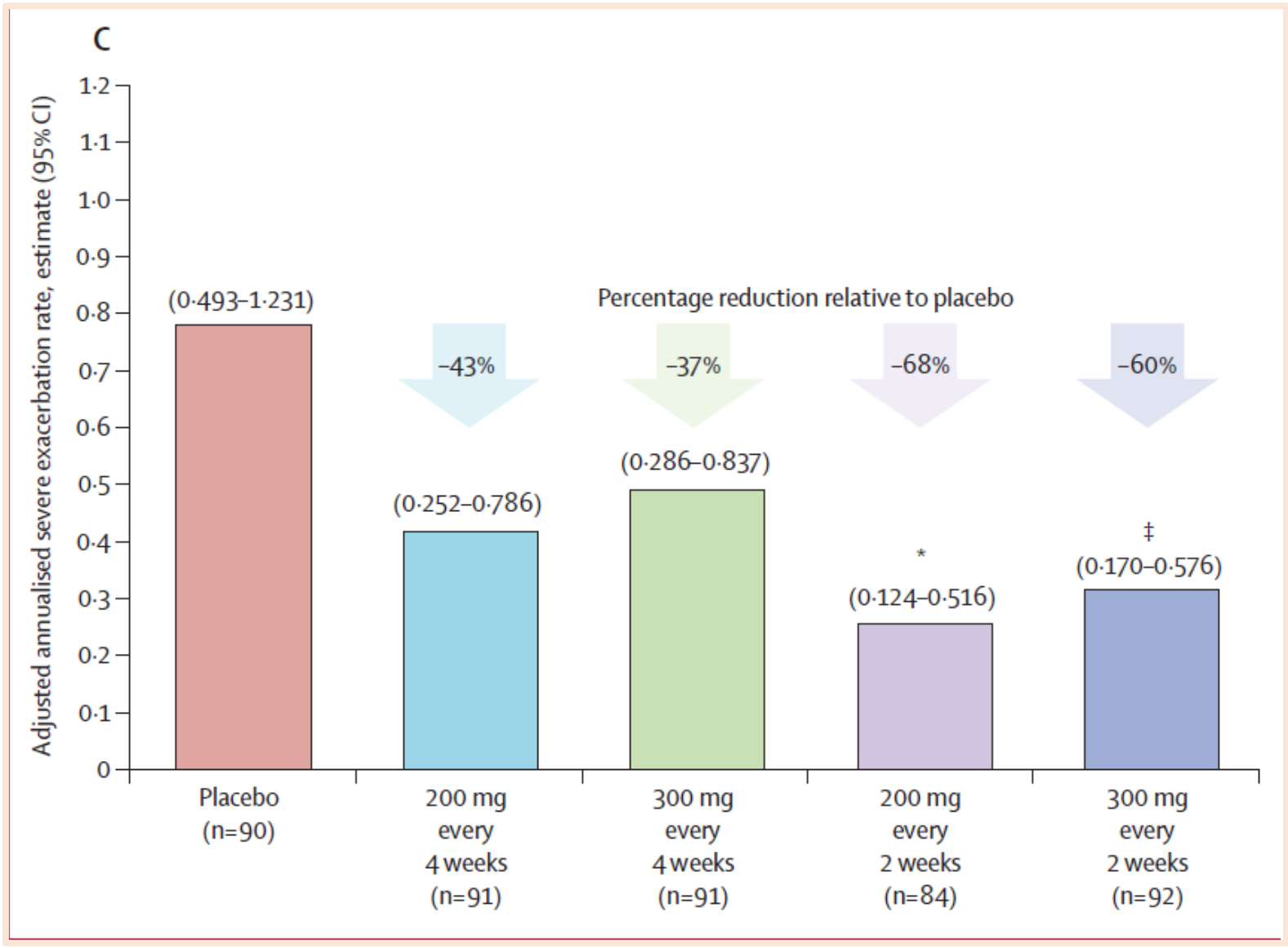
<300 eosinophils per µL (n=451)					
Total number of participants	90	92	91	85	93
LS mean change in FEV_1 from baseline at week 12* (L)	0·10 (0·04); 71	0·19 (0·04); 81	0·18 (0·04); 79	0·25 (0·04); 79	0·22 (0·04); 87
LS mean difference *vs* placebo	..	0·09 (–0·01 to 0·20)	0·08 (–0·02 to 0·18)	0·15 (0·04–0·25)	0·12 (0·01–0·22)
p value *vs* placebo	..	0·0795	0·1231	0·0057	0·0262
LS mean change in FEV_1 from baseline at week 12 (%)	4·82% (2·16); 71	11·03% (2·14); 81	10·02% (2·08); 79	13·63% (2·14); 79	12·56% (2·06); 87
LS mean difference *vs* placebo	..	6·20 (0·37–12·04)	5·20 (–0·61 to 11·01)	8·81 (2·93–14·69)	7·74 (1·98–13·50)
p value *vs* placebo	..	0·0371	0·0791	0·0034	0·0086
LS mean change in FEV_1 from baseline at week 24 (L)	0·09 (0·04); 73	0·21 (0·04); 76	0·20 (0·04); 75	0·23 (0·04); 76	0·23 (0·04); 85
LS mean difference *vs* placebo	..	0·12 (0·01–0·22)	0·10 (–0·00 to 0·21)	0·14 (0·03–0·25)	0·14 (0·03–0·24)
p value *vs* placebo	..	0·0306	0·0536	0·0104	0·0109
LS mean change in FEV_1 from baseline at week 24 (%)	4·65% (2·21); 73	12·04% (2·21); 76	11·62% (2·16); 75	13·41% (2·22); 76	12·55% (2·12); 85
LS mean difference *vs* placebo	..	7·39 (1·38–13·40)	6·97 (0·98–12·95)	8·75 (2·70–14·81)	7·90 (1·98–13·81)
p value *vs* placebo	..	0·016	0·0228	0·0047	0·009
≥1 severe exacerbation event in the 24-week treatment period	22/90 (24%)	16/91 (18%)	18/91 (20%)	8/84 (10%)	10/92 (11%)
Adjusted annualised severe exacerbation event rate estimate	0·779 (0·493–1·231)	0·445 (0·252–0·786)	0·489 (0·286–0·837)	0·253 (0·124–0·516)	0·313 (0·170–0·576)
Risk reduction *vs* placebo (%)	..	42·9% (–15·9 to 71·9)	37·2% (–24·3 to 68·3)	67·6% (24·4–85·9)	59·9% (16·1–80·8)
p value *vs* placebo	..	0·1209	0·1819	0·0081	0·0152


A
Adjusted annualised severe exacerbation rate, estimate (95% CI)
1·2
1·1
1·0
0·9
0·8
0·7
0·6
0·5
0·4
0·3
0·2
0·1
0
(0·619–1·300)
Percentage reduction relative to placebo
–54%
–33%
–70%
–71%
(0·396–0·907)
*
(0·260–0·664)
†
(0·157–0·461)
†
(0·157–0·445)
(n=158)
(n=150)
(n=157)
(n=148)
(n=156)

Eo≥ 300


B
Adjusted annualised severe exacerbation rate, estimate (95% CI)
1·2
1·1
1·0
0·9
0·8
0·7
0·6
0·5
0·4
0·3
0·2
0·1
0
(0·572–1·904)
Percentage reduction relative to placebo
–66%
–35%
–71%
–81%
(0·356–1·290)
*
(0·158–0·809)
‡
(0·133–0·678)
*
(0·078–0·517)
(n=68)
(n=59)
(n=66)
(n=64)
(n=64)

Eo<300


C
Adjusted annualised severe exacerbation rate, estimate (95% CI)
1·2
1·1
1·0
0·9
0·8
0·7
0·6
0·5
0·4
0·3
0·2
0·1
0
(0·493–1·231)
Percentage reduction relative to placebo
–43%
–37%
–68%
–60%
(0·252–0·786)
(0·286–0·837)
*
‡
(0·124–0·516)
(0·170–0·576)
Placebo (n=90)
200 mg every 4 weeks (n=91)
300 mg every 4 weeks (n=91)
200 mg every 2 weeks (n=84)
300 mg every 2 weeks (n=92)

≥300 eosinophils per µL (n=325)					
Total number of participants	68	62	66	65	64
LS mean change in ACQ-5 score* from baseline to week 24	−1·17 (0·13); 52	−1·48 (0·13); 50	−1·38 (0·12); 57	−1·59 (0·12); 59	−1·72 (0·13); 58
LS mean difference *vs* placebo	..	−0·31 (−0·66 to 0·05)	−0·21 (−0·55 to 0·14)	−0·42 (−0·76 to −0·07)	−0·55 (−0·90 to −0·20)
p value *vs* placebo	..	0·0878	0·2371	0·0171	0·0021
LS mean change in AQLQ global score† from baseline to week 24	0·79 (0·13); 53	1·32 (0·14); 50	1·22 (0·13); 57	1·46 (0·13); 58	1·57 (0·13); 56
LS mean difference *vs* placebo	..	0·53 (0·16–0·90)	0·43 (0·07–0·79)	0·67 (0·31–1·03)	0·78 (0·42–1·15)
p value *vs* placebo	..	0·0054	0·0184	0·0003	<0·0001
LS mean change in AM asthma symptom score‡ from baseline to week 24	−0·45 (0·07); 55	0·61 (0·08); 53	−0·72 (0·07); 58	−0·69 (0·07); 59	−0·68 (0·08); 58
LS mean difference *vs* placebo	..	−0·16 (−0·37 to 0·04)	−0·27 (−0·47 to −0·07)	−0·24 (−0·44 to −0·04)	−0·23 (−0·44 to −0·02)
p value *vs* placebo	..	0·1208	0·0094	0·0212	0·0285
LS mean change in PM asthma symptom score‡ from baseline to week 24	−0·45 (0·08); 56	−0·72 (0·09); 53	−0·76 (0·09); 58	−0·72 (0·09); 59	−0·84 (0·09); 58
LS mean difference *vs* placebo	..	−0·28 (−0·52 to −0·04)	−0·31 (−0·55 to −0·08)	−0·28 (−0·51 to −0·04)	−0·39 (−0·63 to −0·15)
p value *vs* placebo	..	0·0237	0·0089	0·0209	0·0014

	Placebo	Dupilumab			
		200 mg every 4 weeks	300 mg every 4 weeks	200 mg every 2 weeks	300 mg every 2 weeks
(Continued from previous page)					
<300 eosinophils per µL (n=451)					
Total number of participants	90	92	91	85	93
LS mean change in ACQ-5 score* from baseline to week 24	−1·13 (0·10); 75	−1·26 (0·10); 76	−1·34 (0·10); 75	−1·46 (0·10); 75	−1·29 (0·10); 87
LS mean difference *vs* placebo	..	−0·13 (−0·41 to 0·14)	−0·21 (−0·49 to 0·06)	−0·33 (−0·61 to −0·05)	−0·17 (−0·44 to 0·10)
p value *vs* placebo	..	0·3505	0·1328	0·0201	0·2259
LS mean change in AQLQ global score† from baseline to week 24	1·01 (0·11); 74	1·05 (0·11); 77	1·20 (0·11); 75	1·06 (0·11); 74	1·07 (0·11); 85
LS mean difference *vs* placebo	..	0·04 (−0·26 to 0·35)	0·19 (−0·11 to 0·49)	0·05 (−0·26 to 0·36)	0·06 (−0·24 to 0·36)
p value *vs* placebo	..	0·7703	0·2176	0·7400	0·6899
LS mean change in AM asthma symptom score‡ from baseline to week 24	−0·30 (0·07); 77	−0·48 (0·06); 81	−0·42 (0·06); 77	−0·50 (0·07); 77	−0·48 (0·06); 87
LS mean difference *vs* placebo	..	−0·18 (−0·35 to 0·00)	−0·12 (−0·30 to 0·06)	−0·20 (−0·38 to −0·02)	−0·18 (−0·35 to −0·00)
p value *vs* placebo	..	0·0517	0·1964	0·0305	0·0444
LS mean change in PM asthma symptom score‡ from baseline to week 24	−0·35 (0·08); 76	−0·40 (0·07); 82	−0·48 (0·07); 78	−0·52 (0·08); 77	−0·46 (0·07); 87
LS mean difference *vs* placebo	..	−0·05 (−0·26 to 0·15)	−0·14 (−0·34 to 0·07)	−0·17 (−0·38 to 0·04)	−0·11 (−0·32 to 0·09)
p value *vs* placebo	..	0·6147	0·1987	0·1040	0·2733

- Dupilumab’ın her iki haftada bir kez uygulanması alevlenmeleri azaltıp, FEV1 olumlu düzelmeler
- Add on tedavi olarak etkili
- Atopik dermatit ve nazal polip gibi ko-morbid durumlarda etkili tek biolojik ajan

OLGU

Tedavi öncesi

- Hemogram
  - Eozinofil sayısı: 0.75 (10e3/ul) %14.8
- Solunum fonksiyon testi :
  - FEV1:1.93 (%56) rev: %26
  - FVC: 1.36 (% 50)
  - FEV1%: % 70
- AKT: 8
- Total IgE: 160
- ACQ 5≥ 1.5

Tedavi sonrası

- Eozinofilleri de 0.44 %4.8
- FEV1 ↑
  - FEV1: 2.07 (%76)
  - FVC:2.79 (%79)
  - FEV1: %77
- Ataklarda ↓
- AKT: 21
- Total IgE: 50
- ACQ<1.5

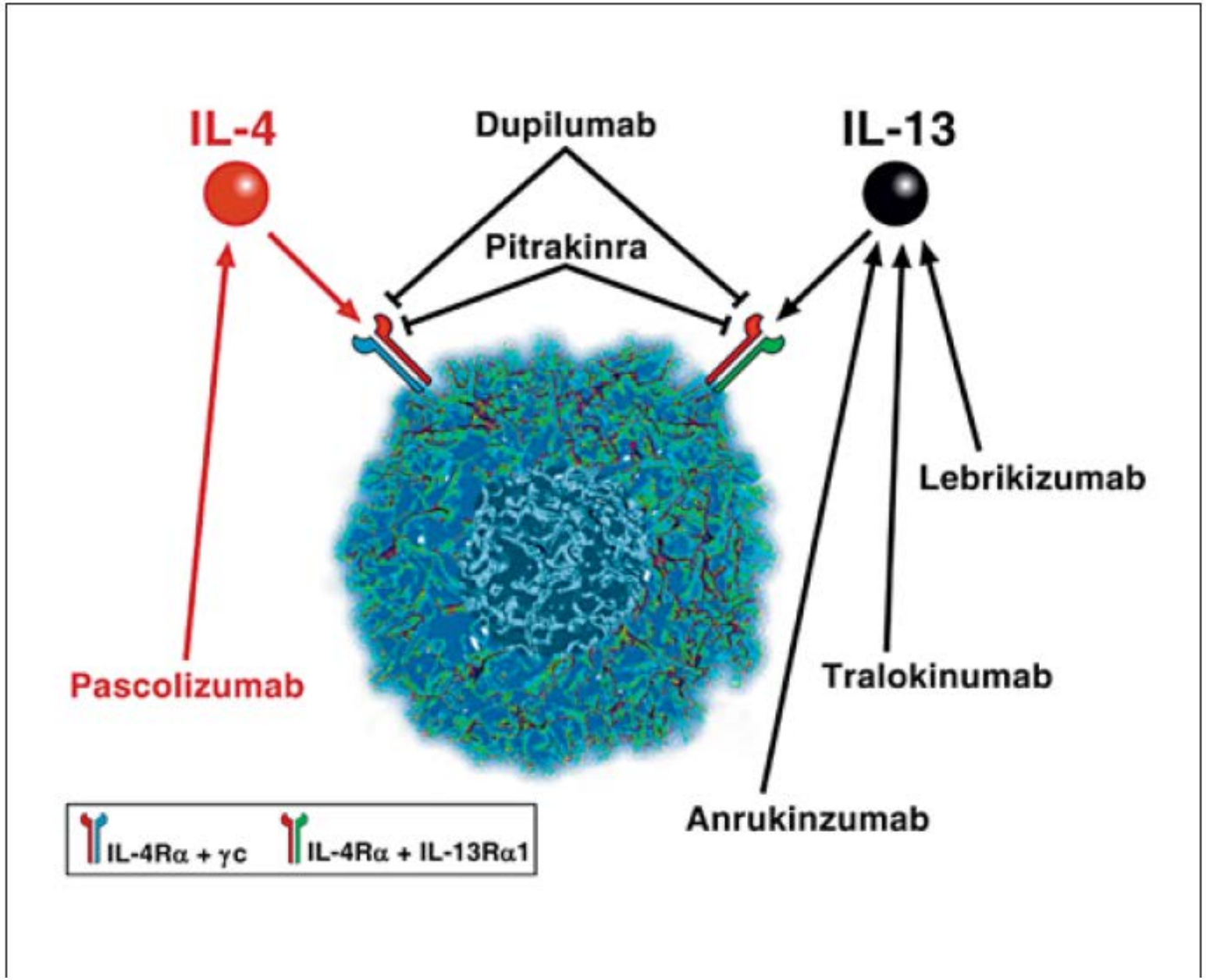

IL-4
Dupilumab
IL-13
Pitrakinra
Lebrikizumab
Pascolizumab
Tralokinumab
Anrukinzumab
IL-4Rα + γc
IL-4Rα + IL-13Rα1

Table 1. Promising drugs and their target compounds. (Information from the clinical trials was retrieved on the web https://clinicaltrials.gov/).

Drugs	Molecular Target	Mode of Action	Experimental Discoveries	Clinical Trials	Refs.
SP600125 (Anthrapyrazolone)	c-Jun N-terminal kinase (JNK)	JNK inhibitor	Decreased migration of cells to bronchoalveolar lavage and downregulate the expression of TLR9.	-----	[26, 27]
Lebrikizumab	IL-13	Blocks IL-13	Decreased asthma exacerbation in patients. Phase III studies in progress.	NCT01867125 NCT01868061 NCT01875003	[28-34]
Benralizumab	IL-5	Blocks IL-5	Phase I, II and III clinical studies have shown a decrease in eosinophil counts as well as a reduction in the effect of asthma in patients.	NCT00768079 NCT02918071 NCT02821416	[35-39]
Tralokinumab	IL-13	Blocks IL-13	Tralokinumab inhibited the development of the phenotype in animals. In humans, FEV1 improved. Clinical studies still in progress.	NCT02902809 NCT01592396 NCT02194699 NCT02161757	[40-42]
Ligustrazine	p38 MAPK	Inhibition of p38 MAPK	Activates lymphocyte recruitment and infiltration.	-----	[43, 44]
Dupilumab	Receptor IL-4	Inhibits signaling of IL-4 and IL-13	Effective not only for asthma but also for the treatment of atopic dermatitis, chronic sinusitis and nasal polyps. Phase III clinical study with asthmatic patients in progress.	NCT02134028 NCT03020810 NCT02573233 NCT02414854	[45-50]
Omazilumab	IgE	Binds to immunoglobulin E	Reduces inflammation of the IgE-mediated airways.	-----	[51]
Ligelizumab	IgE	Binds to immunoglobulin E	Greater efficacy than omalizumab in inhibiting the bronchial allergen response.	NCT02075008	[52]
Mepolizumab	IL-5	Blocks IL-5	Decreases exacerbation of asthma. Phase III clinical trials are in progress.	NCT01463644 NCT02105948 NCT02105961	[53, 54]
Reslizumab	IL-5	Blocks IL-5	Decreases recruitment and activation of human eosinophils.	NCT02452190 NCT02293265	[55, 56]
Fervipiprant	Prostaglandin D2	Prostaglandin D2 receptor antagonist	Reduces eosinophilic inflammation of the airways and is well tolerated in patients with moderate to severe persistent asthma.	-----	[57-59]

Lebrikizumab

- Humanize monoklonal antikor
- IL-4Rα/IL-13Rα1 yüksek affinitesi olan solubl IL-13'ü bağlıyor.
- Faz 2 çalışmalarda periostin yüksek grubta alevlenmeleri azaltıp solunum fonsiyonlarını düzelttiğini göstermiş.
- Lavolta 1 ve Lavolta 2 faz 3 çalışmaları yapılmış

LAVOLTA çalışmaları

- Randomize, çift-kör plasebo kontrollü
- 18-75 yaş maksimum tedaviye rağmen kontrolsüz astım
- Periostin ve eozinofil düzeyleri
- 52 haftalık çalışma
  - Primer sonlanım noktası:
    - alevlenmelerin azalması
  - Sekonder sonlanım:
    - prebronkodilatör FEV1'de bazale göre mutlak değişim
    - İlk astım atağına göre geçen süre

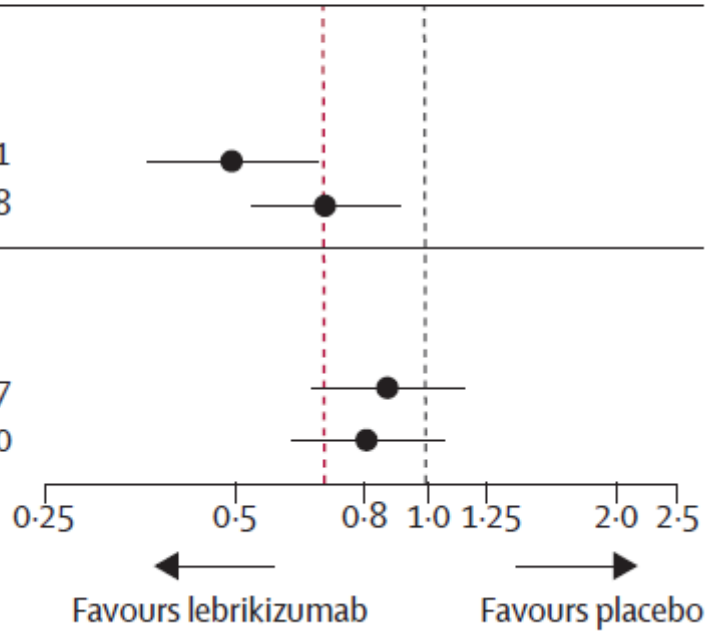
Hanania NA, Lancet Respir Med 2016;4:781-96

LAVOLTA 1:1081

LAVOLTA 2:1067

plasebo, 37,5 mg ve 125 mg

	n	Adjusted exacerbation rate (per patient per year)	Rate difference (lebrikizumab–placebo)	Rate reduction (%)	Rate ratio (lebrikizumab *vs* placebo, 95% CI)	p value
LAVOLTA I						
Placebo	362	0·84				
Lebrikizumab 37·5 mg	360	0·42	−0·42	50%	0·50 (0·37–0·67)	<0·0001
Lebrikizumab 125 mg	359	0·59	−0·25	30%	0·70 (0·54–0·91)	0·0078
LAVOLTA II						
Placebo	354	0·61				
Lebrikizumab 37·5 mg	356	0·52	−0·09	14%	0·86 (0·66–1·12)	0·2607
Lebrikizumab 125 mg	357	0·48	−0·13	21%	0·79 (0·61–1·04)	0·0920



	Biomarker high			Biomarker low		
	Placebo	Lebrikizumab 37·5 mg	Lebrikizumab 125 mg	Placebo	Lebrikizumab 37·5 mg	Lebrikizumab 125 mg
Change from baseline in FEV_1 (mL)						
LAVOLTA I						
Adjusted mean (SE)	98 (25)	201 (25)	211 (25)	25 (33)	38 (32)	150 (33)
Difference in means (95% CI)		103 (34 to 172)	113 (44 to 182)		13 (−78 to 104)	126 (35 to 217)
p value		0·0034	0·0013		0·7792	0·0070
LAVOLTA II						
Adjusted mean (SE)	96 (25)	184 (25)	179 (25)	87 (41)	88 (43)	107 (41)
Difference in means (95% CI)		88 (18 to 158)	82 (12 to 152)		1 (−117 to 118)	19 (−96 to 135)
p value		0·0139	0·0217		0·9889	0·7442
Time to first exacerbation						
LAVOLTA I						
Patients with event (n, %)	99 (39%)	74 (30%)	78 (31%)	35 (33%)	22 (20%)	30 (29%)
Median time to event (weeks)	..	..	..	..	..	..
Hazard ratio (95% CI)		0·58 (0·42 to 0·79)	0·65 (0·47 to 0·89)		0·52 (0·30 to 0·89)	0·59 (0·35 to 0·98)
p value		0·0007	0·0071		0·0183	0·0435
LAVOLTA II						
Patients with event (n, %)	94 (38%)	75 (29%)	72 (29%)	27 (25%)	32 (32%)	25 (24%)
Median time to event (weeks)	..	..	..	..	..	..
Hazard ratio		0·77 (0·56 to 1·06)	0·73 (0·53 to 1·01)		1·37 (0·80 to 2·37)	0·95 (0·54 to 1·66)
p value		0·1151	0·0550		0·2536	0·8544

Change from baseline in AQLQ(S) score						
LAVOLTA I						
Adjusted mean (SE)	0·78 (0·064)	0·93 (0·063)	0·91 (0·064)	0·85 (0·098)	0·73 (0·096)	0·86 (0·097)
Difference in means (95% CI)		0·14 (−0·03 to 0·32)	0·13 (−0·05 to 0·30)		−0·12 (−0·38 to 0·15)	0·01 (−0·26 to 0·28)
p value		0·1098	0·1623		0·4015	0·9293
LAVOLTA II						
Adjusted mean (SE)	0·80 (0·065)	0·81 (0·064)	1·05 (0·064)	0·70 (0·102)	0·80 (0·105)	0·62 (0·100)
Difference in means (95% CI)		0·01 (−0·16 to 0·19)	0·25 (0·07 to 0·43)		0·10 (−0·18 to 0·39)	−0·08 (−0·36 to 0·20)
p value		0·8704	0·0061		0·4808	0·5857
Change from baseline in rescue medication use (puffs per day)						
LAVOLTA I						
Adjusted mean (SE)	−0·6 (0·1)	−1·1 (0·1)	−1·1 (0·1)	−0·8 (0·2)	−0·8 (0·2)	−1·2 (0·2)
Difference in means (95% CI)		−0·5 (−0·9 to −0·1)	−0·5 (−0·9 to −0·1)		0·0 (−0·6 to 0·7)	−0·4 (−1·0 to 0·3)
p value		0·0256	0·0121		0·9337	0·2696
LAVOLTA II						
Adjusted mean (SE)	−0·6 (0·2)	−1·0 (0·2)	−1·1 (0·2)	−0·3 (0·2)	−0·7 (0·2)	−0·5 (0·2)
Difference in means (95% CI)		−0·4 (−0·9 to 0·0)	−0·6 (−1·0 to −0·1)		−0·3 (−0·8 to 0·2)	−0·1 (−0·6 to 0·3)
p value		0·0478	0·0100		0·1849	0·5231

- Çalışma primer sonlanım noktası açısından etkinliği göstermemiş.
- Biomarker yüksekliği de bu tedaviden yarar görebilecekleri yeterli derecede belirleyememiş.
- Periostinin akciğer dokusundaki değerleri?
- Aplastik anemi, eozinofilik pnömoni, Churg Strauss gibi ciddi yan etkiler

Diğer

- Tralokinumab IgG-4 monoklonal antikor IL-13 antikoru
- 194 orta-ağır astım olgu
- 13 hafta 2 haftada 1 kez
- ACQ skorlarında ve FEV1’de plasebo ile anlamlı fark yok

Brightling CE, et al. Lancet Respir Med 2015;3: 692-701

Özet

- Tek başına IL-13 blokajını hedef alan çalışmalar etkinlik anlamında şüpheli sonuçlar
- IL-4 ve IL-13 her ikisini hedef alan dupilumab gibi anti IL-4'e yönelik ajanlar alevlenmeyi, semptomları kontrol etmede ve FEV1'de düzelme açısından da yararlı.