Biomarkers and Treatment Strategies in Type2-high Asthma

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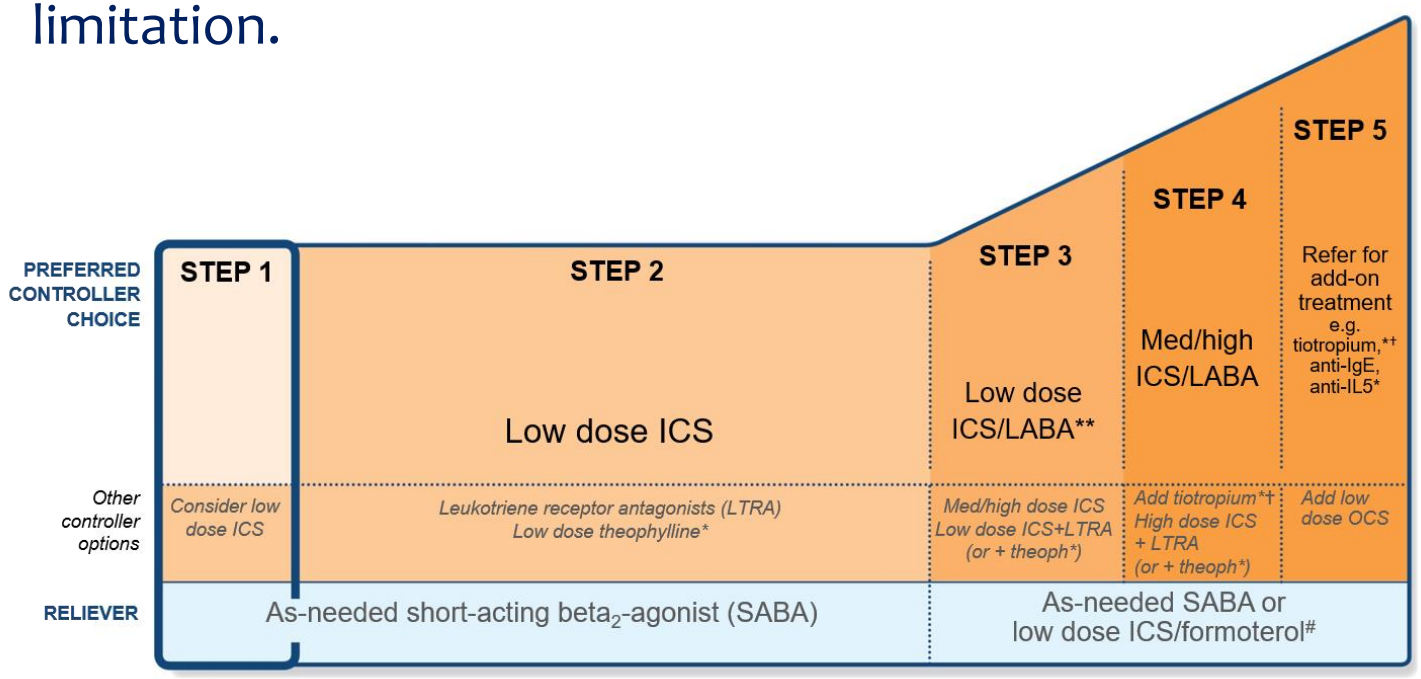
CONTENTS

Bronchial Asthma

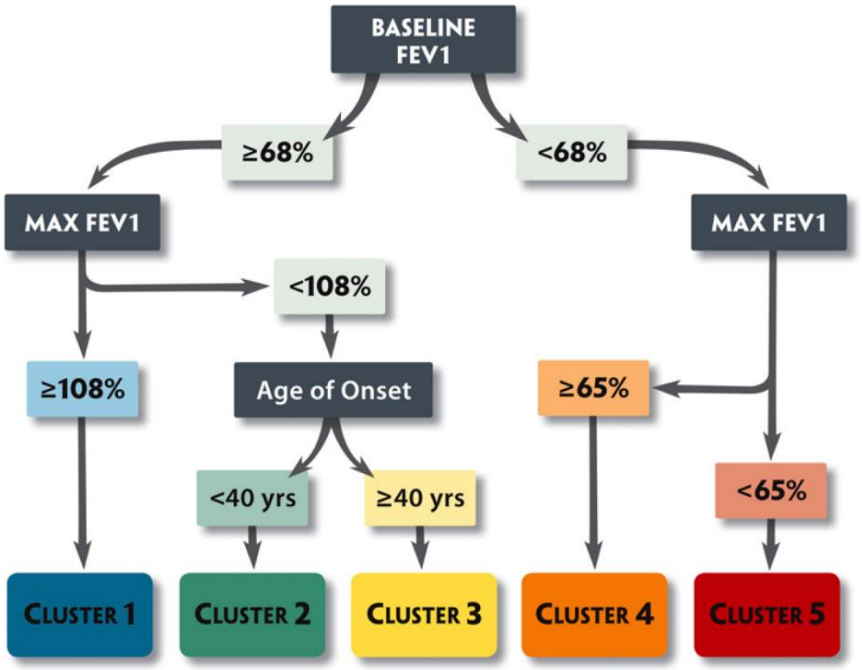
- The pathophysiology of asthma is very complex and includes several disease variants.
- Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation with variable expiratory airflow limitation.



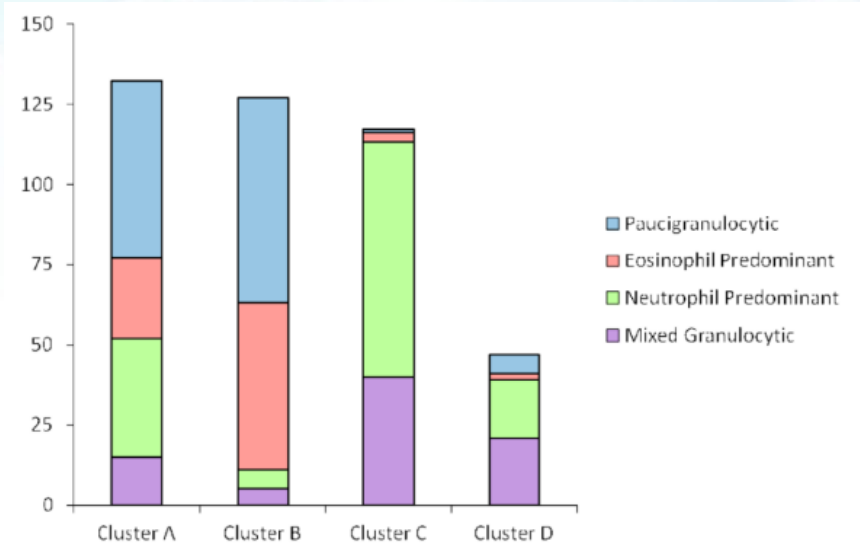
GINA guideline

Phenotypes of Asthma

- **Phenotype:** used to define the clinically observable characteristics
- no direct relationship to the disease mechanisms



Moore WC, et al. AJRCCM 2010;181:315-23

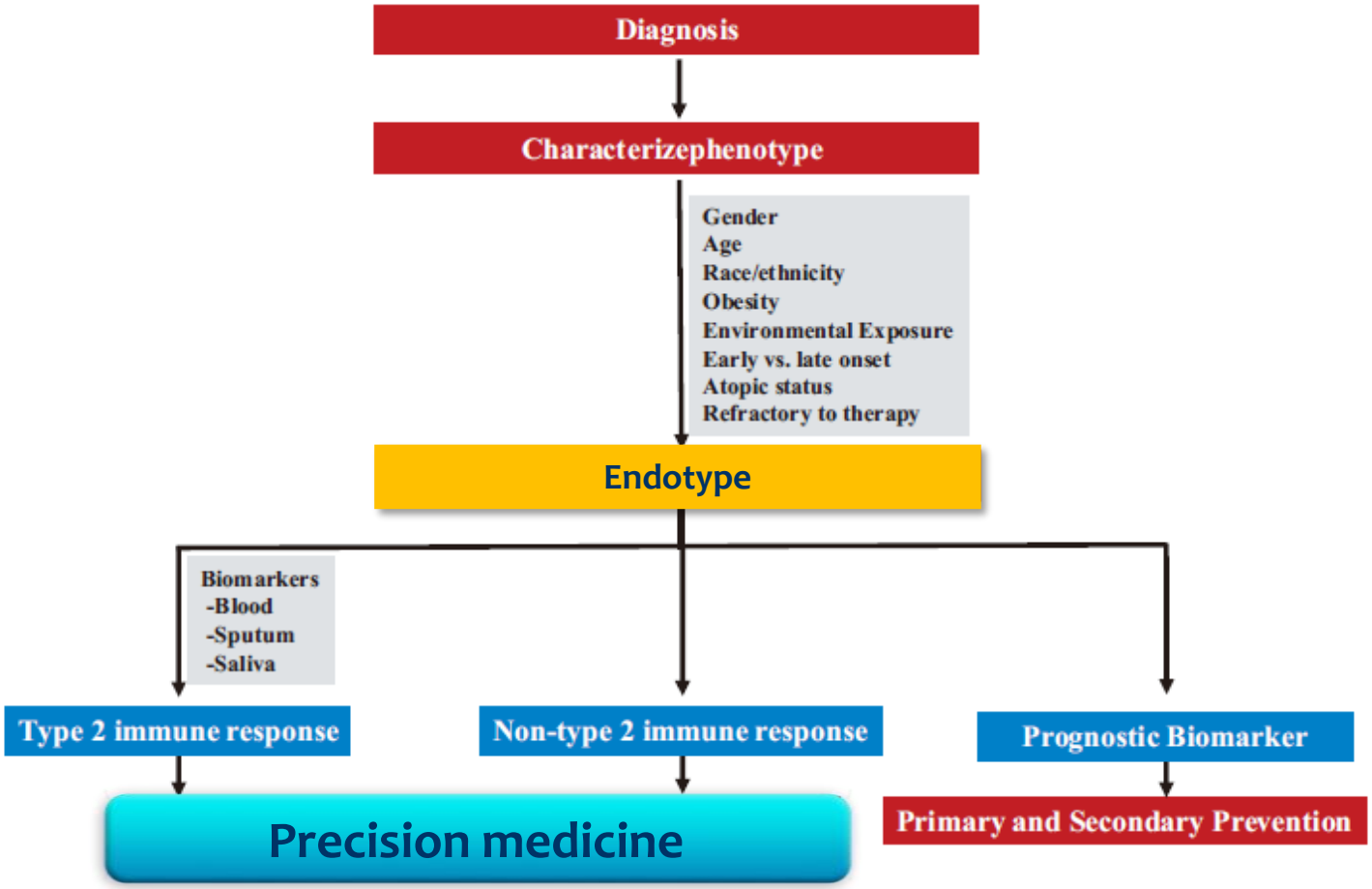


- A. Early-onset atopic asthma, and normal lung function, younger subjects
- B. Early-onset atopic asthma, slightly older mostly female, with more medication use
- C. Older obese women, late-onset, less likely atopic with decreased PFT
- D. More severe asthma

Moore WC, et al, JACI 2014;133:1557-63

Endotypes of Asthma

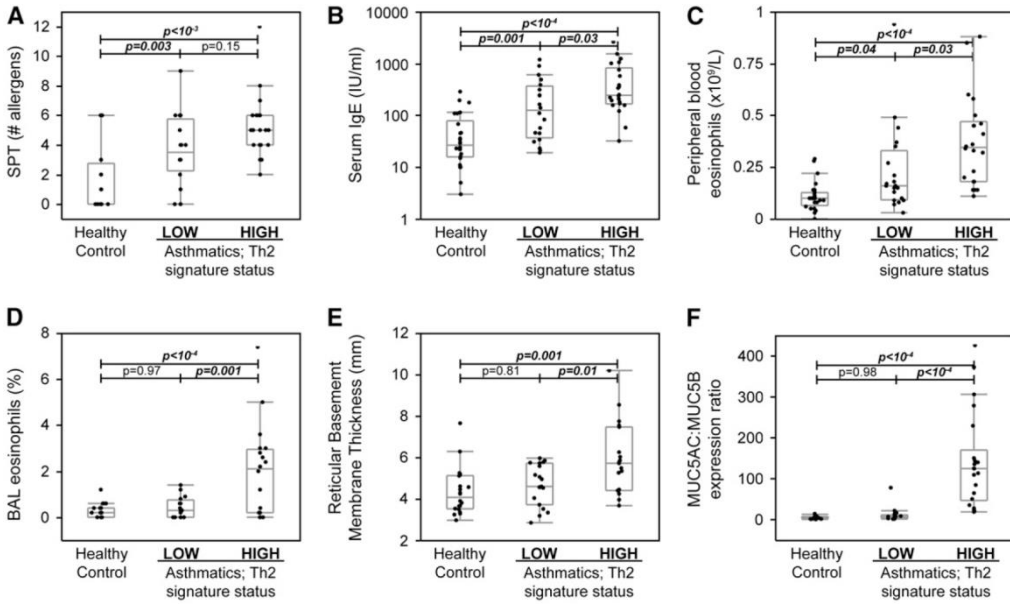
- **Endotype:** a term used to define the pathobiologic mechanisms

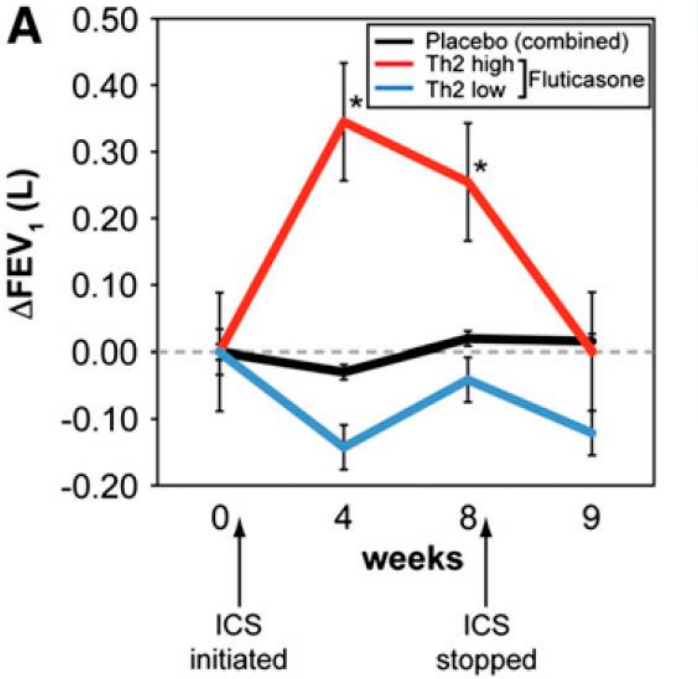


Muraro A, et al, J Allergy Clin Immunol 2016;137:1347-58

Potential Implications for Therapy

- A ‘Th2-high’ identifies patients with high eosinophilia and good therapeutic response to corticosterids.

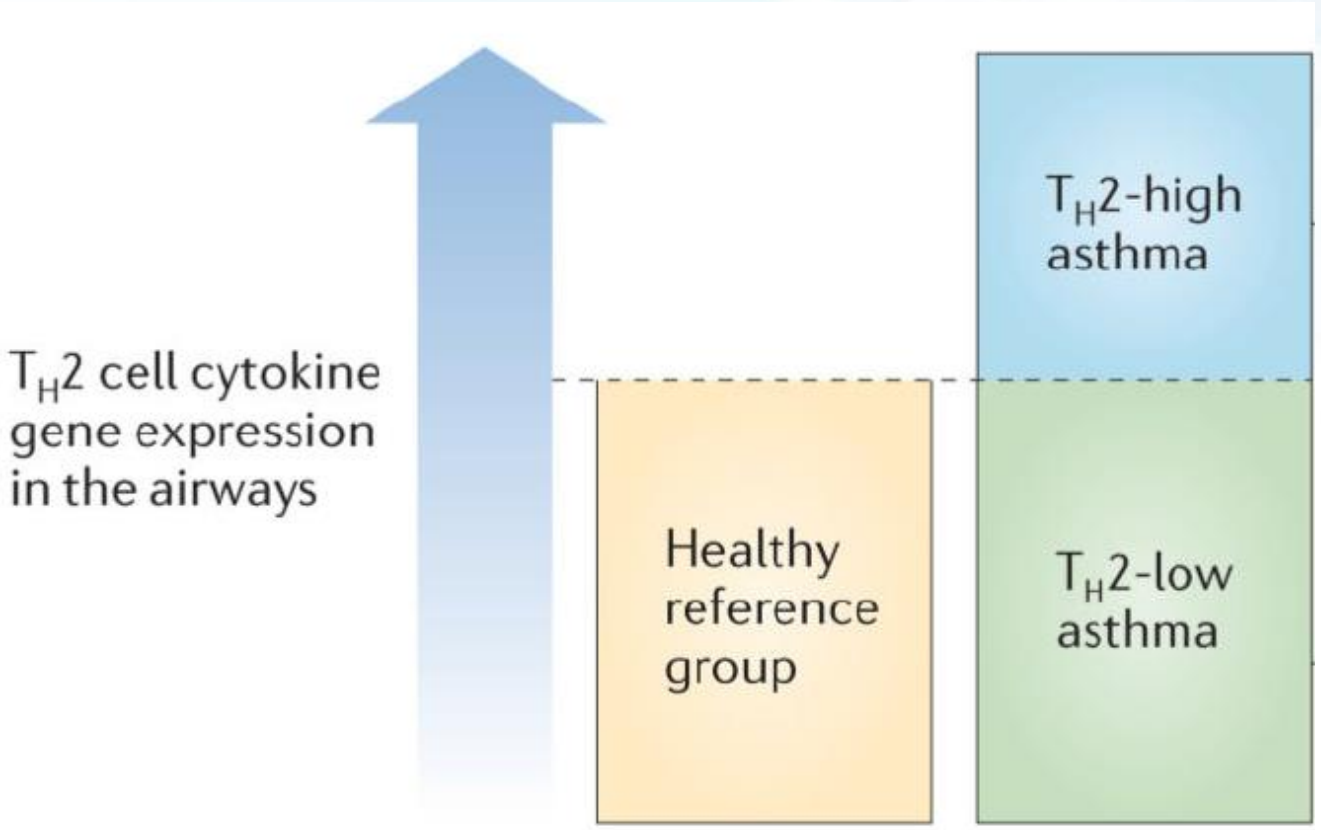




Woodruff PG, et al. Am J Respir Crit Care Med 2009;180:388-95

Th2-High vs Th2-Low Asthma

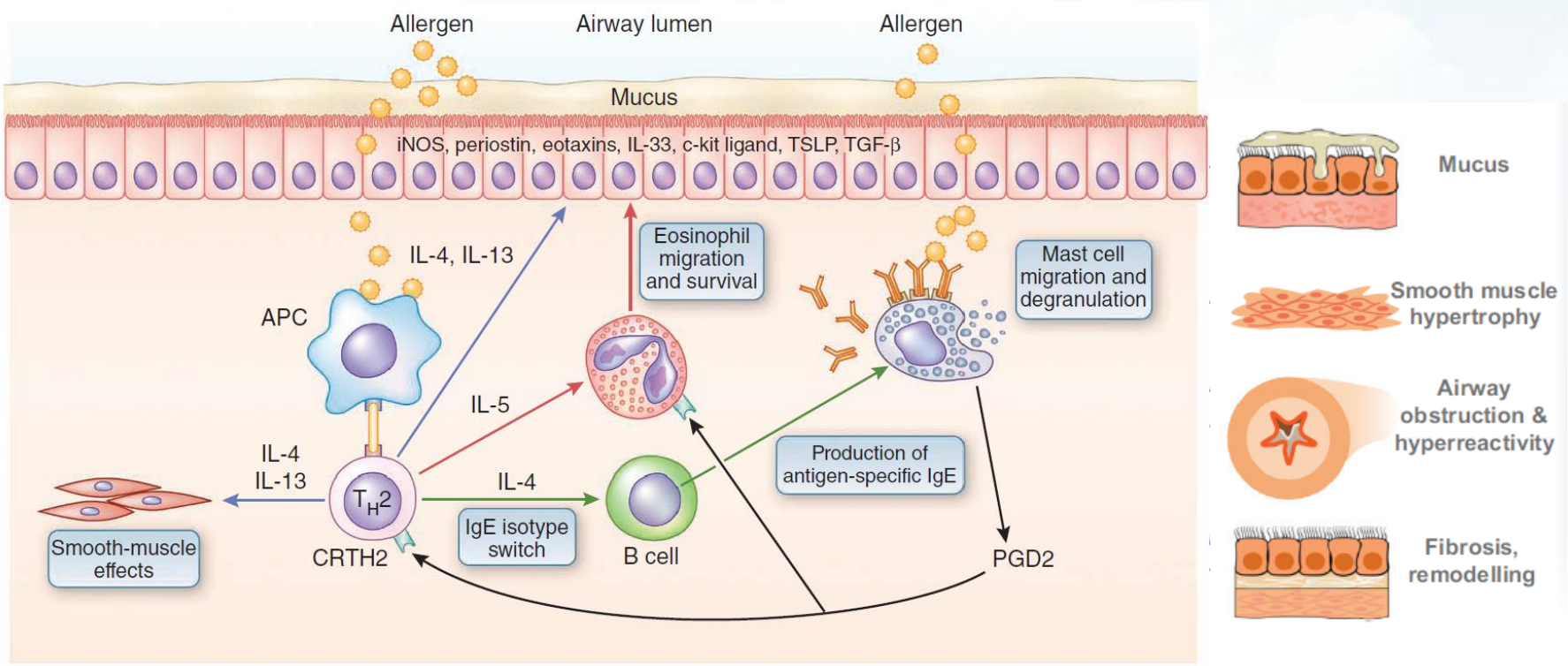
- Patients with Th2-high asthma have eosinophilia and other signs of airway type 2 inflammation and good response to ICS.



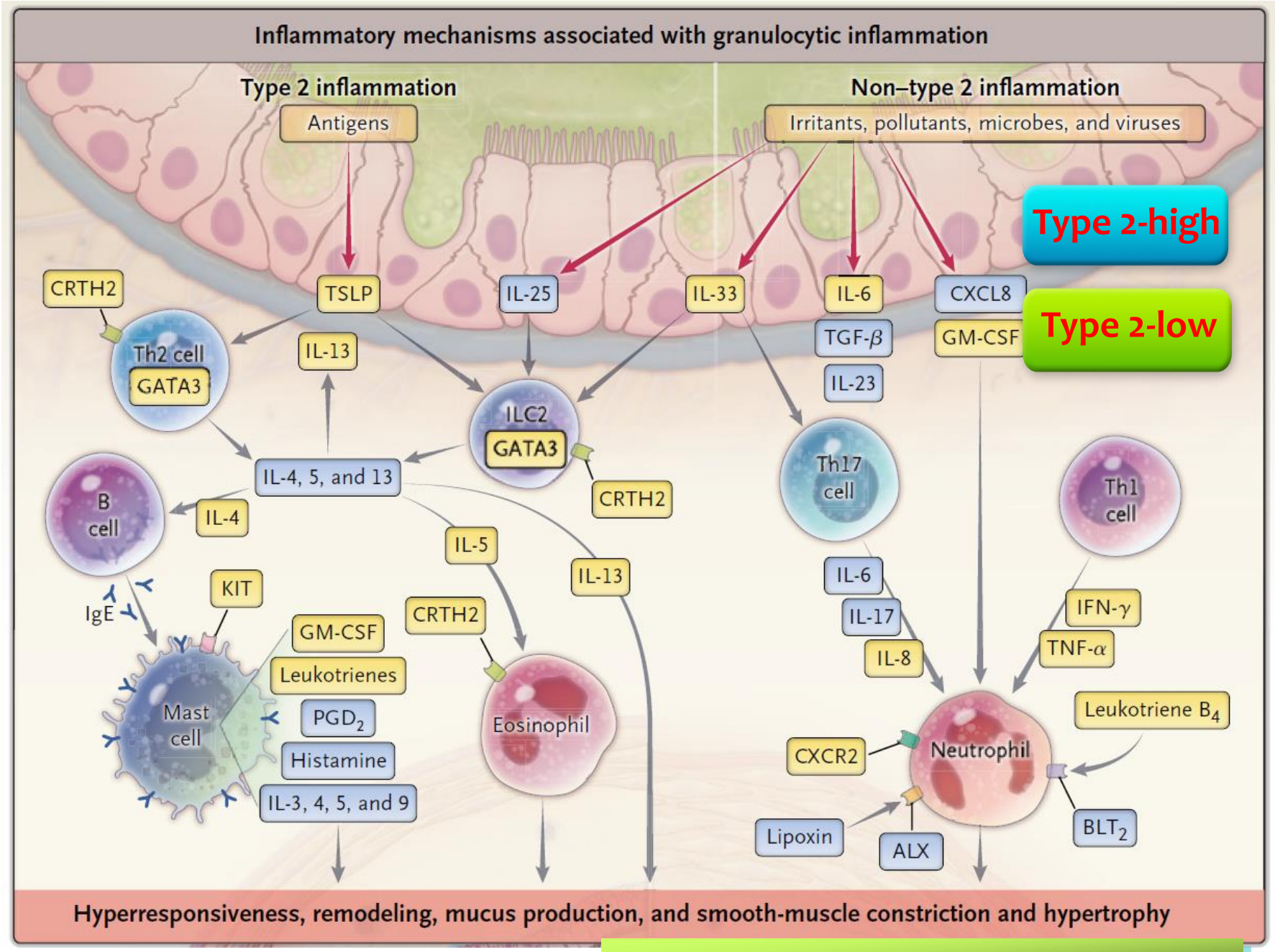
Fahy JV. Nat Med 2015;15:57-65

Th2 Immune Processes in Asthma

- Th2 cells produce the cytokines IL-4, IL-5, and IL-13.
- These cytokines stimulate allergic and eosinophilic inflammation as well as epithelial and smooth muscle changes.



Wenzel SE. Nat Med 2012;12:716-25



Israel E, et al. N Eng J Med 2017;377:965-76

Type2-High vs Type2-Low Asthma

Type 2-high

- Airway and systemic eosinophilia
- Responsiveness to glucocorticoids
- Responsiveness to inhibitors of type 2 inflammation

Type 2-low

- Absence of airway and systemic eosinophilia
- Lack of responsiveness to glucocorticoids
- Lack of responsiveness to inhibitors of type 2 inflammation

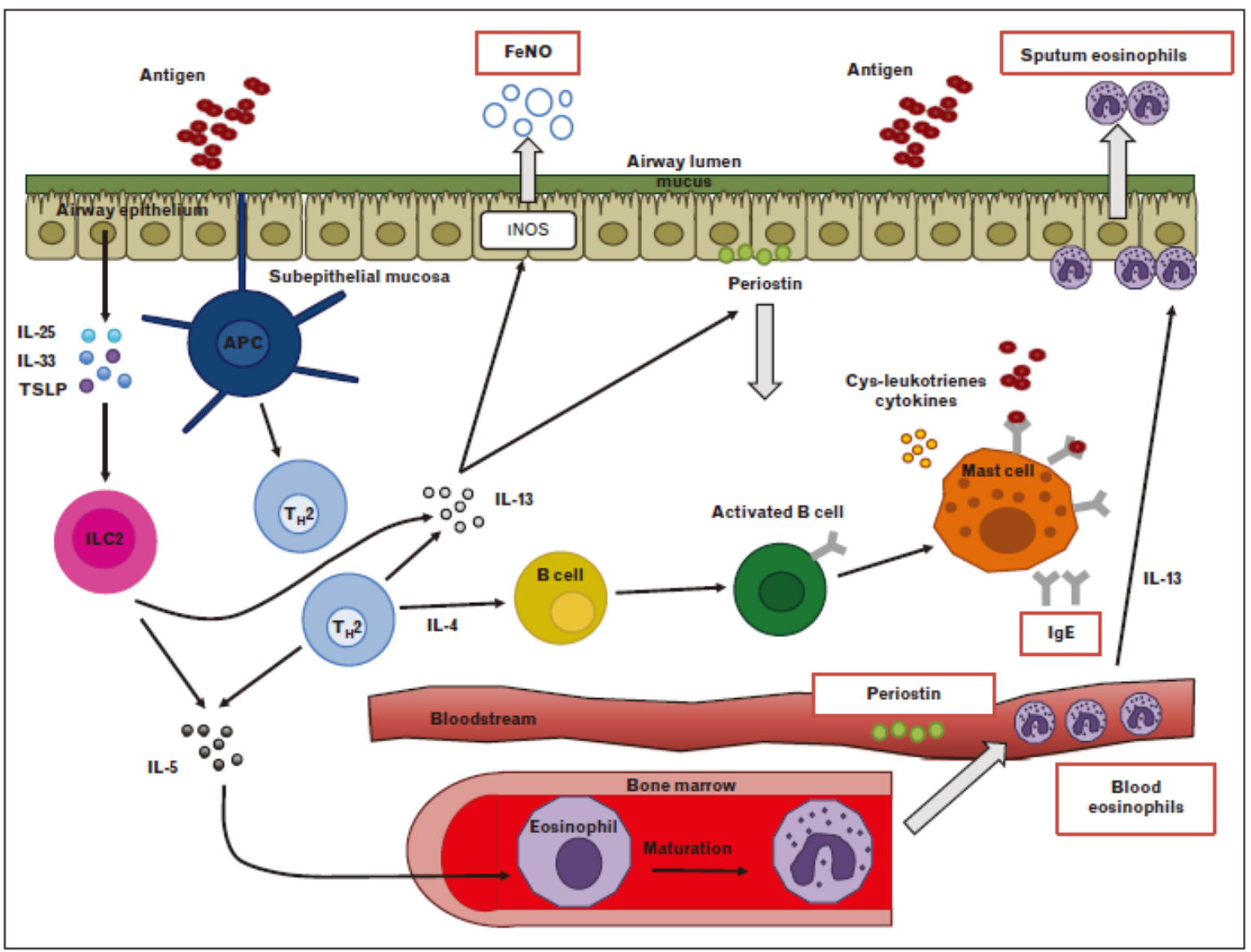
Wenzel SE. Nat Med 2012;12:716-25

1 Type2-High Asthma

2 Biomarkers for Type2-High Asthma

3 Treatment of Type2-High Asthma

Type 2 Inflammatory Biomarkers



Parulekar AD, et al. Curr Opin Pul Med 2016;22:59-68

Sputum Eosinophils

- The most unambiguous, limited invasive method
- correlate with disease severity, asthma control, exacerbation risk, healthcare utilization.
- Predict therapeutic responses to corticosteroid and Th2-targeting therapies.

Limitations

- Inadequate sputum samples are common
- Analysis can be technically challenging
- Sputum induction is not a feasible procedure for children younger than 8 years of age.
- No standard cut-off : 2-3% of the total cell count
- Further analysis of DREAM study

  : not predict response of mepolizumab

Katz LE, et al. Ann Am Thorac Soc 2014;11:531-6

Blood Eosinophils

- can distinguish between eosinophilic and non-eosinophilic asthma based on a cut-off of 300 cells/μL.
- correlate with disease severity and exacerbation risk.
- predict therapeutic responses to corticosteroids or biologic agents (such as anti-IL-5).

Limitations

- Low specificity for asthma
  - Other allergies, autoimmune disease, parasitic infections
- A wide range of cut-off values in clinical studies
  - Meaningful reduction in exacerbation using mepolizumab: 150
  - Reslizumab: 400
- The sensitivity is reduced if IL-5 targeted therapy is initiated.

IgE

- One of the first biomarkers used for stratification of patients for biological therapies.
- used for determining atopy, dosing omalizumab and monitoring therapeutic response to anti-IgE therapy

Limitations

- Low specificity for detecting sputum eosinophilia
- Poor correlations with airflow obstruction and disease severity
- could not predict therapeutic responses to omalizumab

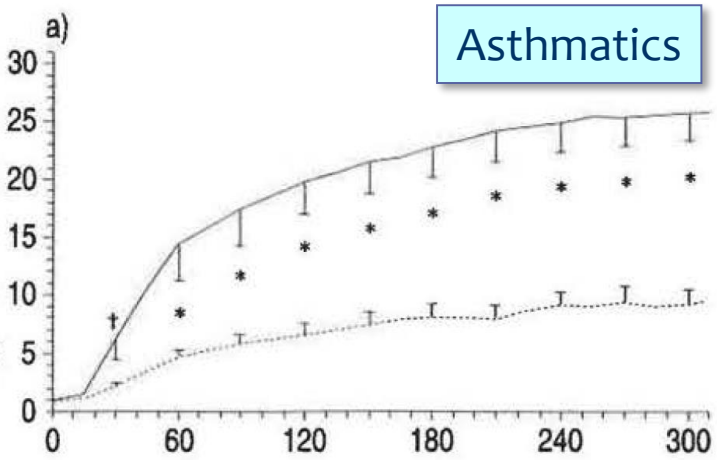
What's new in GINA 2018? : Fractional Concentration of Exhaled NO (FENO)

This test is becoming more widely available in some countries. All sections about FENO throughout the report have been reviewed and the text edited for clarity, and to take new data into account. These sections include diagnosis (p. 20), alternative strategies for adjusting asthma treatment (p. 38), recommendations about initial controller treatment (p. 42), management of asthma in pregnancy (p. 68) and prediction of asthma in children (p.104). The section on FENO-guided treatment (p. 38) has been updated to reflect the results of new meta-analyses that separately analyzed studies in which the control algorithm was reasonably close to current guidelines-based treatment, and therefore provided a clinically relevant comparator. In studies involving children and young adults, these analyses showed that FENO-guided treatment was associated with significantly fewer exacerbations and lower exacerbation rate than treatment based on current guidelines. For adults, no significant difference was seen with FENO-guided treatment compared with treatment based on current guidelines. Further studies are needed to identify the populations most likely to benefit from FENO-guided treatment, and the optimal frequency of monitoring.

GINA 2018

FENO in Asthmatics

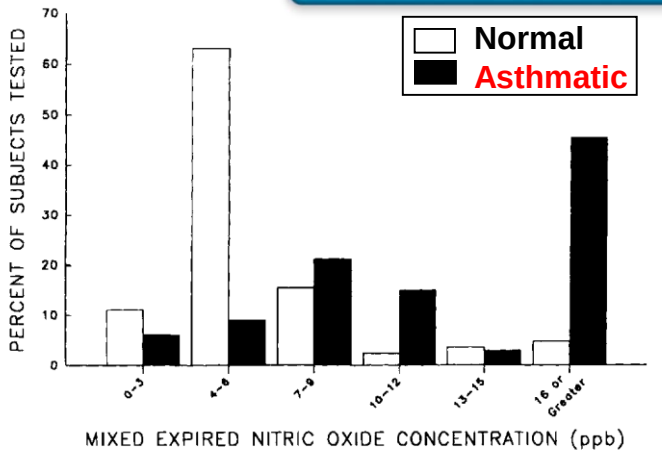
- 8 asthma patients
- 12 control



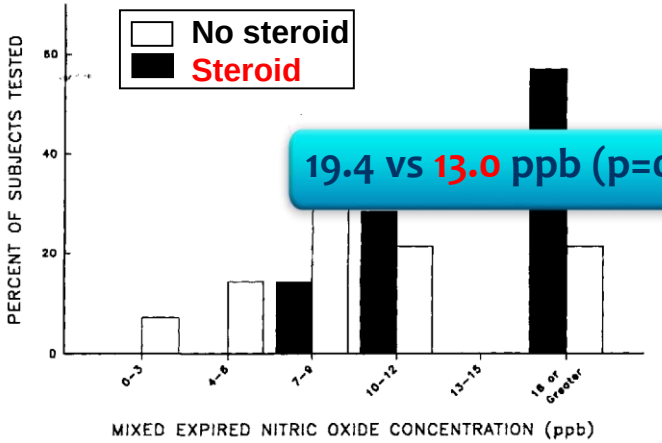
Alving K, et al. Eur Respir J 1993;6:1368-1370

- 43 asthma patients
- 90 normal subjects

6.2 vs 13.9 ppb (p <0.001)



19.4 vs 13.0 ppb (p=0.02)



Massaro AF, et al. AJRCCM 1995;152:800-3

FENO and Sputum Eosinophils

- Relationship of FENO and sputum eosinophils
- n=566

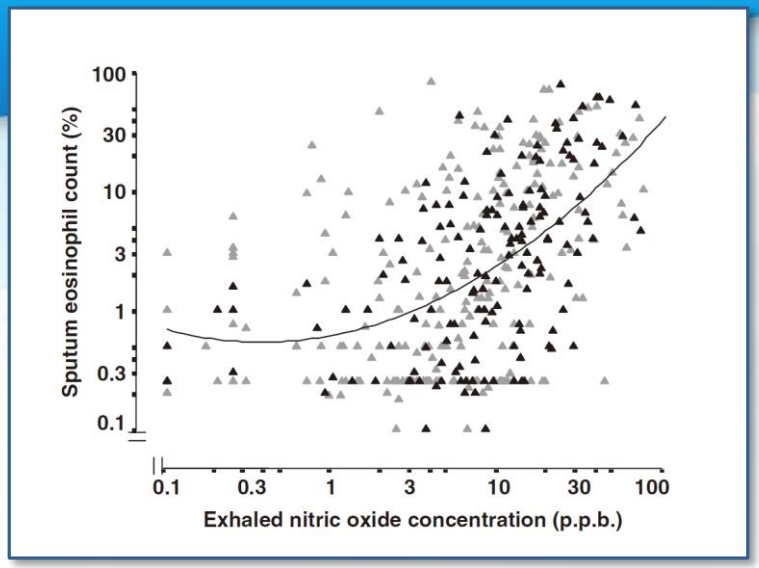


Table 3. Table of analysis of ROC curves of exhaled nitric oxide (NO) concentration at different flows to determine a sputum eosinophil count of >3% and correlation co-efficients for the association between exhaled NO concentration and sputum eosinophil counts at different flows

								Correlations	
Flow (mL/s)	Number	AUC	95% CI	*P*	Value (ppb)	Sensitivity	Specificity	Coefficient	*P*
10	60	0.68	0.54, 0.83	0.02	112	70	70	0.32	0.013
30	60	0.75	0.61, 0.88	0.002	53	74	72	0.37	0.004
50	60	0.77	0.63, 0.9	0.001	36	78	72	0.39	0.002
100	60	0.76	0.63, 0.89	0.001	22	78	72	0.39	0.002
200	60	0.73	0.59, 0.87	0.004	13	74	72	0.30	0.018
250	405	0.77	0.73, 0.82	<0.001	8.3	71	72	0.47	<0.001
CbrMax*	60	0.76	0.63, 0.89	0.001	87†	83	69	0.43	0.001

Measurement of FENO is associated with levels of sputum and blood eosinophils.

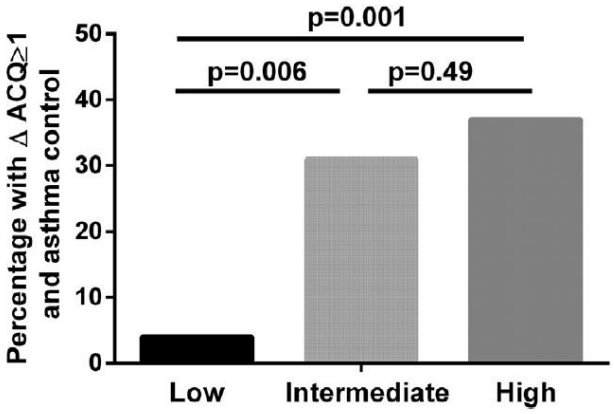
Berry MA, et al. Clin Exp Allergy 2005;35:1175-79

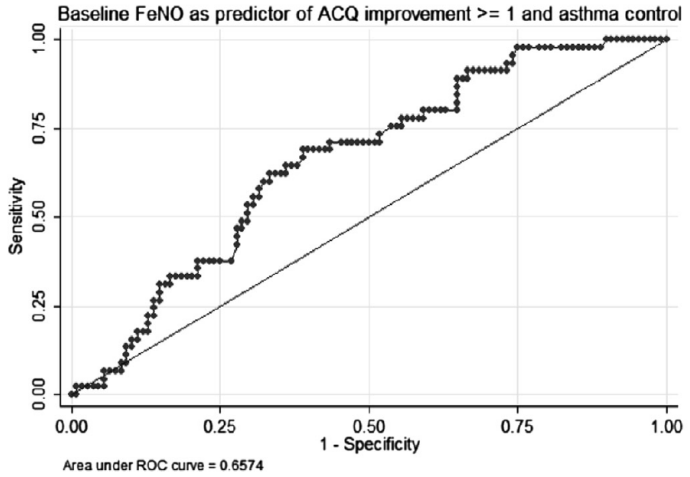
FENO as a Predictor of ICS response

- 153 steroid-naïve subjects with asthma

Table 2
Factors associated with achieving asthma improvement and/or control ($n = 146$). Results presented as adjusted odds ratios (aOR) and 95% confidence interval (CI) from multiple logistic regression analyses where all variables listed in the first column were predictors and achieving asthma improvement and/or control was outcome. An association is significant if the CI does not include 1.

	Achieving improvement of ACQ with 0.5 ($n = 123$)	Achieving improvement of ACQ with 1 ($n = 100$)	Achieving improvement of ACQ with 1 and asthma control (ACQ $\leqslant$ 0.75) ($n = 45$)
Displaying intermediate FeNO vs low FeNO	1.53 (0.33, 7.12)	7.63 (1.65, 35.3)	9.46 (1.11, 80.8)
Displaying high FeNO vs low FeNO	1.23 (0.33, 4.63)	4.10 (1.10, 15.2)	14.0 (1.75, 112)
ACQ at initial visit (per ACQ unit)	3.27 (1.86, 5.76)	5.81 (3.17, 10.7)	1.32 (0.92, 1.88)
Height (per 10 cm)	1.06 (0.47, 2.40)	1.40 (0.65, 3.03)	1.28 (0.67, 2.42)
Age (per 10 years)	1.22 (0.84, 1.77)	1.07 (0.74, 1.55)	1.03 (0.77, 1.37)
FEV_1 (per 10% pred)	1.20 (0.84, 1.70)	1.20 (0.88, 1.65)	1.20 (0.94, 1.54)
Female gender	1.02 (0.23, 4.61)	1.41 (0.34, 5.84)	1.87 (0.59, 5.93)
Atopy	1.31 (0.23, 7.35)	0.34 (0.06, 1.97)	0.73 (0.22, 2.41)
Time to follow-up (per 10 days)	0.99 (0.98, 1.01)	0.99 (0.98, 1.01)	1.00 (0.98, 1.01)
Dose of ICS (per 100 microgram)	1.05 (0.85, 1.30)	0.91 (0.77, 1.08)	0.96 (0.85, 1.10)





Malinovschi A, et al. Nitric Oxide 2014;40:110-6

FENO to Guide Treatment of Asthma

- Seven RCTs (1,546 patients)

Comparison 1. Asthma treatment tailored on FeNO versus clinical symptoms

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants who had ≥ 1 exacerbations over study period	5	1005	Odds Ratio (Fixed, 95% CI)	0.60 [0.43, 0.84]
2 Number of exacerbations per 52 weeks (exacerbation rates)	5	842	Rate Ratio (Fixed, 95% CI)	0.59 [0.45, 0.77]
3 Severe exacerbations requiring oral corticosteroids	3	495	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.50, 1.48]
4 Severe exacerbations requiring hospitalisation	3	488	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.67]
5 FEV_1 % pred at final visit	4	802	Mean Difference (Fixed, 95% CI)	0.11 [-1.15, 1.37]
6 FeNO level at final visit	5	668	Std. Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.16, 0.15]
7 Symptom score as per Asthma Control Test	4	707	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.18, 0.01]
8 Symptom score as per AQLQ	2		Mean Difference (Fixed, 95% CI)	0.00 [-0.10, 0.10]
9 ICS dose at final visit (microgram per day)	4	582	Mean Difference (IV, Random, 95% CI)	-147.15 [-380.85, 86.56]
10 Subgroup (control guideline use): Number of participants who had ≥ 1 exacerbations over study period	5		Odds Ratio (Fixed, 95% CI)	0.60 [0.43, 0.84]
10.1 Guideline control	2		Odds Ratio (Fixed, 95% CI)	0.87 [0.47, 1.61]
10.2 Other control	3		Odds Ratio (Fixed, 95% CI)	0.51 [0.34, 0.76]

Petsky HL, et al. Cochrane Database Syst Rev 2016: CD011440

FENO Measurement

NIOX MINO
(Aerocrine, Sweden)

NIOX VERO
(Aerocrine, Sweden)

Nobreath
(Bedfont, UK)

Noninvasive, easy to perform, objective, and safe method

Limitation of FENO

- Children younger than 4 years
- Cut-off values
- Adding costs to the care of asthmatic patients
- FENO is elevated in non-asthma conditions (e.g. eosinophilic bronchitis, atopy, allergic rhinitis, eczema).

Increase	Decrease
Bronchodilator	Smoking
Airway infection	ICS therapy
Allergic rhinitis	Exercise
Nitrate-rich diet	Spirometric maneuvers
Height	Alcohol consumption
	Brochoconstriction
	Ciliary dyskinesia
	Pulmonary hypertension
	Cystic fibrosis

Mummadi SR, et al. Chest. 2016;149:1340-4

Serum Periostin

- Extracellular matrix protein produced by bronchial epithelial cells in response to stimulation with IL-4 and IL-13
- 67 patients with asthma

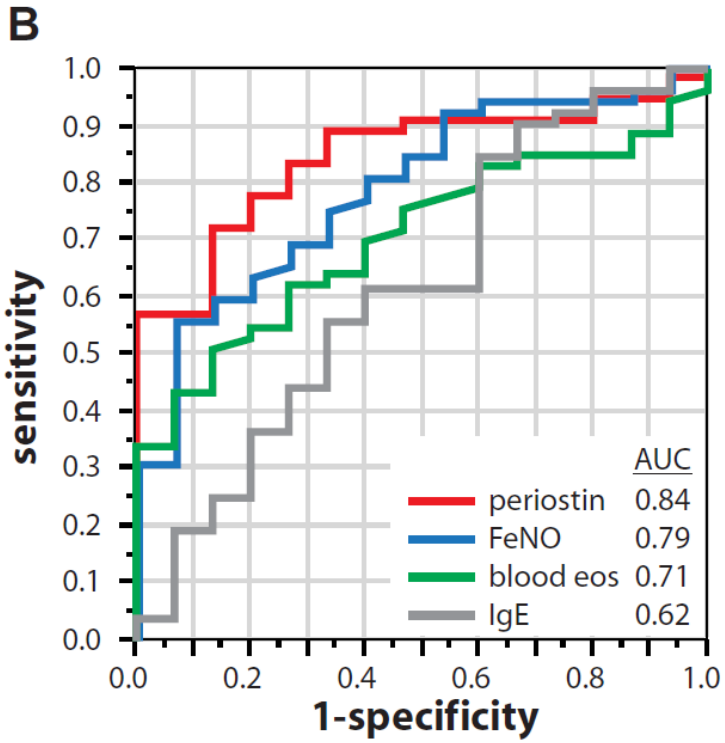


TABLE II. Logistic regression model of biomarkers versus eosinophil status in BOBCAT (n = 59)

	Estimate	SE	*z* Score	*P* value
Age	−0.0396	0.039	−1.015	.31
Sex (male)	−0.2031	0.889	−0.229	.82
Body mass index	−0.1004	0.066	−1.527	.13
Blood eosinophils	1.7482	3.621	0.483	.63
Serum IgE	−0.0002	0.001	−0.100	.92
FENO	0.0476	0.038	1.238	.22
Serum periostin	0.2491	0.092	2.719	.007

Jia G, et al. J Allergy Clin Immunol 2012;130:647-54

Limitation of Serum Periostin

- Not widely available
- Inconsistent results about the association of periostin serum concentrations and eosinophilic airway inflammation
- Lack of a universal cut-off value and standardization of measurement technique
- increased by conditions other than asthma, such as atopic dermatitis, allergic rhinitis, scleroderma, bone metastases, bone fractures, osteoporosis, renal insufficiency and cardiovascular disorders
- Inconsistent results regarding the use of periostin for predicting treatment response to IL-13 targeting therapeutic lebrikizumab

Periostin: Lebrikizumab Response

	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						
Biomarker high						
Placebo	256	0·94				
Lebrikizumab 37·5 mg	251	0·46	–0·48	51%	0·49 (0·34–0·69)	<0·0001
Lebrikizumab 125 mg	255	0·66	–0·28	30%	0·70 (0·51–0·95)	0·0232
Biomarker low						
Placebo	106	0·60				
Lebrikizumab 37·5 mg	109	0·33	–0·27	45%	0·55 (0·32–0·95)	0·0318
Lebrikizumab 125 mg	104	0·44	–0·17	28%	0·72 (0·44–1·19)	0·2013
LAVOLTA II						
Biomarker high						
Placebo	247	0·72				
Lebrikizumab 37·5 mg	257	0·54	–0·19	26%	0·74 (0·54–1·01)	0·0609
Lebrikizumab 125 mg	251	0·54	–0·19	26%	0·74 (0·54–1·02)	0·0626
Biomarker low						
Placebo	107	0·34				
Lebrikizumab 37·5 mg	99	0·50	0·16	–46%	1·46 (0·87–2·45)	0·1519
Lebrikizumab 125 mg	106	0·36	0·02	–6%	1·06 (0·61–1·83)	0·8346

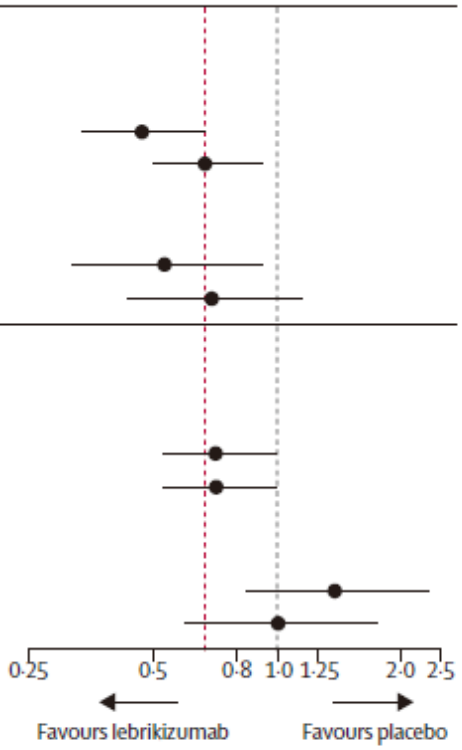


Figure 2: **Rate of asthma exacerbations over 52 weeks by biomarker group**

- The biomarker strategy, which focused on patients who were in the high groups for either eosinophils or periostin, did not consistently identify those who achieved benefit from lebrikizumab treatment.

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

Markers for Airway Eosinophilia in Asthma

- Diagnostic accuracy for detection of airway eosinophilia

: meta-analysis of 32 studies (24 in adults and 8 in children)

	Studies in adults*			
	Studies assessing marker (n)	AUCs included (n)	Patients (n)	AUC† (pooled 95% CI)
FeNO	17	19	3216	0·75 (0·72–0·78)
Blood eosinophils	14	14	2405	0·78 (0·74–0·82)
Serum IgE	7	7	942	0·65 (0·61–0·69)
Serum periostin	2	3	204	0·65 (0·49–0·81)
Serum ECP	2	2	174	0·72 (0·64–0·81)
EBC pH	2	2	96	0·76 (0·63–0·90)

Korevaar DA, et al. Lancet Respir Med 2015;3:290-300

Markers for Airway Eosinophilia in Asthma

	Sputum eosinophils ≥3%				Sputum eosinophils ≥2%			
	Studies (n)	Patients (n)	Sensitivity (95% CI)	Specificity (95% CI)	Studies (n)	Patients (n)	Sensitivity (95% CI)	Specificity (95% CI)
FeNO (ppb)	12	1720	0·66 (0·57–0·75)	0·76 (0·65–0·85)	9	1667	0·65 (0·55–0·74)	0·75 (0·62–0·84)
Blood eosinophils (per µL)	12	1967	0·71 (0·65–0·76)	0·77 (0·70–0·83)	6	1180	0·66 (0·56–0·75)	0·83 (0·62–0·94)
Blood eosinophils (%)	5	920	0·76 (0·52–0·90)	0·74 (0·67–0·80)	2	171	..	..
Serum IgE (IU/mL)	6	699	0·64 (0·42–0·81)	0·71 (0·42–0·89)	4	754	0·63 (0·36–0·84)	0·59 (0·37–0·79)

FeNO=fraction of exhaled nitric oxide. ppb=parts per billion.

Table 2: **Summary estimates of sensitivity and specificity for detecting sputum eosinophilia in adults**

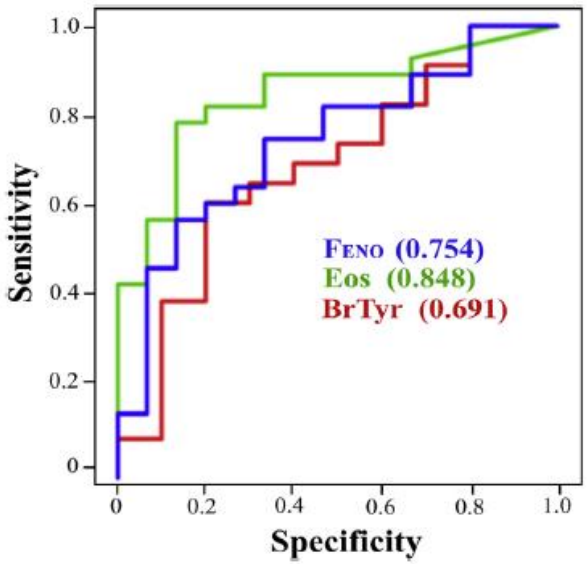
FENO, blood eosinophils, and IgE have moderate diagnostic accuracy for detection of airway eosinophilia in asthma.

Korevaar DA, et al. Lancet Respir Med 2015;3:290-300

Novel Potential Type2-High Biomarkers

- Dipeptidyl peptidase 4 (DPP-4)
  - better at predicting treatment response to tralokinumab (IL-13 targeting agent) than periostin
- Eosinophilic cationic protein (ECP)
  - Universal cut-off values and standardiszation of measurement technique are currently lacking
- Cysteinyl leukotrienes
  - Correlation between urinary LTE4 and sputum eosinophilia
  - Replication of the results and validation of measurement technique are essential before this marker can be utilized
  - Universal cut-off values and standardiszation of measurement technique are currently lacking

Novel Potential Type2-High Biomarkers



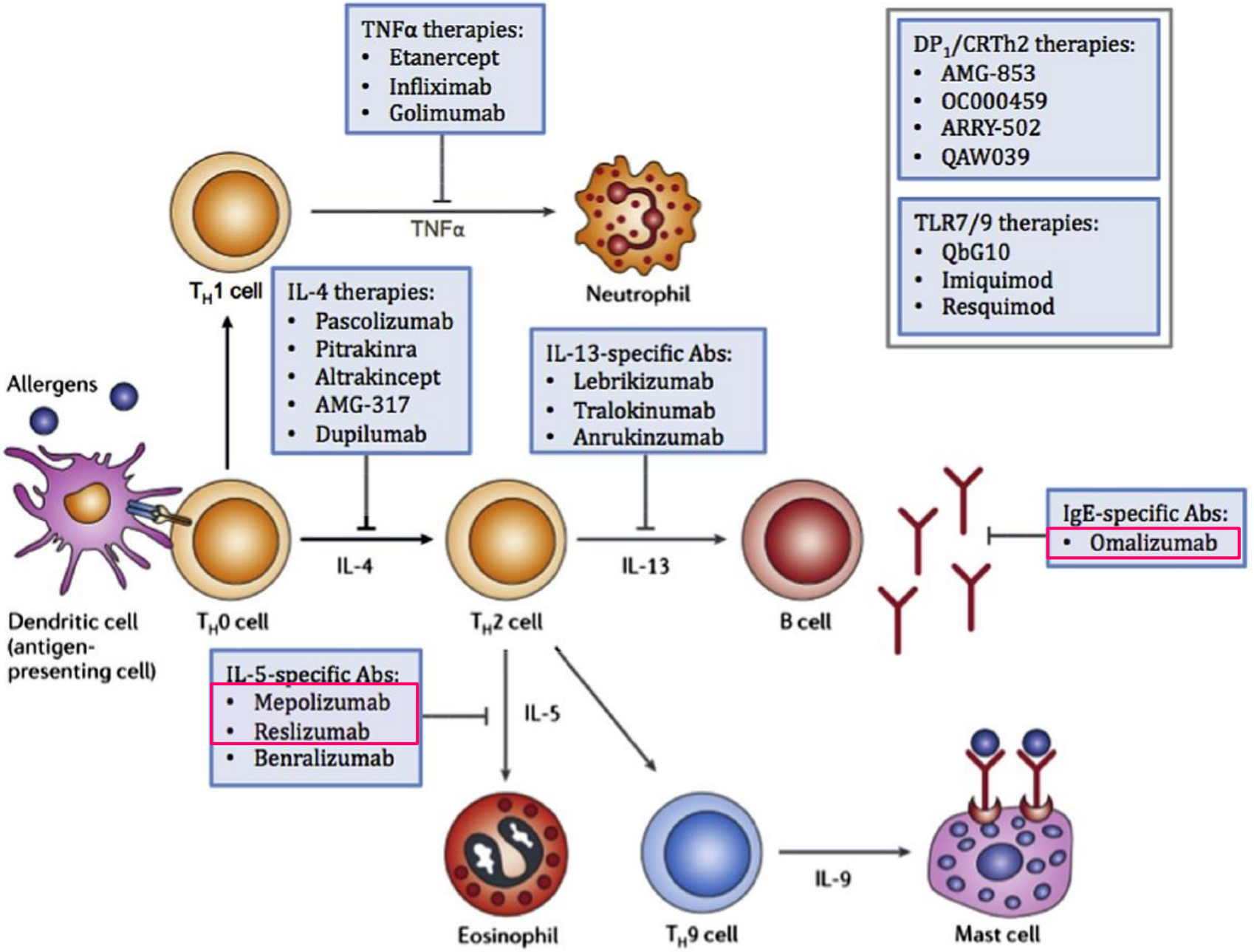
- Bromotyrosine
  - Urinary bromotyrosine are associated with asthma control and exacerbation risk
  - estimating corticosteroid reactivity
- Vascular endothelial growth factor (VEGF)
  - Sputum VEGF concentrations correlate with the extent of airway obstruction and disease severity
  - Serum VEGF concentrations correlate with asthma severity and can serve as a marker for exacerbation risk
- Galectin-3
  - Correlation between sputum galectin-3 and sputum eosinophilia
  - Reductions in expression of galectin-3 after 36 months of omalizumab appear indicative for improvements in airway remodelling in lung function

Cowan DC, et al. JACI 2015

1 Type2-High Asthma

2 Biomarkers for Type2-High Asthma

3 Treatment of Type2-High Asthma



Bice JB, et al. Ann Alelrgy Asthma Immunol 2014;112:108-15

Biologic Approaches for Type 2-High Asthma

Biologic	Type	Drug	Potential biomarkers
Omalizumab	Anti-IgE	Xolair; Genentech, Novartis	Blood Eos, FENO, Periostin
Mepolizumab	Anti-IL-5	Nucala; GSK	Eos ≥300 cells/µL (≥150 cells/µL-screen)
Reslizumab	Anti-IL-5	Cinqair; Teva	Eos ≥400 cells/µL
Benralizumab	Anti-IL-5Rα	Fasenra; AstraZeneca	Eos ≥300 cells/µL
Lebrikizumab	Anti-IL-13	Genentech	Periostin ≥50 ng/mL Eos ≥300 cells/µL
Tralokinumab	Anti-IL-13	AstraZeneca	Periostin, DPP-4 (median)
Dupilumab	Anti-IL-4Rα	Regeneron	Eos ≥300 cells/µL FENO

Robinson C, et al. Clin Exp Allergy 2017;47:16-75

Omalizumab (Anti-Ig E)

- Approval by the FDA in 2003
- A good treatment solution for severe asthma

- Multiple clinical studies have revealed that omalizumab significantly reduces the rate of asthma exacerbations, decreases ICS requirement, and improves lung function and QOL compared with placebo or best standard care.

Hanania NA, et al. Ann Intern Med 2011;154:573-82

Soler M, et al. Eur Respir J 2001;18:254-61

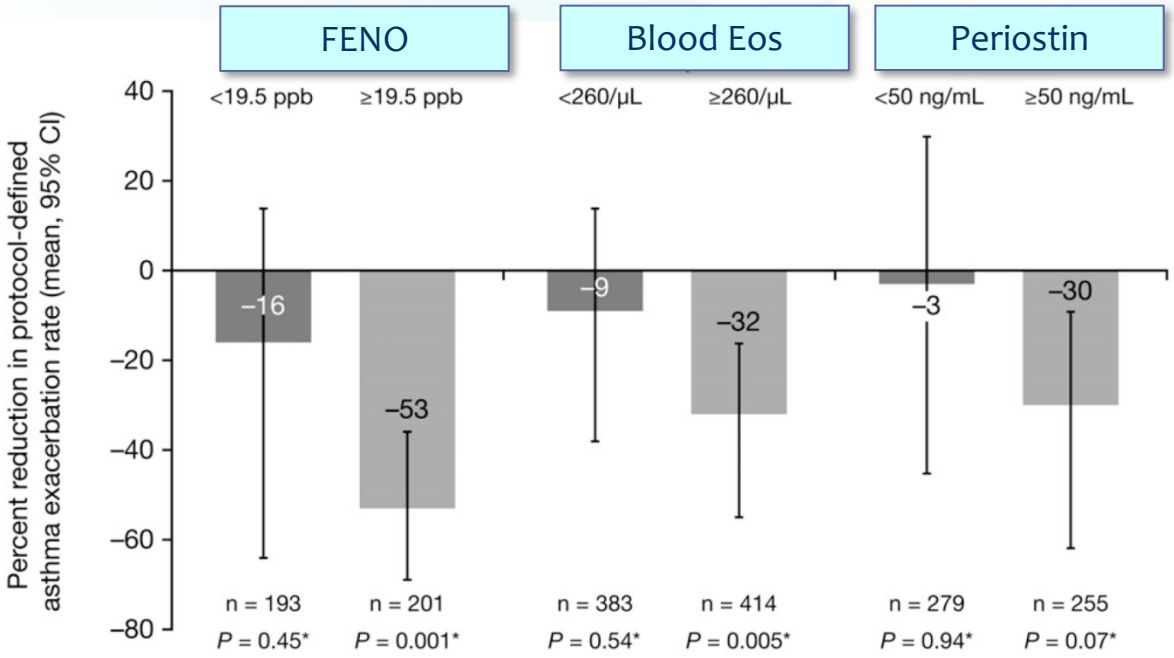
- Omalizumab has a good safety profile, with a comparable rate of adverse events compared with other treatments.
- Omalizumab has performed similarly well in observational real-world studies, reducing exacerbations and improving QOL.

Peters SP, et al. J Allergy Clin Immunol Pract 2017;5:S15-24

Predictor of Effects of Omalizumab

Exploring the Effects of Omalizumab in Allergic Asthma

- An Analysis of Biomarkers in the EXTRA Study



Exacerbation rates						
	Low FeNO at baseline	High FeNO at baseline	Low eosinophils at baseline	High eosinophils at baseline	Low periostin at baseline	High periostin at baseline
Omalizumab	0.60	0.50	0.65	0.70	0.73	0.66
Placebo	0.71	1.07	0.72	1.03	0.72	0.93

Hanania N, et al. Am J Respir Crit Care Med 2013;187:804-11

Mepolizumab (Anti-IL-5)

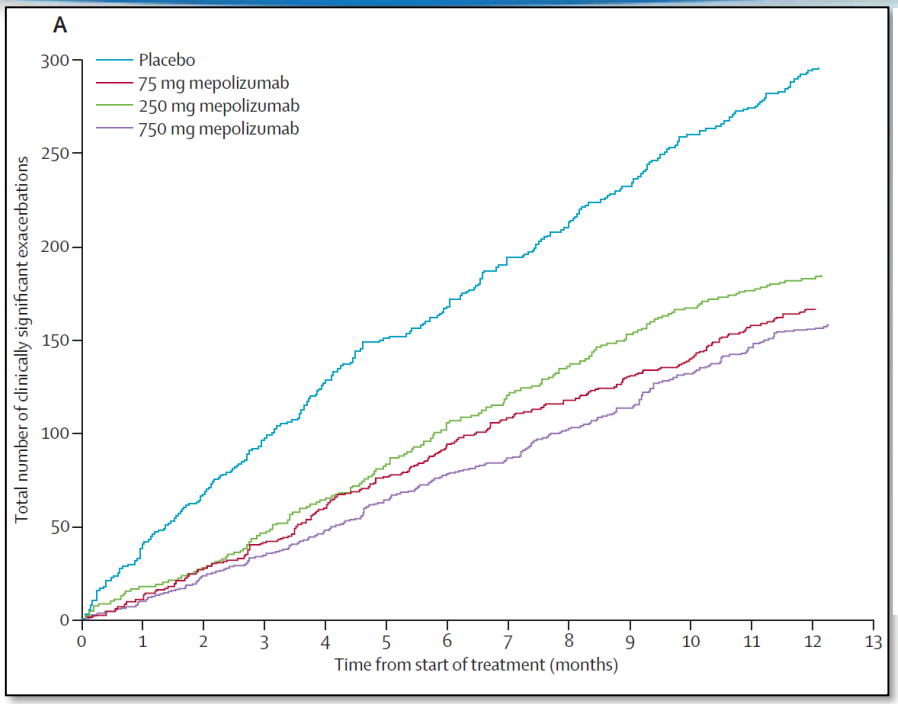
- Mepolizumab for severe eosinophilic asthma (DREAM)
  - A multicenter, double-blind, phase 3, placebo-controlled trial
  - 621 patients (81 centers in 13 countries)

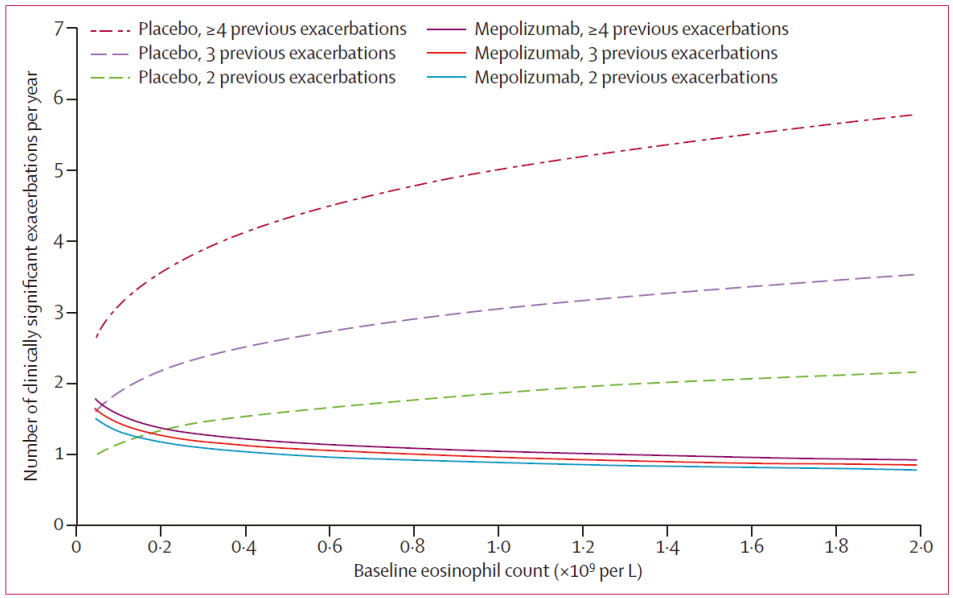
- a history of two or more exacerbations requiring systemic corticosteroid
- evidence of eosinophilic inflammation as shown by one or more criteria at study entry or in the previous year:
  a sputum eosinophil count of 3% or more,
  an FENO of 50 ppb or more,
  an peripheral blood eosinophil count ≥300 cells/μL

- Mepolizumab IV - 75 mg, 250 mg, 750 mg

Pavord ID, et al. Lancet 2012;380:651-9

Mepolizumab: Reduction of Exacerbation Risk





Exacerbation rate

	Placebo	75 mg Mepolizumab	250 mg Mepolizumab	750 mg Mepolizumab
Rate	2.40	1.24	1.46	1.15
Rate reduction (95% CI)		48% (0.31-0.61)	39% (0.19-0.54)	52% (0.36-0.64)

Pavord ID, et al. Lancet 2012;380:651-9

Mepolizumab (Anti-IL-5)

- MEpolizumab as Adjunctive Therapy IN Patients with Severe Asthma (MENSA)
  - A multicenter, randomized, double-blind, double-dummy, phase 3, placebo-controlled trial
  - 576 patients (119 centers in 16 countries)
  - Mepolizumab 75mg IV or 100 mg SC every 4 weeks for 32 weeks

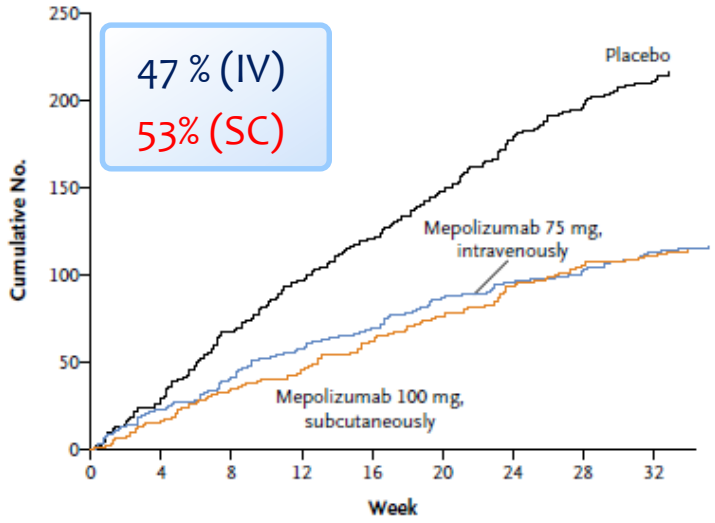
- at least two exacerbations in the previous year that were treated with systemic glucocorticoids (despite high doses of ICS)

- Blood eosinophil count of at least 150 cells/µL at screening or at least 300 cells/µL at some time during the previous year

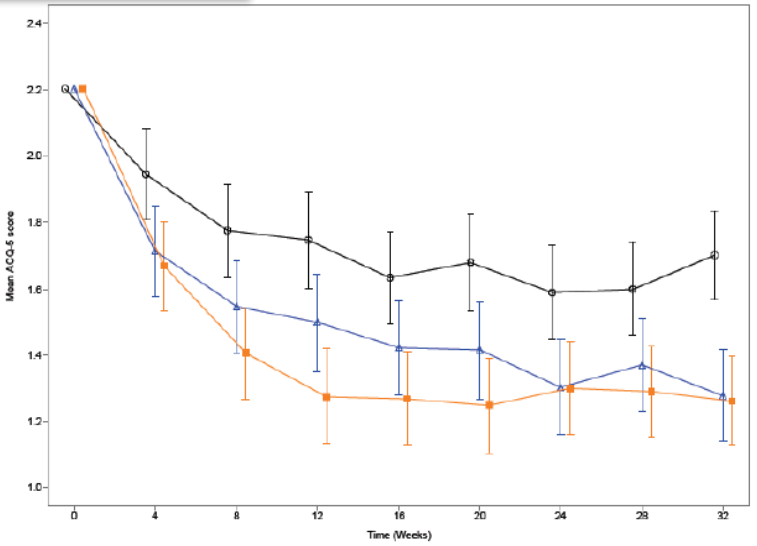
Ortega HG, et al. N Engl J med 2014;371:1198-207

Exacerbation

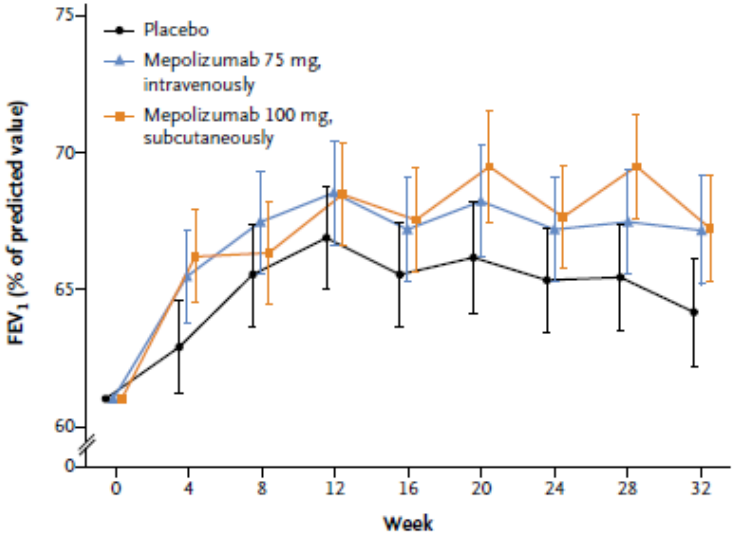
47 % (IV)
53% (SC)



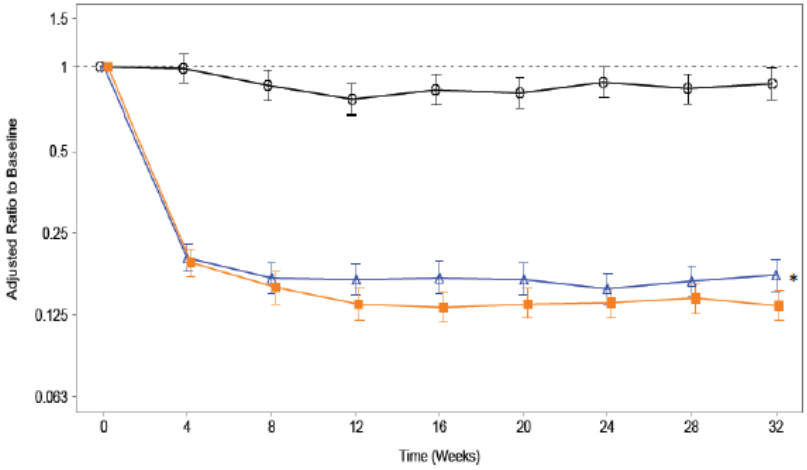
ACQ-5



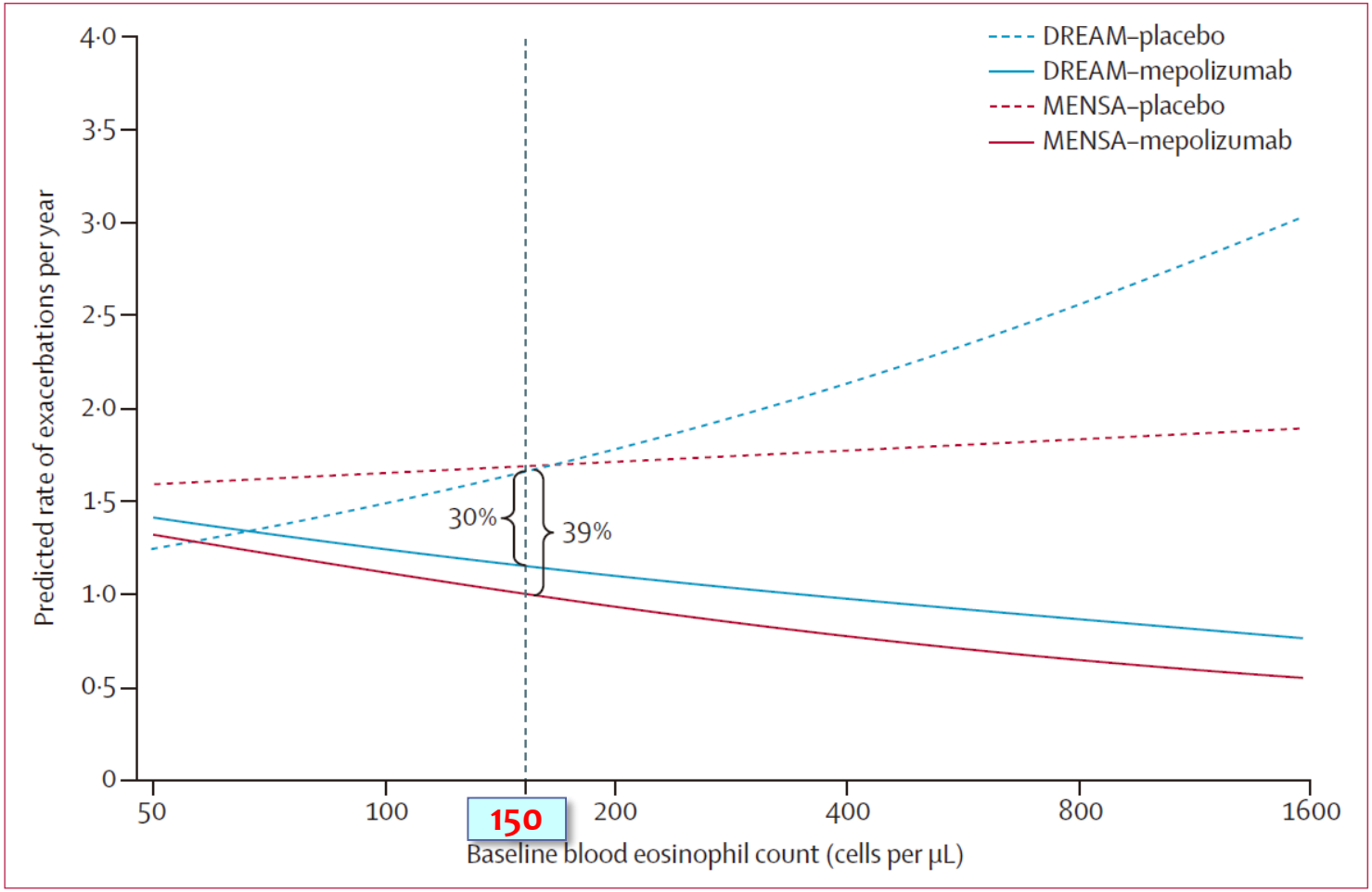
FEV_1



Blood Eosinophil



Blood Eosinophils in Mepolizumab Responsiveness



Overall exacerbation rate: 47% reduction

rbations per year against baseline blood eosinophil counts

n the DREAM and MENSA studies. Graph shows the

percentage differences in exacerbation ra

baseline blood eosinophil count of 150 ce

Ortega HG, et al. Lancet Respir Med 2016;4:549-56

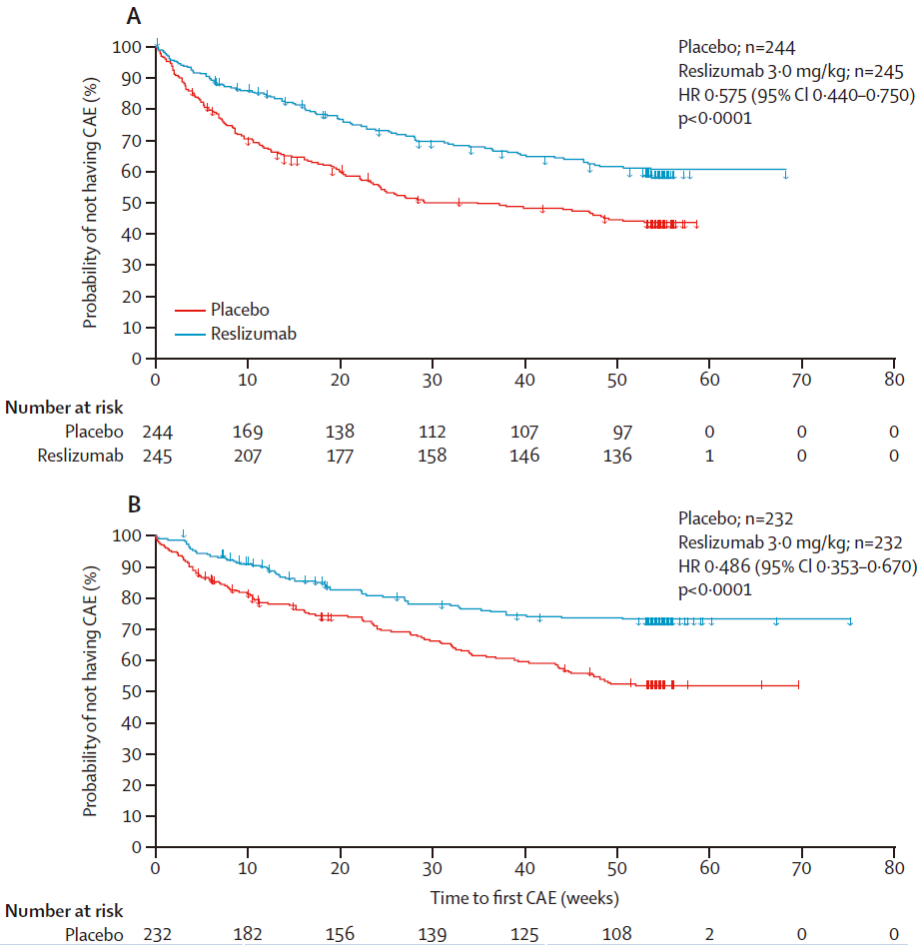
Reslizumab (Anti-IL-5)

- Two duplicate, multicenter, randomized, double-blind, double-dummy, phase 3, placebo-controlled trial
- 953 asthma patients (128 centers) that was inadequately controlled by medium-to-high doses of ICS based therapy and who had blood eosinophils of 400 cells/μL or higher and one or more exacerbations in the previous year

- randomly assigned (1:1) to receive either intravenous reslizumab (3.0 mg/kg) or placebo every 4 weeks for 1 year
- primary outcome : annual frequency of exacerbations

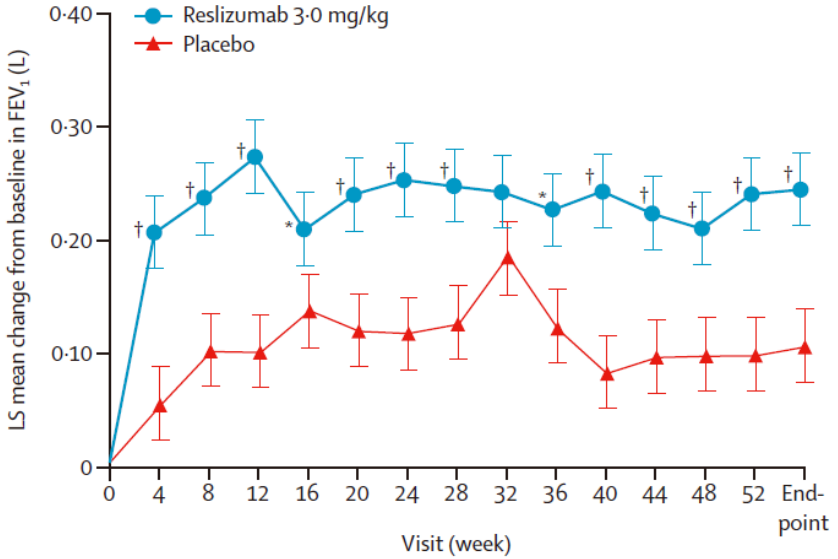
Castro M, et al. Lancet Respir Med 2015;3:355-66

Exacerbation

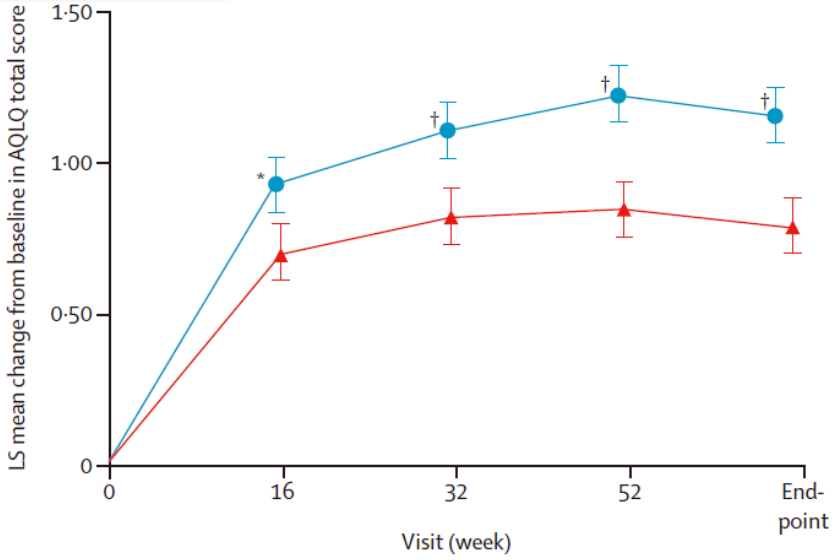


	Study1	Study2
Rate ratio (95% CI)	0.50 (0.37-0.57)	0.41 (0.28-0.59)

FEV_1

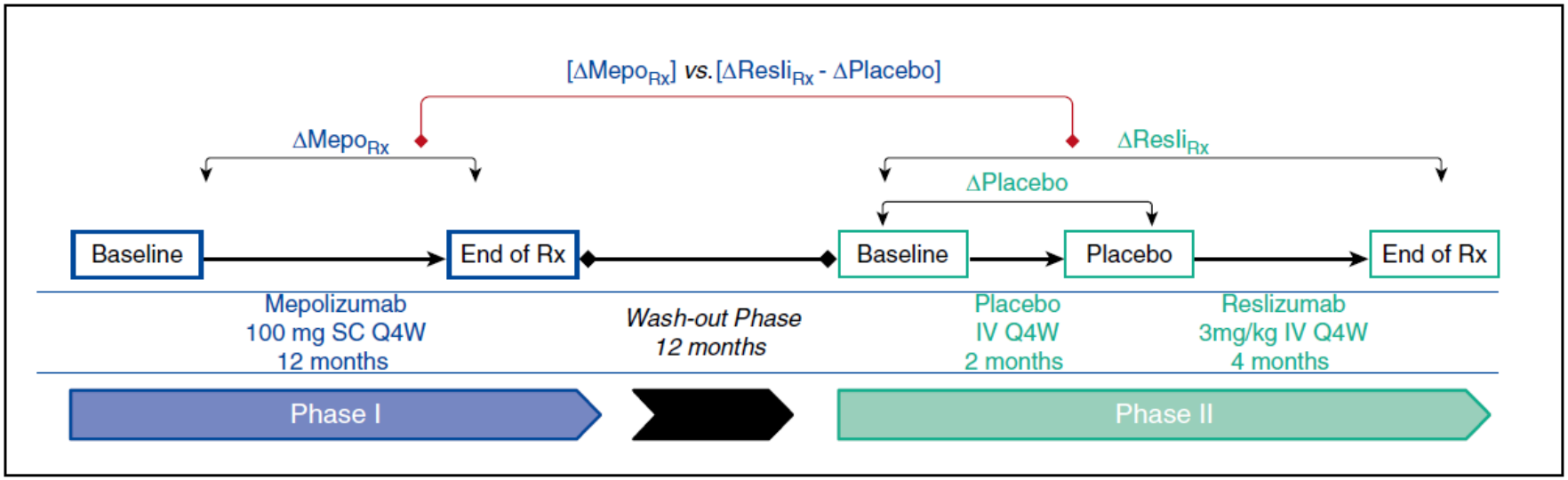


AQLQ



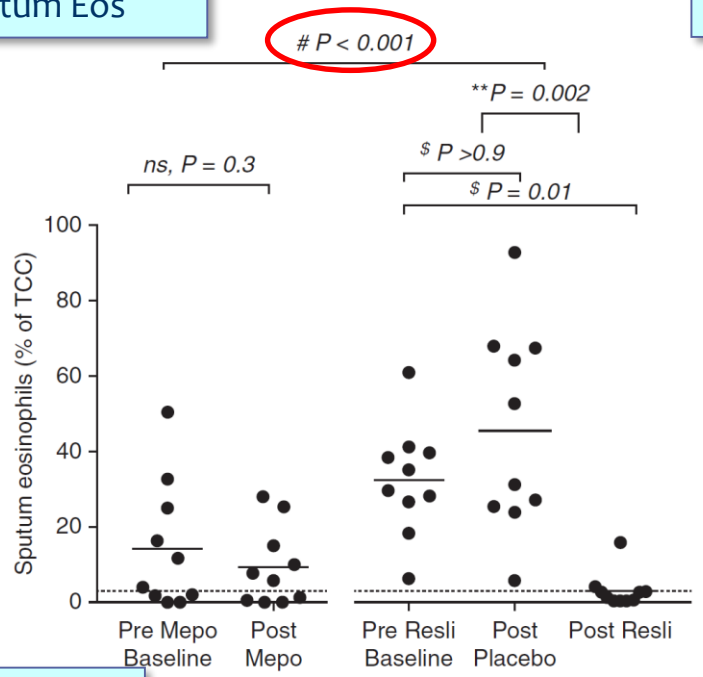
Reslizumab and Mepolizumab

- Two treatment phases separated by a wash-out period
- 10 prednisone-dependent asthma (sputum Eo>3% and blood Eo>300 cells/µL)

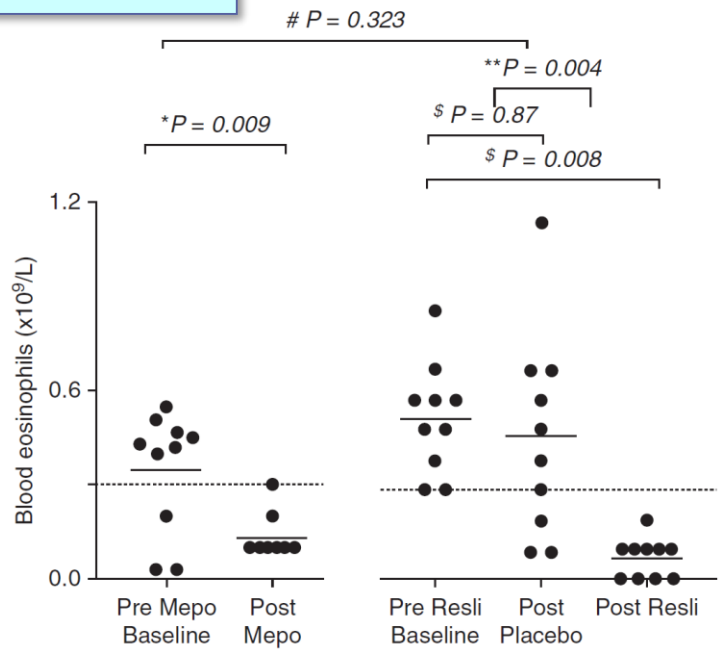


Mukherjee M, et al. Am J Respir Crit Care Med 2018;197:38-46

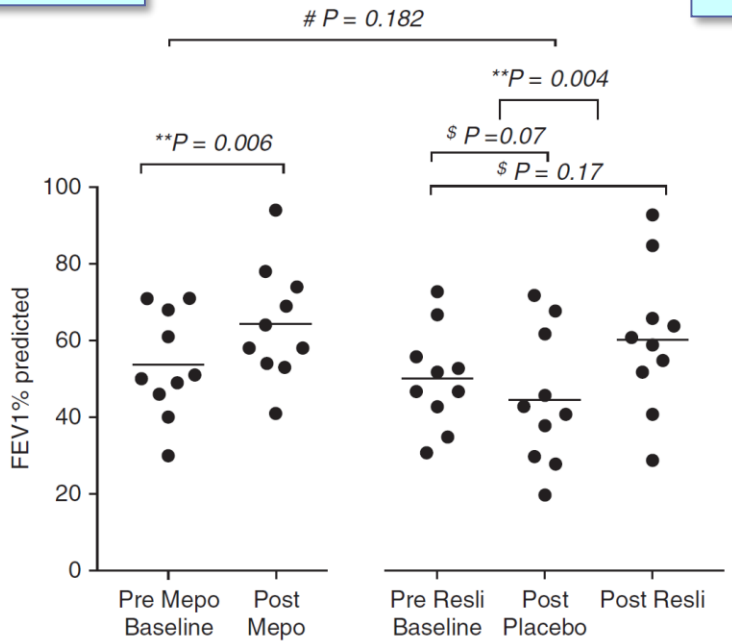
Sputum Eos



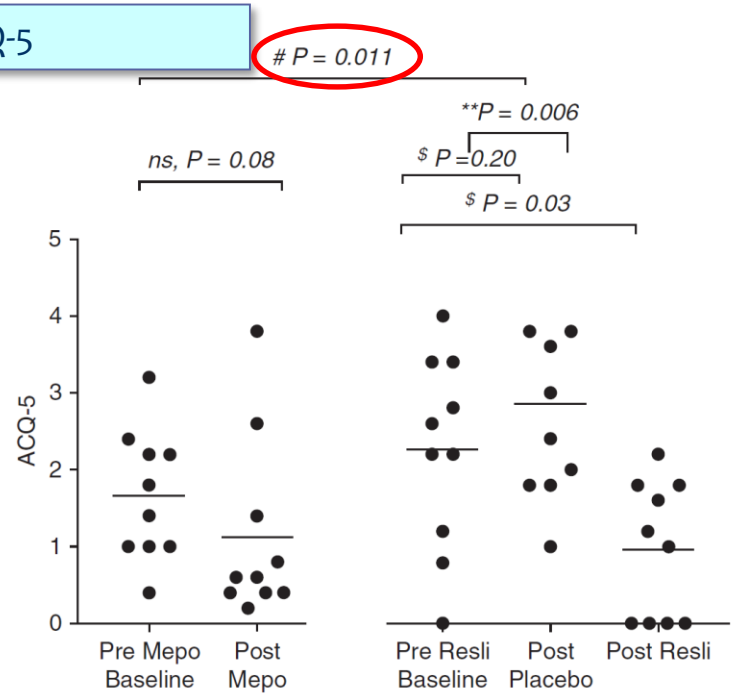
Blood Eos



FEV$_1$



ACQ-5



Benralizumab (Anti-IL-5Rα)

Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial

*Eugene R Bleecker, J Mark FitzGerald, Pascal Chanez, Alberto Papi, Steven F Weinstein, Peter Barker, Stephanie Sproule, Geoffrey Gilmartin, Magnus Aurivillius, Viktoria Werkström, Mitchell Goldman, on behalf of the SIROCCO study investigators**

Bleecker ER, et al. Lancet 2016;388:2115-27

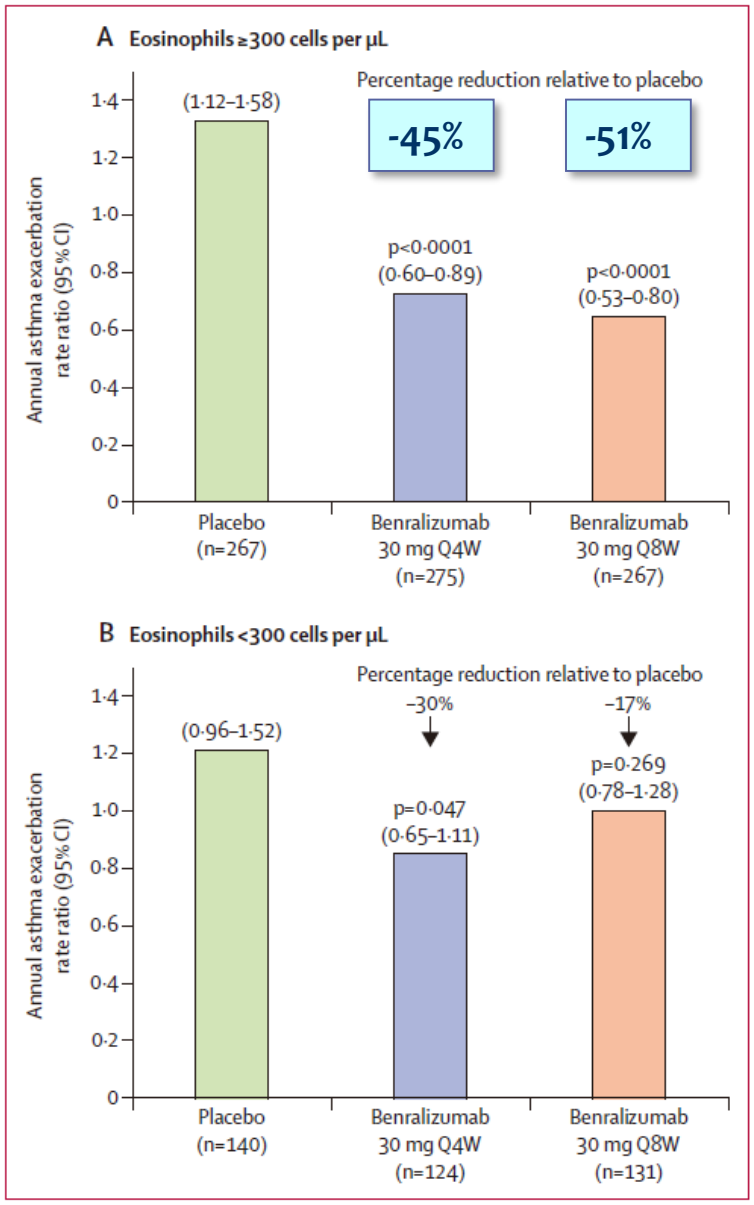
Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial

*J Mark FitzGerald, Eugene R Bleecker, Parameswaran Nair, Stephanie Korn, Ken Ohta, Marek Lommatzsch, Gary T Ferguson, William W Busse, Peter Barker, Stephanie Sproule, Geoffrey Gilmartin, Viktoria Werkström, Magnus Aurivillius, Mitchell Goldman, on behalf of the CALIMA study investigators**

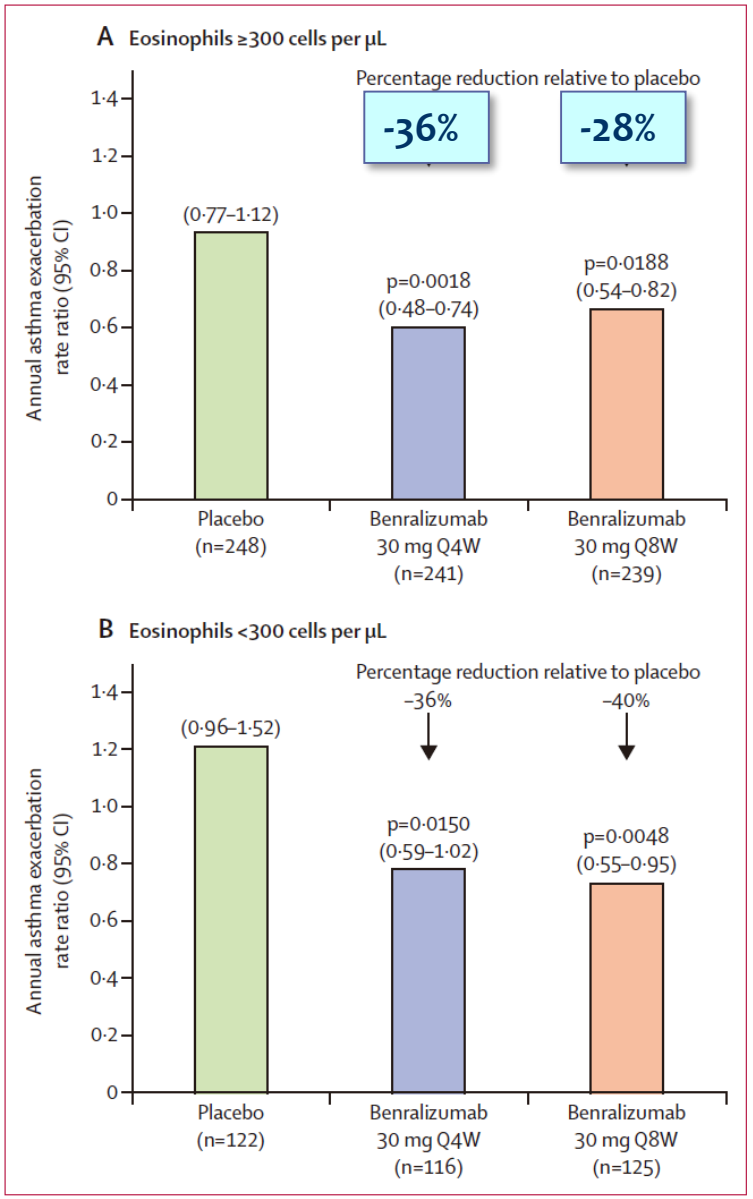
FitzGerald JM, et al. Lancet 2016;388:2128-41

Benralizumab 30 mg SC (4wk)/ 30 mg SC (8 wk)

SIROCCO (1,205)



CALIMA (1,306)



Predictors of Benralizumab Response

Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies

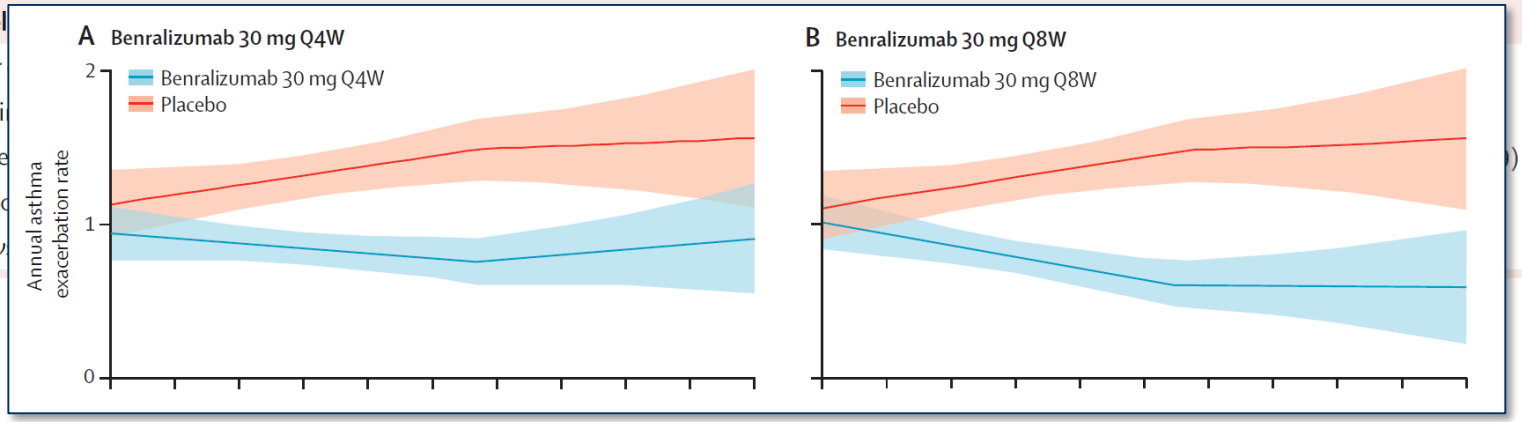
J Mark FitzGerald, Eugene R Bleecker, Andrew Menzies-Gow, James G Zangrilli, Ian Hirsch, Paul Metcalfe, Paul Newbold, Mitchell Goldman

- 2,295 patients with severe, uncontrolled asthma
- Primary endpoint: annual exacerbation rate

	Two exacerbations in previous year			Three or more exacerbations in previous year		
	Placebo	Benralizumab Q4W	Benralizumab Q8W	Placebo	Benralizumab Q4W	Benralizumab Q8W
Annual exacerbation rate						
Number of patients analysed	300	322	308	215	194	198
Rate estimate (95% CI)	0·80 (0·67 to 0·96)	0·52 (0·42 to 0·63)	0·58 (0·48 to 0·71)	1·79 (1·51 to 2·14)	0·98 (0·80 to 1·21)	0·82 (0·65 to 1·02)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·28 (−0·46 to −0·10)	−0·22 (−0·40 to −0·03)	..	−0·81 (−1·18 to −0·44)	−0·98 (−1·34 to −0·62)
Rate ratio *vs* placebo (95% CI)	..	0·65 (0·49 to 0·85)	0·73 (0·55 to 0·95)	..	0·55 (0·42 to 0·72)	0·45 (0·34 to 0·60)
p value *vs* placebo	..	0·0016	0·0194	..	<0·0001	<0·0001

FitzGerald JM, et al. Lancet Respir Med 2018;6:51-64

	Placebo (n=777)	Benralizumab Q4W (n=756)	Benralizumab Q8W (n=762)
≥0 cells per µL			
Number of patients analysed	770	748	751
Rate estimate (95% CI)	1·16 (1·05 to 1·28)	0·73 (0·65 to 0·82)	0·75 (0·66 to 0·84)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·43 (−0·57 to −0·28)	−0·41 (−0·56 to −0·27)
Rate ratio *vs* placebo (95% CI)	..	0·63 (0·54 to 0·74)	0·64 (0·55 to 0·75)
p value *vs* placebo	..	<0·0001	<0·0001
≥150 cells per µL			
Number of patients analysed	648	647	646
Rate estimate (95% CI)	1·14 (1·02 to 1·28)	0·69 (0·61 to 0·79)	0·72 (0·63 to 0·82)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·45 (−0·60 to −0·29)	−0·42 (−0·58 to −0·27)
Rate ratio *vs* placebo (95% CI)	..	0·61 (0·51 to 0·72)	0·63 (0·53 to 0·74)
p value *vs* placebo	..	<0·0001	<0·0001
≥300 cells per µL			
Number of patients analysed	511	511	499
Rate estimate (95% CI)	1·14 (1·00 to 1·29)	0·68 (0·59 to 0·78)	0·65 (0·56 to 0·75)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·46 (−0·64 to −0·29)	−0·49 (−0·67 to −0·32)
Rate ratio *vs* placebo (95% CI)	..	0·59 (0·49 to 0·72)	0·57 (0·47 to 0·69)
p value *vs* placebo	..	<0·0001	<0·0001
≥450 cel			
Number			
Rate esti			
Absolute			)
Rate ratio			
p value *v*			



Lebrikizumab (Anti-IL-13)

Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo-controlled trials

Nicola A Hanania, Phillip Korenblat, Kenneth R Chapman, Eric D Bateman, Petr Kopecky, Pierluigi Paggiaro, Akihito Yokoyama, Julie Olsson, Sarah Gray, Cecile T J Holweg, Mark Eisner, Charles Asare, Saloumeh K Fischer, Kun Peng, Wendy S Putnam, John G Matthews

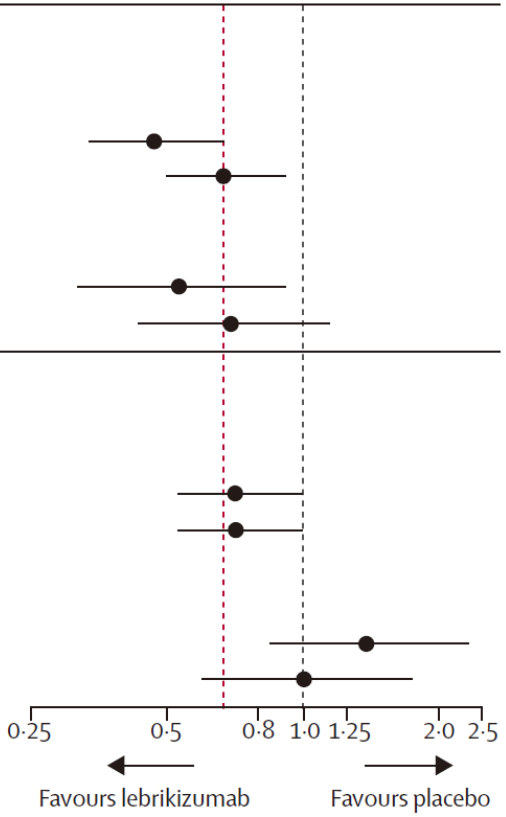
- Two duplicate, multicenter, randomized, double-blind, phase 3, placebo-controlled trial
- 1,081 (LAVOLTA I) + 1,067 (LAVOLTA II) patients with uncontrolled asthma
- Primary endpoint: exacerbation rate over 52 weeks in biomarker-high patients (Periostin ≥50 ng/mL or blood Eos ≥300 cells/μL)

Lebrikizumab 37.5 mg SC (4wk)
Lebrikizumab 125 mg SC (4wk)
Placebo

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

Lebrikizumab (Anti-IL-13)

	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						
Biomarker high						
Placebo	256	0·94				
Lebrikizumab 37·5 mg	251	0·46	−0·48	51%	0·49 (0·34–0·69)	<0·0001
Lebrikizumab 125 mg	255	0·66	−0·28	30%	0·70 (0·51–0·95)	0·0232
Biomarker low						
Placebo	106	0·60				
Lebrikizumab 37·5 mg	109	0·33	−0·27	45%	0·55 (0·32–0·95)	0·0318
Lebrikizumab 125 mg	104	0·44	−0·17	28%	0·72 (0·44–1·19)	0·2013
LAVOLTA II						
Biomarker high						
Placebo	247	0·72				
Lebrikizumab 37·5 mg	257	0·54	−0·19	26%	0·74 (0·54–1·01)	0·0609
Lebrikizumab 125 mg	251	0·54	−0·19	26%	0·74 (0·54–1·02)	0·0626
Biomarker low						
Placebo	107	0·34				
Lebrikizumab 37·5 mg	99	0·50	0·16	−46%	1·46 (0·87–2·45)	0·1519
Lebrikizumab 125 mg	106	0·36	0·02	−6%	1·06 (0·61–1·83)	0·8346



- No consistent significant reduction in biomarker-high patients

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

Tralokinumab (Anti-IL-13)

Efficacy and safety of tralokinumab in patients with severe uncontrolled asthma: a randomised, double-blind, placebo-controlled, phase 2b trial

Christopher E Brightling, Pascal Chanez, Richard Leigh, Paul M O'Byrne, Stephanie Korn, Dewei She, Richard D May, Katie Streicher, Koustubh Ranade, Edward Piper

- Multicenter, randomized, double-blind, phase 2b, placebo-controlled trial
- 452 patients with severe uncontrolled asthma
- Primary endpoint: annual exacerbation rate over 52 weeks

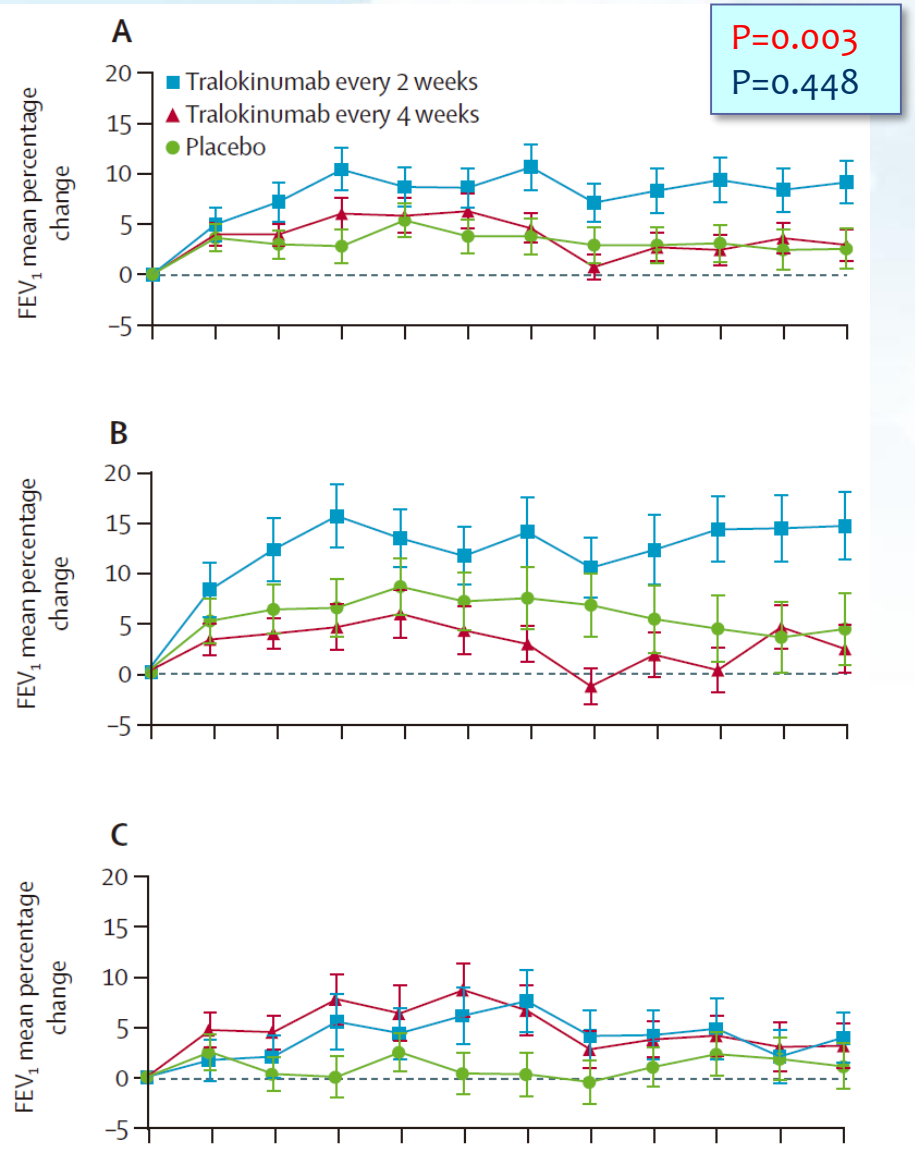
Tralokinumab 300 mg (2wk)
Tralokinumab 300 mg (4wk)
Placebo

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

Tralokinumab (Anti-IL-13)

Annual asthma exacerbation

	Placebo	Tralokinumab Q 2W	Tralokinumab Q 4W
Rate	0.90 (0.75-1.08)	0.91 (0.76-1.08)	0.97 (0.81-1.14)
Rate ratio		0.94 (P=0.709)	1.02 (P=0.904)



Dupilumab (Anti-IL-4Rα)

Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma

M. Castro, J. Corren, I.D. Pavord, J. Maspero, S. Wenzel, K.F. Rabe, W.W. Busse, L. Ford, L. Sher, J.M. FitzGerald, C. Katelaris, Y. Tohda, B. Zhang, H. Staudinger, G. Pirozzi, N. Amin, M. Ruddy, B. Akinlade, A. Khan, J. Chao, R. Martincova, N.M.H. Graham, J.D. Hamilton, B.N. Swanson, N. Stahl, G.D. Yancopoulos, and A. Teper

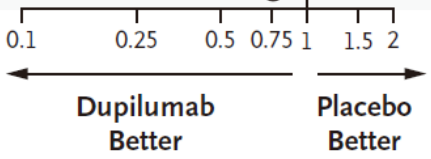
- Randomized, double-blind, phase 3, placebo-controlled, parallel-group trial
- 1,902 patients with uncontrolled asthma
- Primary endpoint: annual severe exacerbation rate for 52 weeks and FEV1 before bronchodilator at week 12

Dupilumab 200 mg SC (2wk)
Dupilumab 300 mg SC (2wk)
Placebo

Castro M, et al. N Engl J med 2018, in press

A Dupilumab, 200 mg Every 2 Wk, vs. Matched Placebo

Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	317	631	0.52 (0.41–0.66)
Eosinophil count			
≥300 cells/mm³	148	264	0.34 (0.24–0.48)
≥150 to <300 cells/mm³	84	173	0.64 (0.41–1.02)
<150 cells/mm³	85	193	0.93 (0.58–1.47)
FE_{NO}			
≥50 ppb	71	119	0.31 (0.18–0.52)
≥25 to <50 ppb	91	180	0.39 (0.24–0.62)
<25 ppb	149	325	0.75 (0.54–1.05)



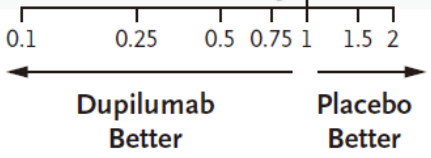
-48%

-66%

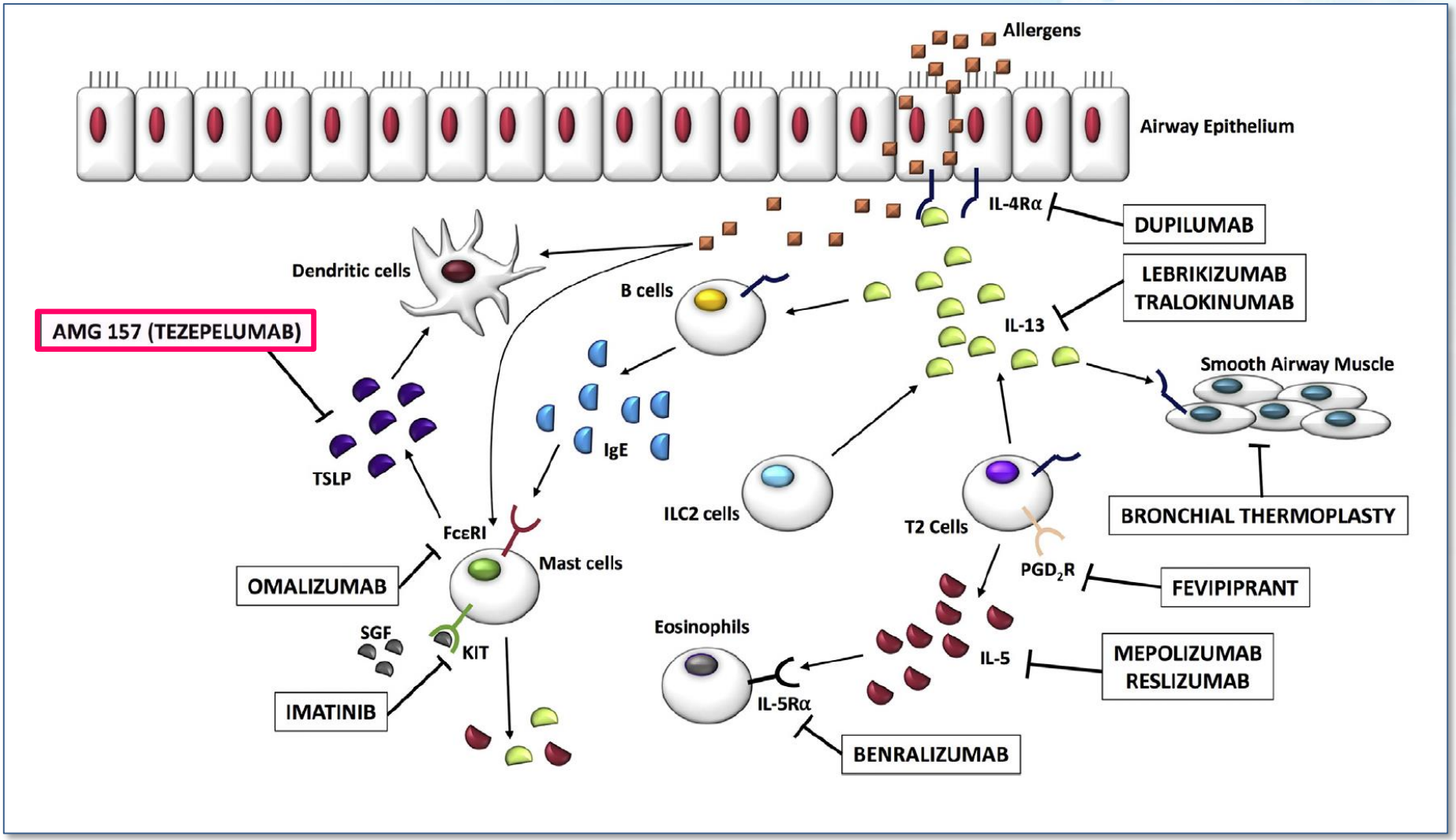
-69%

B Dupilumab, 300 mg Every 2 Wk, vs. Matched Placebo

Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	321	633	0.54 (0.43–0.68)
Eosinophil count			
≥300 cells/mm³	142	277	0.33 (0.23–0.45)
≥150 to <300 cells/mm³	95	175	0.56 (0.35–0.89)
<150 cells/mm³	83	181	1.15 (0.75–1.77)
FE_{NO}			
≥50 ppb	75	124	0.31 (0.19–0.49)
≥25 to <50 ppb	97	186	0.44 (0.28–0.69)
<25 ppb	144	317	0.79 (0.57–1.10)



Biologic Therapies for Asthma



Peters SP, et al. J Allergy Clin Immunol Pract 2017;5:S15-24

Tezepelumab (AMG 157): AB specific for TSLP

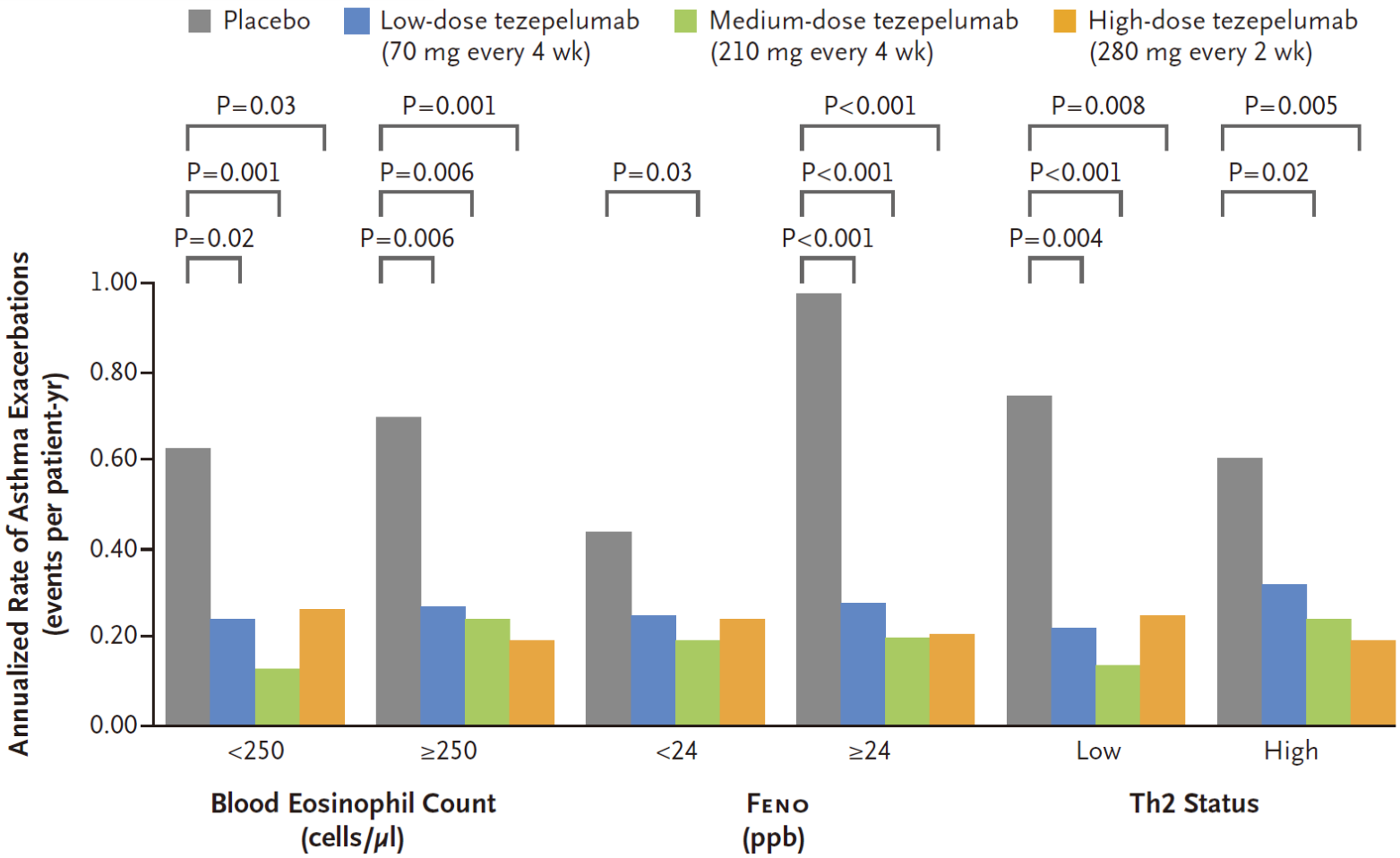
- Phase 2, randomized, double-blind, placebo-controlled trial
  - Tezepelumab SC over a 52-weeks treatment period

Variable	Placebo (N=148)	Low-Dose Tezepelumab (N=145)	Medium-Dose Tezepelumab (N=145)	High-Dose Tezepelumab (N=146)
Annualized rate of asthma exacerbations through wk 52 — events per patient-yr (90% CI)	0.67 (0.57 to 0.80)	0.26 (0.19 to 0.34)	0.19 (0.13 to 0.27)	0.22 (0.16 to 0.30)
Relative reduction vs. placebo — % (90% CI)	—	61 (39 to 75)	71 (53 to 82)	66 (47 to 79)
P value	—	<0.001	<0.001	<0.001
FEV_1 before bronchodilation				
No. of patients evaluated	141	137	128	125
Least-squares mean change from baseline at wk 52 — % of predicted value	−0.99	7.11	7.27	9.37
Difference vs. placebo (95% CI)	—	8.11 (2.39 to 13.82)	8.26 (2.50 to 14.03)	10.36 (4.60 to 16.13)
P value*	—	0.006	0.005	<0.001
Least-squares mean change from baseline at wk 52 — liters	−0.05	0.07	0.06	0.11
Difference vs. placebo (95% CI)	—	0.12 (0.02 to 0.21)	0.11 (0.02 to 0.20)	0.15 (0.06 to 0.25)
P value*	—	0.01	0.02	0.002

Corren J, et al. N Engl J Med 2017;377:936-46

Rate of Asthma Exacerbations

Subpopulation analysis



Biomarkers for Type 2-High Asthma

Biomarker	Strengths	Weakness
Sputum eosinophils	The most unambiguous method Correlation with disease severity, asthma control, and steroid responsiveness	Difficult to obtain Analysis is technically challenging
Blood eosinophils	Easy to measure, inexpensive, Correlation with disease severity and steroid responsiveness	Not specific for asthma or atopy
IgE	Easy to measure, inexpensive Determination of atopy status	Low specificity for sputum eosinophilia
FENO	Simple and non-invasive method Predictor of steroid responsiveness and therapy compliance	Expensive Multiple confounders
Serum periostin	Sensitive indicator of Th2 airway inflammation	Expensive, Not widely available, Inconsistent results in therapeutic response

Biologic Approaches for Type 2-High Asthma

Biologic	Target	Potential biomarkers	Main effects	Other
Omalizumab	IgE	Bood Eos, FENO, Periostin	↓ exacerbation and OCS ↑ PFT, QOL	
Mepolizumab	IL-5	Eos ≥300 cells/μL (≥150 cells/μL-screen)	↓ exacerbation and OCS ↑ PFT, QOL	
Reslizumab	IL-5	Eos ≥400 cells/μL	↓ exacerbation ↑ PFT, QOL	IV
Benralizumab	IL-5Rα	Eos ≥300 cells/μL	↓ exacerbation and OCS ↑ PFT, QOL (Q8W)	Q8W All
Lebrikizumab	IL-13	Periostin ≥50 ng/mL Eos ≥300 cells/μL	↓ exacerbation (trend) ↑ PFT	
Tralokinumab	IL-13	Periostin, DPP-4 (median)	↑ PFT (Q2W)	2b
Dupilumab	IL-4Rα	Eos ≥300 cells/μL FENO	↓ exacerbation ↑ PFT	Q2W All
Tezepelumab	TSLP		↓ exacerbation ↑ PFT	2

Thank You for Your Attention