PNEUMOLOGIA 2018 - Come sta cambiando la terapia del paziente con asma bronchiale

Con il Patrocinio di:

OMCeO Milano

AIPO

Dr. Claudio Micheletto

Dipartimento Medicina Interna

UOC di Pneumologia

Ospedale Mater Salutis

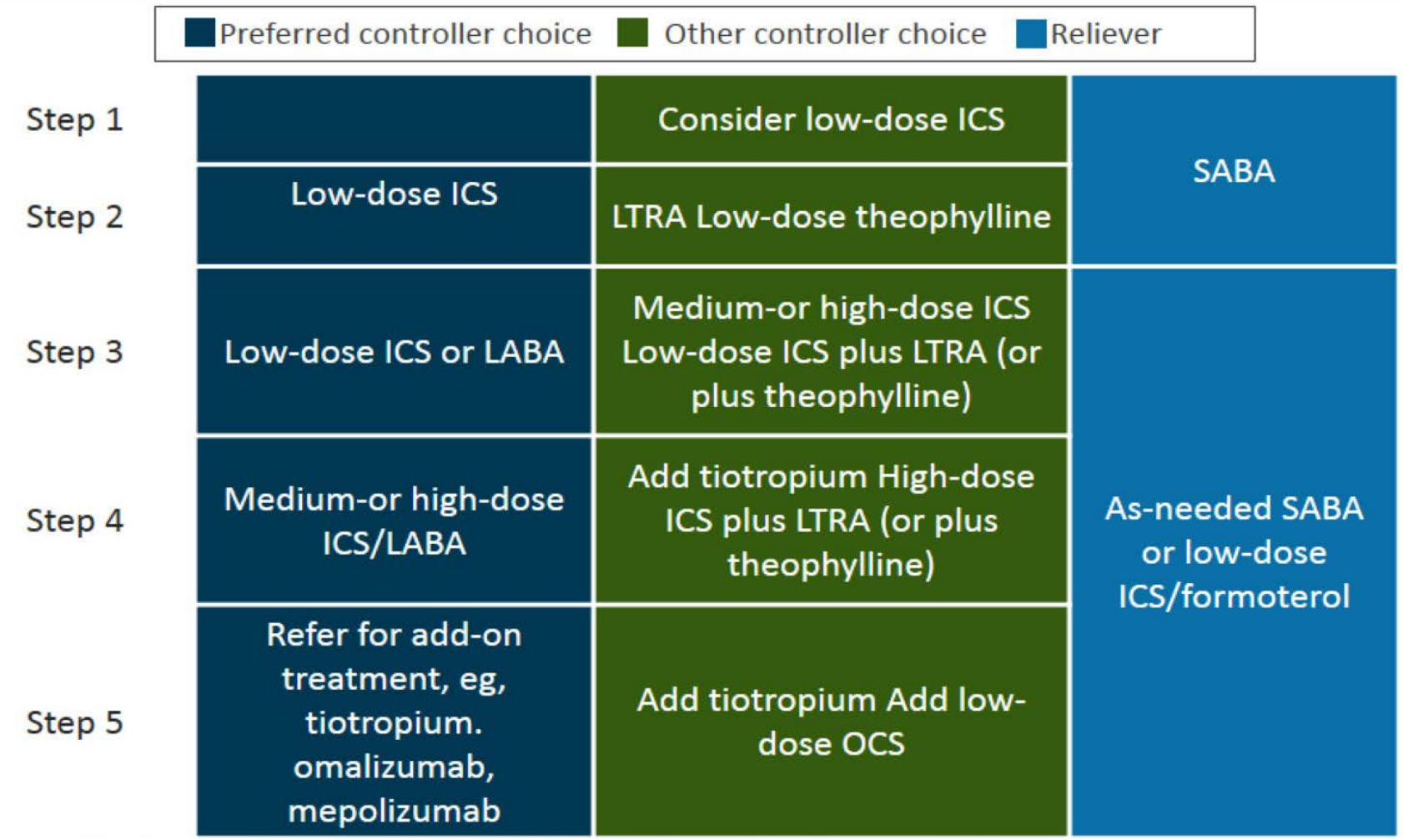
Legnago (VR)

claudio.micheletto@aulss9.veneto.it

REGIONE DEL VENETO

ULSS9 SCALIGERA

GINA-Based treatment Steps



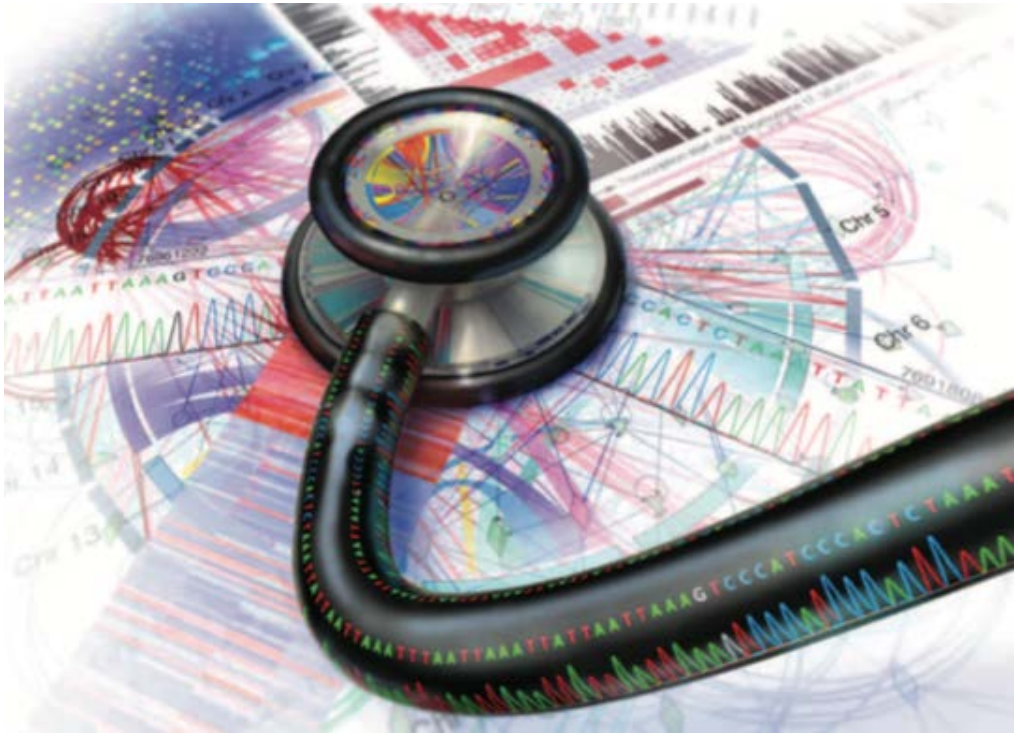
Holgate ST, et al. Nat Rev Dis Prim 2015

A Precision Medicine Approach to Clinical Trials

Rita Rubin, MA

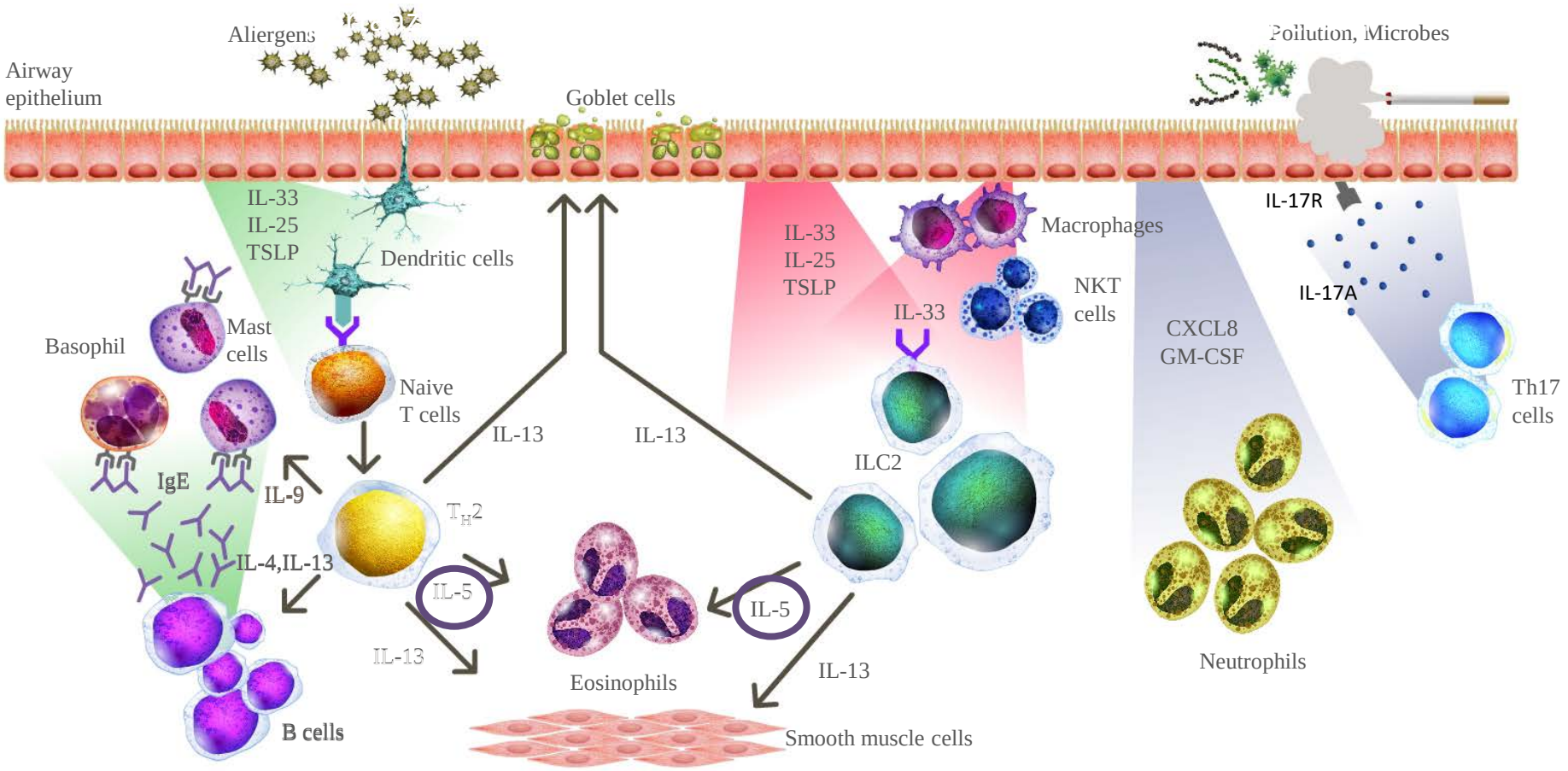
Evolutionary, Not Revolutionary

While President Obama launched the Precision Medicine Initiative only a year-and-a-half ago, the concept—"delivering the right treatment at the right time, every time, to the right person," as Obama described it—is as old as medicine itself, noted US Food and Drug Administration (FDA) Commissioner Robert Califf, MD, a cardiologist and clinical trials expert.



JAMA Published online October 19, 2016

Indentificazione di un TARGET molecolare

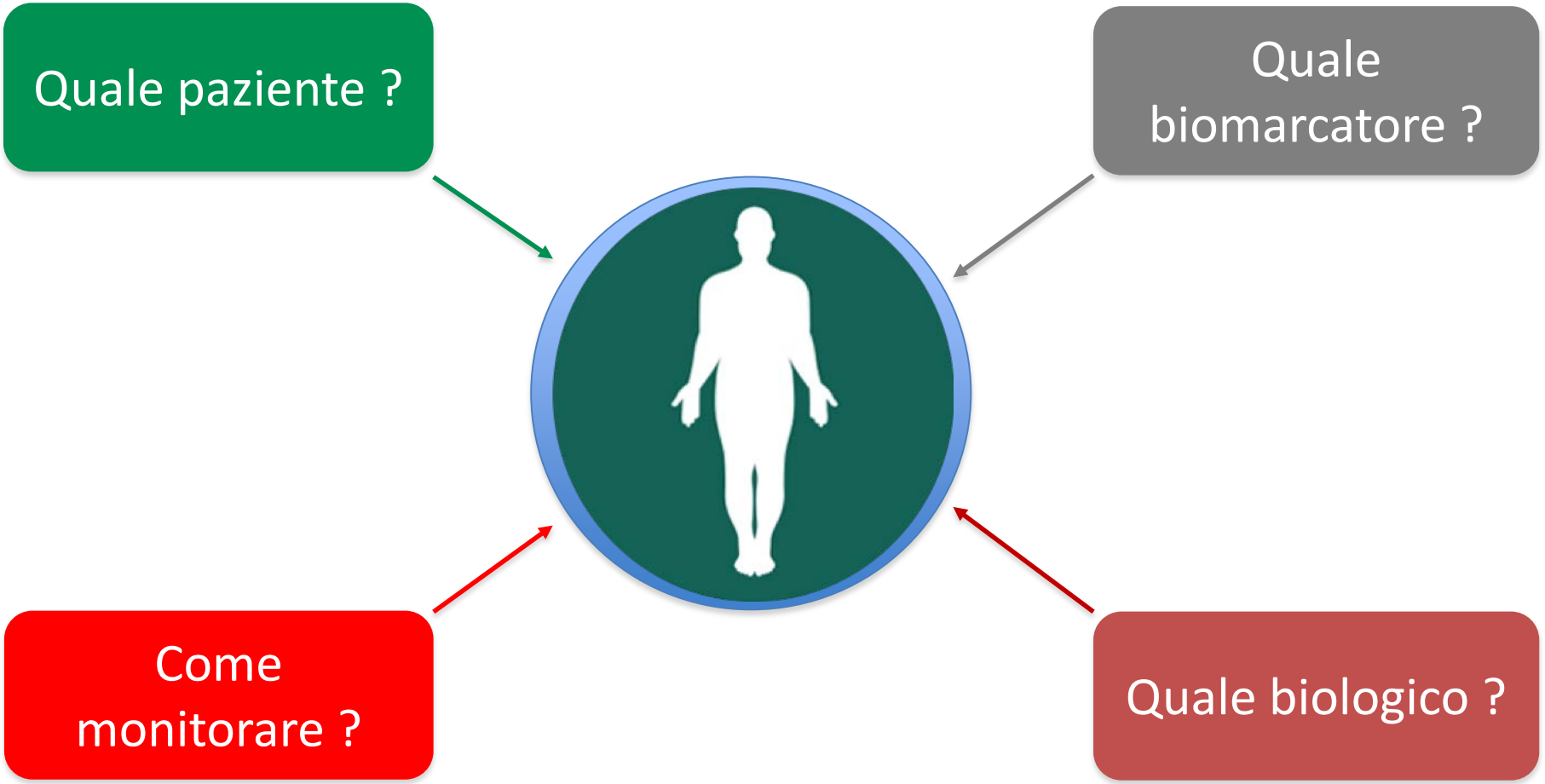


Asma Atopico | **Asma eosinofilo non-atopico** | **Asma neutrofilico**

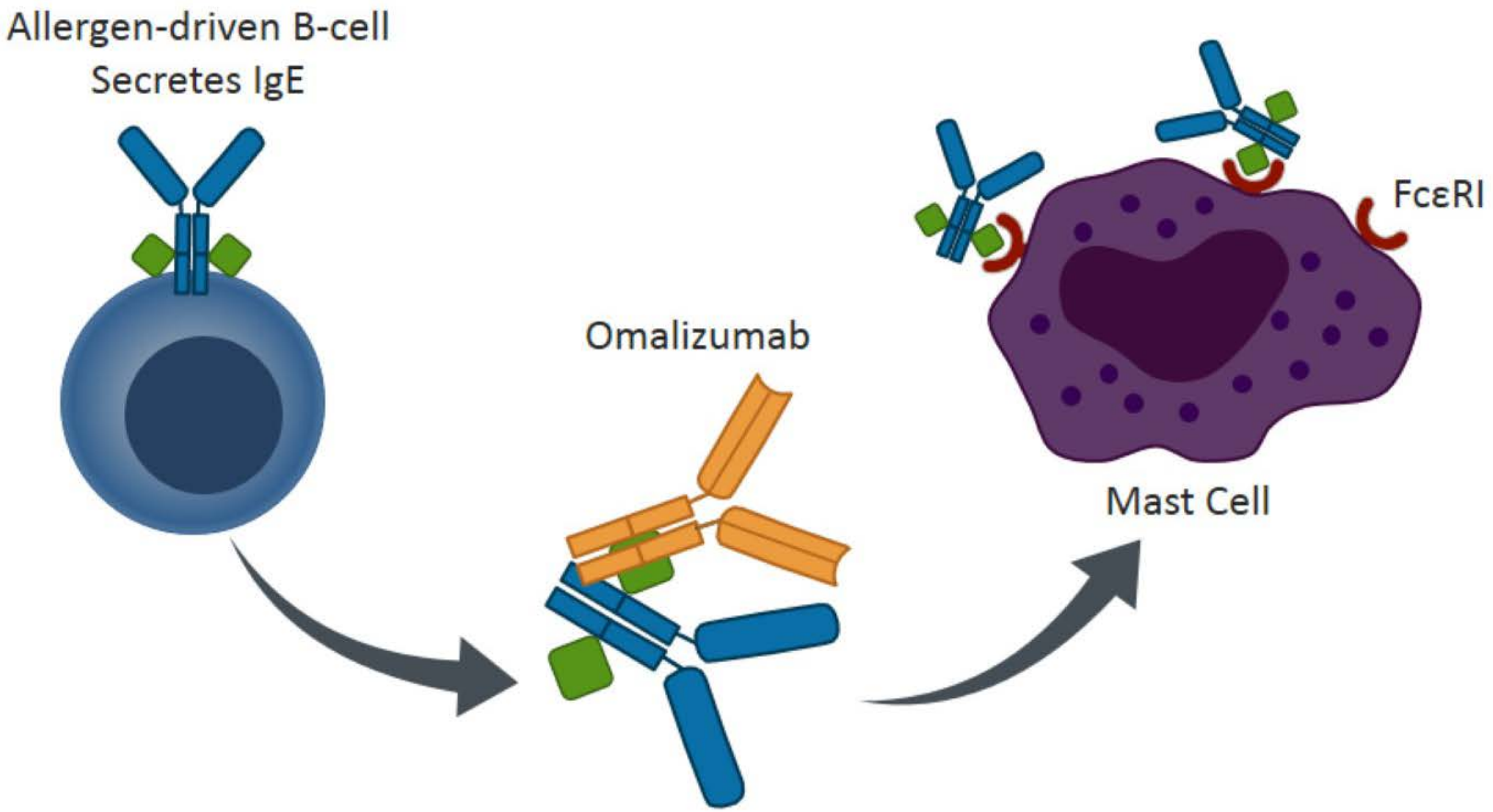
Ig = immunoglobulin; IL = interleukin; NKT cells = natural killer T cells;
TSLP = thymic stromal lymphopoietin; TSLPR = thymic stromal lymphopoietin receptor

Brusselle G, et al. Ann Am Thorac Soc. 2014; 11: S322-S328.

Considerazioni cliniche per la terapia biologica nell'asma severa

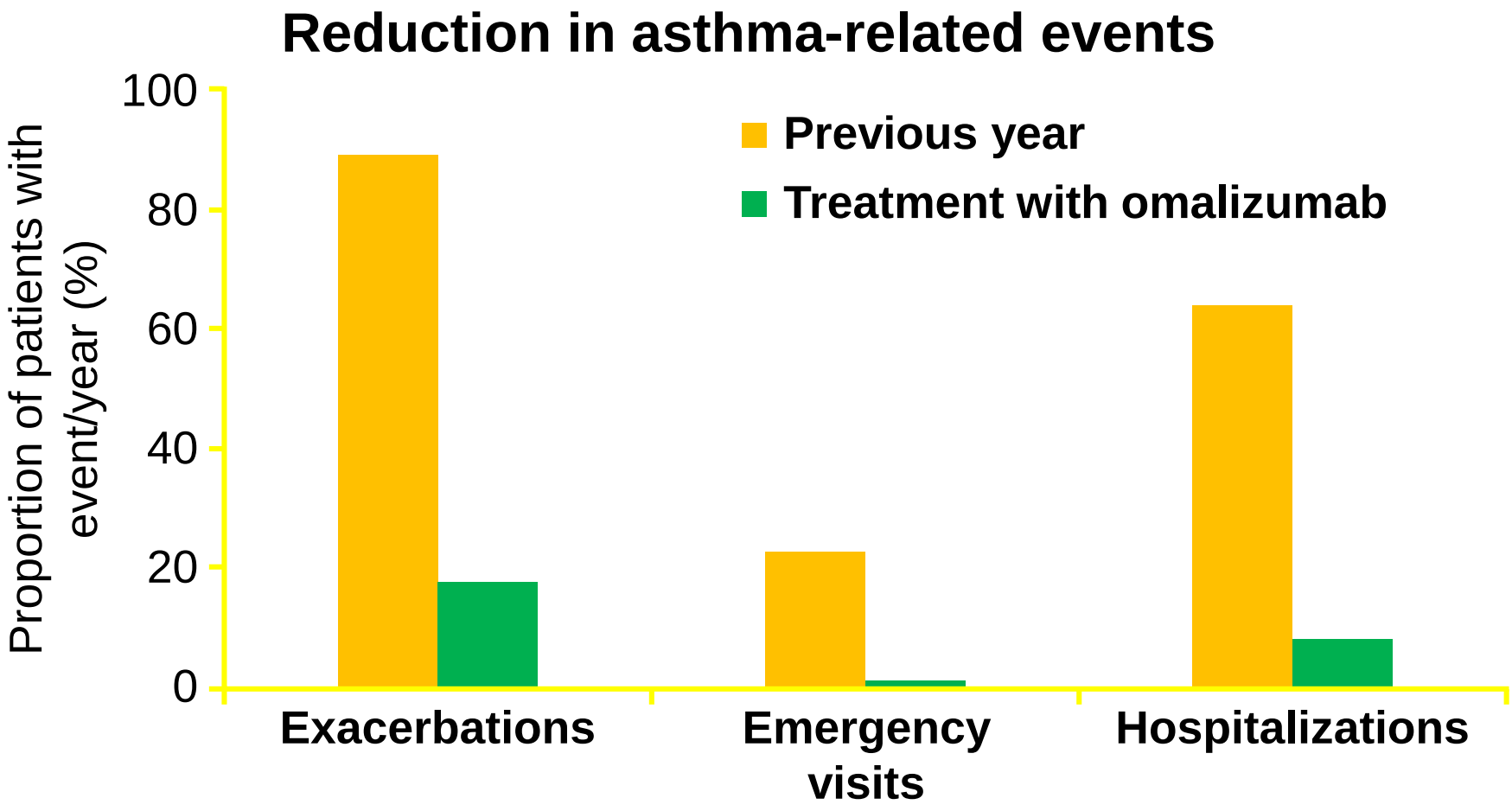


Blocking the allergic cascade by omalizumab



Busse W, et al. *J Allergy Clin Immunol.* 2001;108:184-190.
Presta LG, et al. *J Immunol.* 1993;151:2623-2632.

Italian real – life experience of Omalizumab

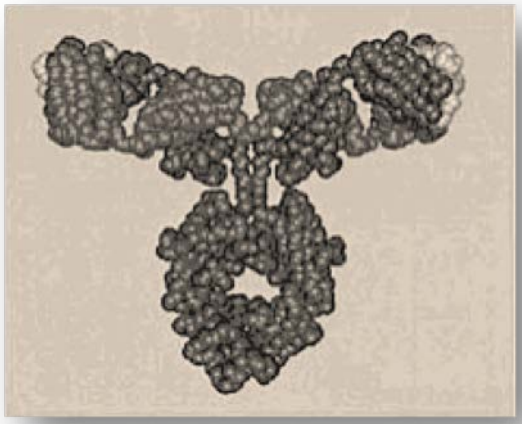


Cazzola M, et al. Respir Med 104:1410-1416, 2010

Omalizumab modulates bronchial reticular basement membrane thickness and eosinophil infiltration in severe persistent allergic asthma patients.

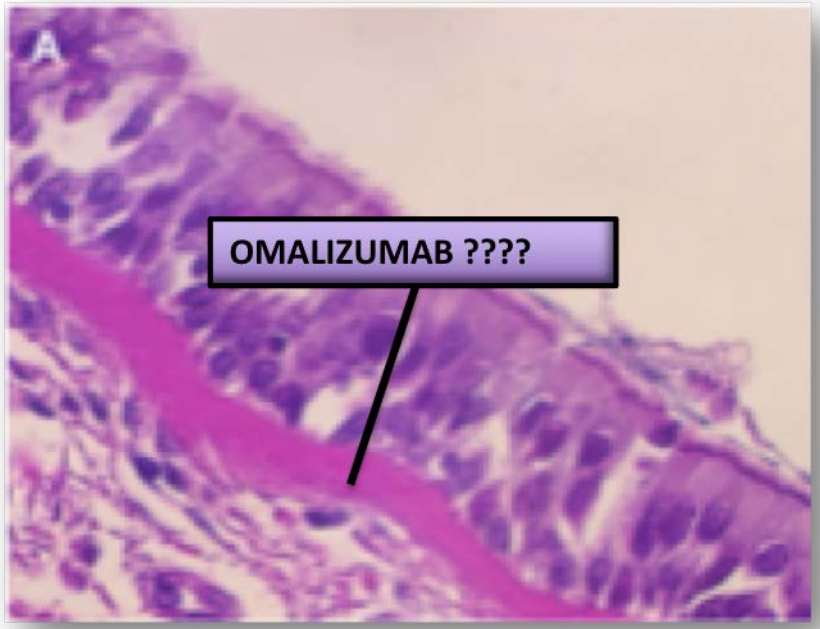
Riccio AM, Dal Negro RW, Micheletto C, De Ferrari L, Folli C, Chiappori A, Canonica GW.
Int J Immunopathol Pharmacol 2012; 25(2):475-84

Applying stereology to measure thickness of the basement membrane zone in bronchial biopsy



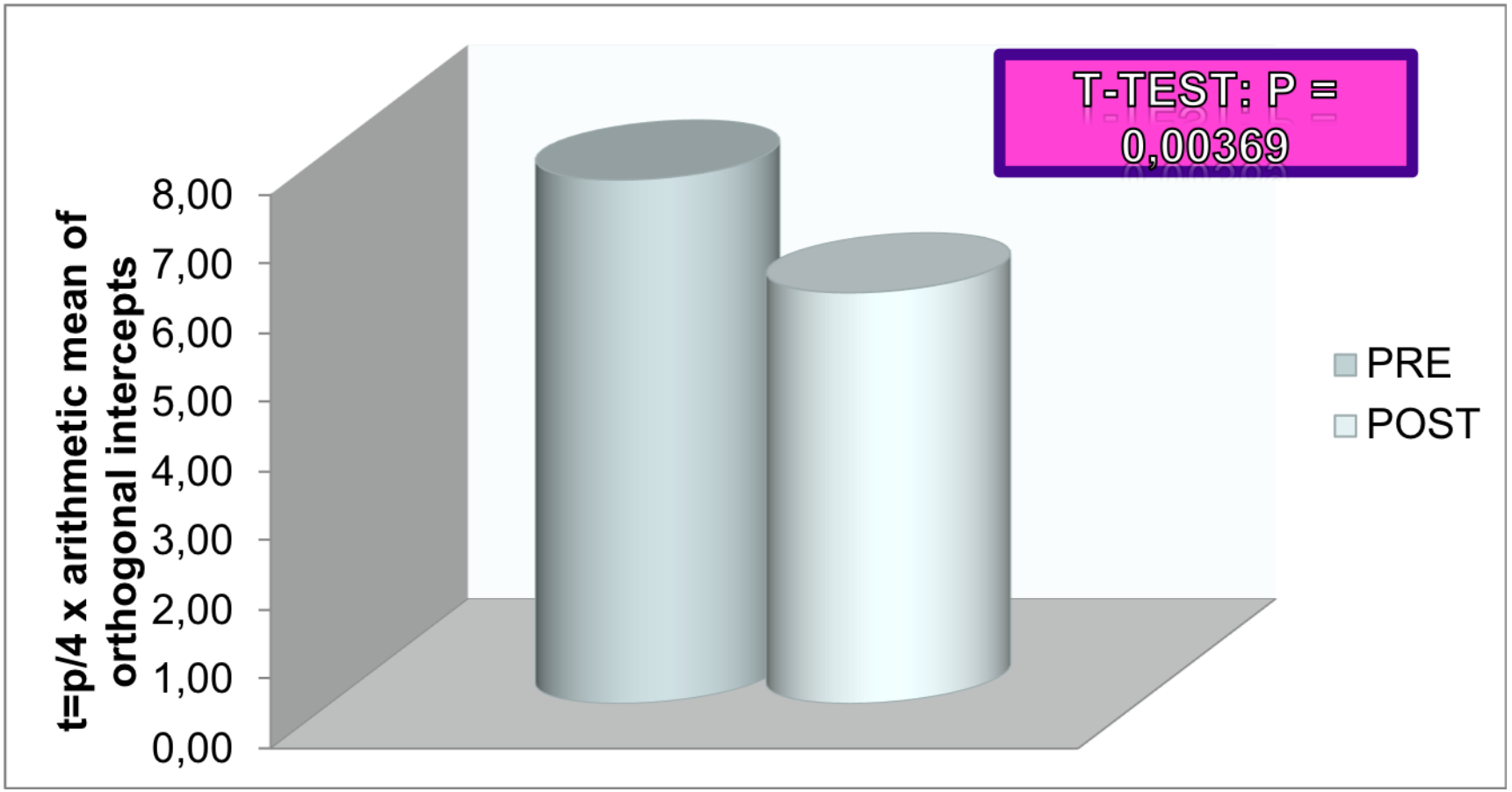
Objective

We examined the effect of anti-IgE on the basement membrane thickness in bronchial biopsies taken in patients with severe asthma



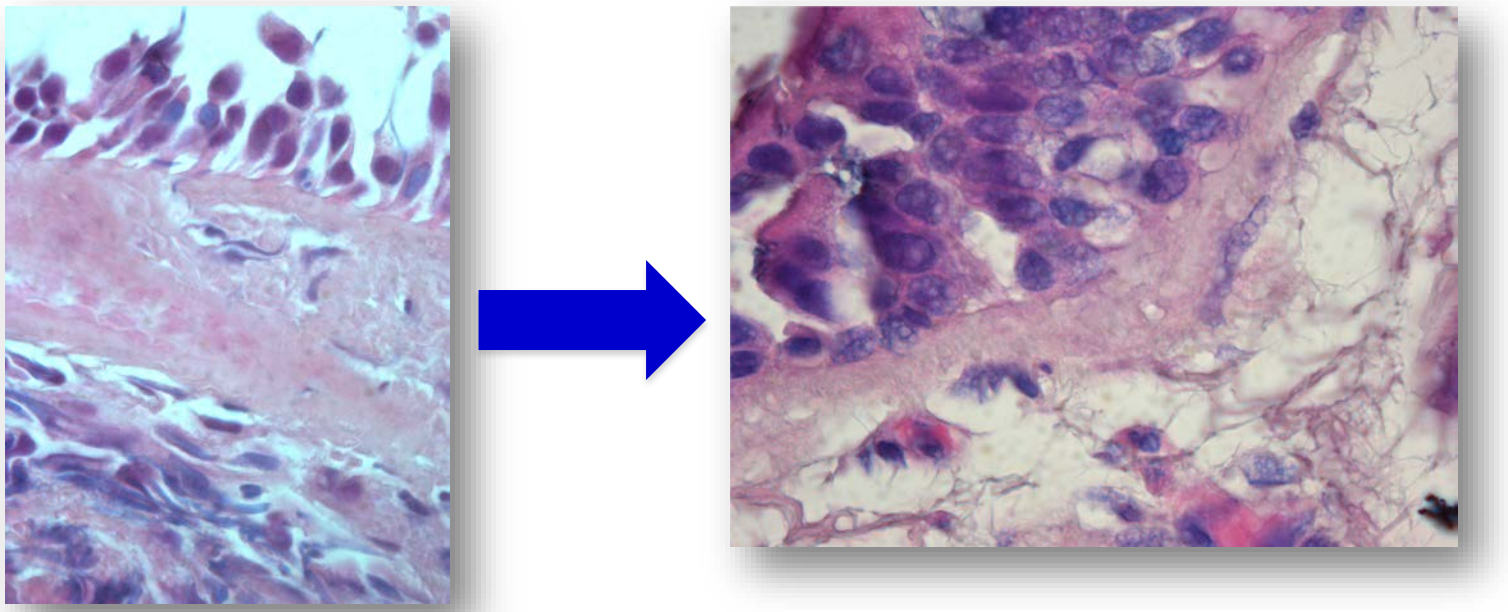
Int J Immunopathol Pharmacol 2012; 25(2):475-84

Results



Int J Immunopathol Pharmacol 2012; 25(2):475-84

Case 1



RBM thickness reduced after 12 month Omalizumab Therapy

Int J Immunopathol Pharmacol 2012; 25(2):475-84

Proteomics of bronchial biopsies: Galectin-3 as a predictive biomarker of airway remodelling modulation in omalizumab-treated severe asthma patients

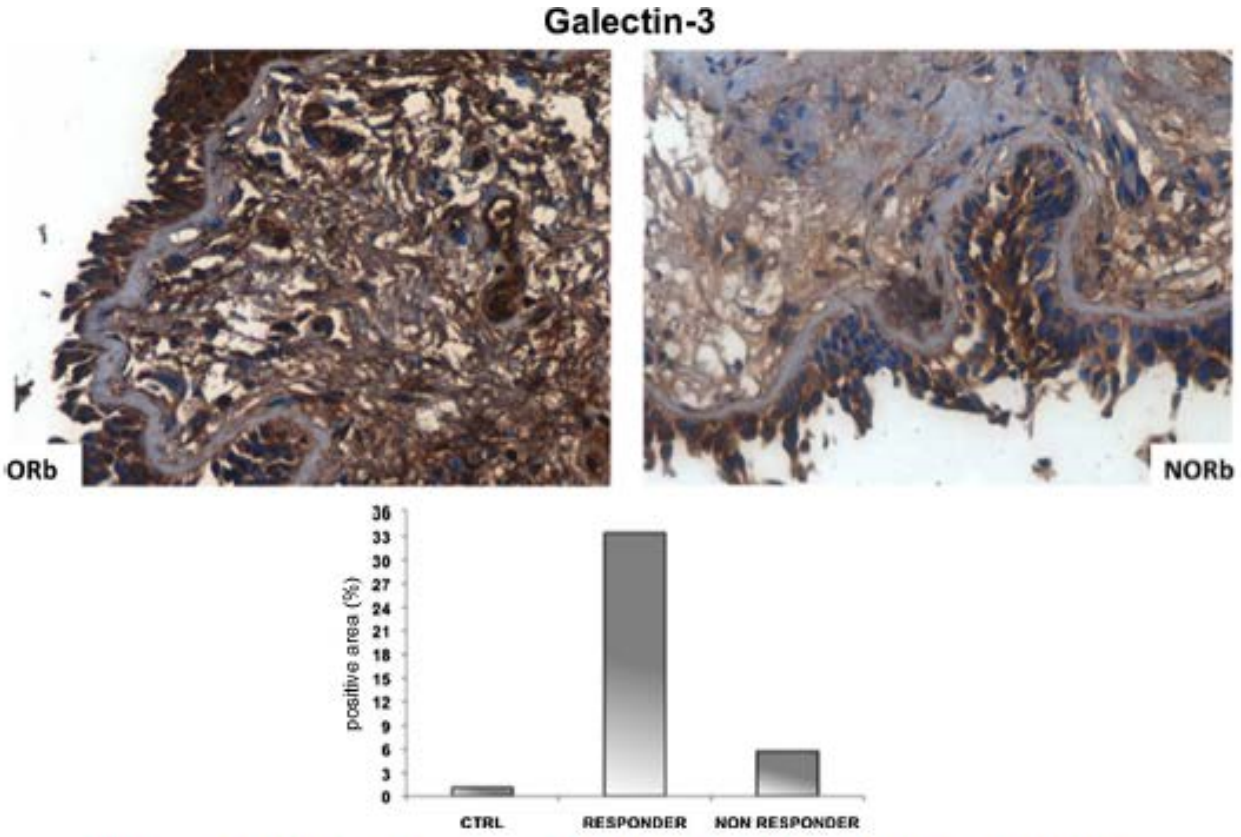


Fig. 6. IHC analysis for galectin-3 in responder (ORb) and non-responder (NORb) patients before anti-IgE treatment.

P Mauri, et al. Immunology Letters 2015

Riccio *et al. Clin Transl Allergy (2017) 7:6*
DOI 10.1186/s13601-017-0143-1

Clinical and Translational Allergy

RESEARCH Open Access

Galectin-3: an early predictive biomarker of modulation of airway remodeling in patients with severe asthma treated with omalizumab for 36 months

Anna Maria Riccio[1†], Pierluigi Mauri[2†], Laura De Ferrari[1], Rossana Rossi[2], Dario Di Silvestre[2], Louise Benazzi[2], Alessandra Chiappori[1], Roberto Walter Dal Negro[3], Claudio Micheletto[4] and Giorgio Walter Canonica[1,5*]

Conclusions: Our results showed that omalizumab can be considered a disease-modifying treatment in OR. The proteomic signatures confirmed the presence of Gal-3 at baseline to be a biomarker of long-term reduction in bronchial RBM thickness, eosinophilic inflammation, and muscular and fibrotic components in omalizumab-treated patients with severe asthma. Our findings suggest a possible relationship between Gal-3 positivity and improved pulmonary function.

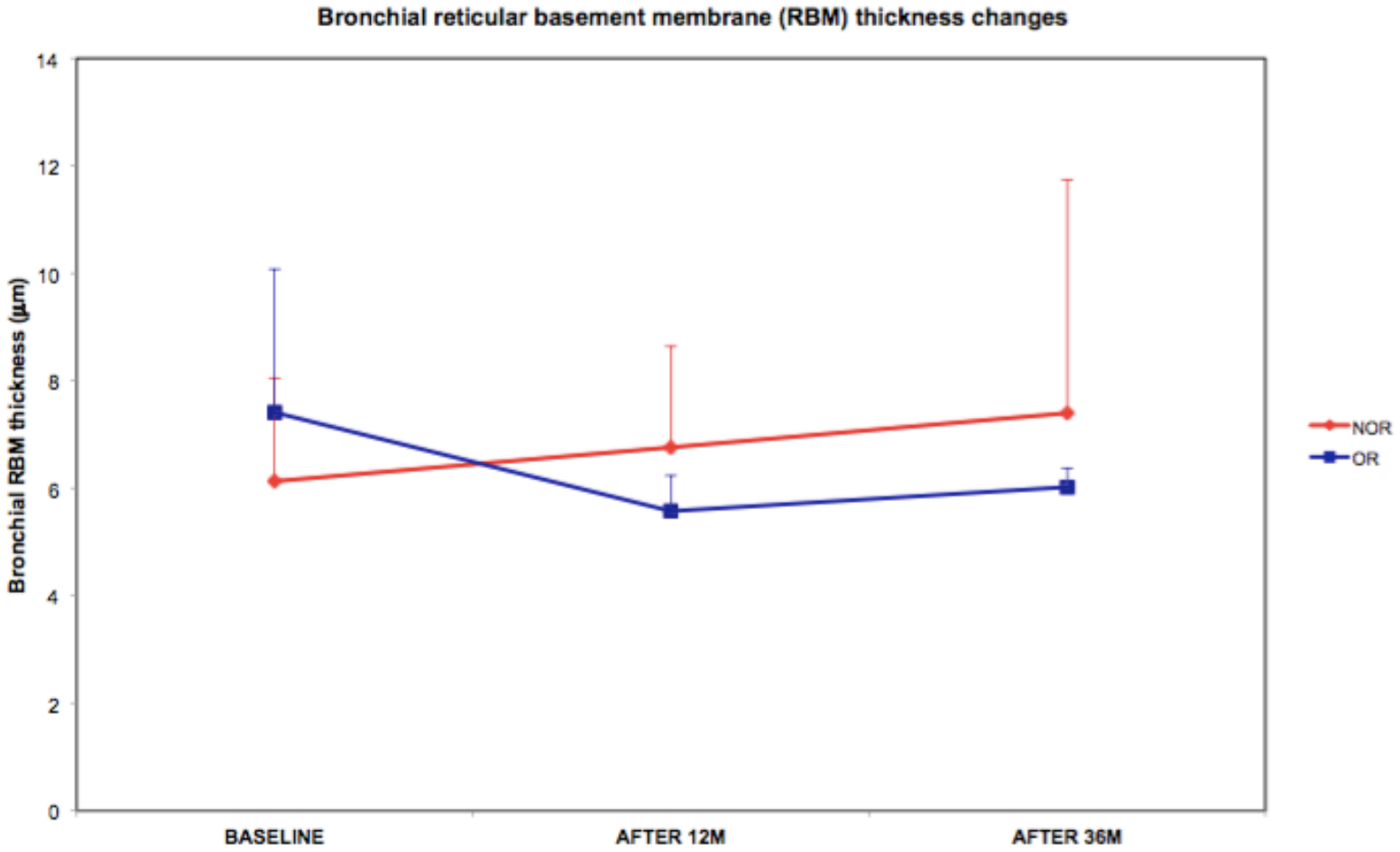
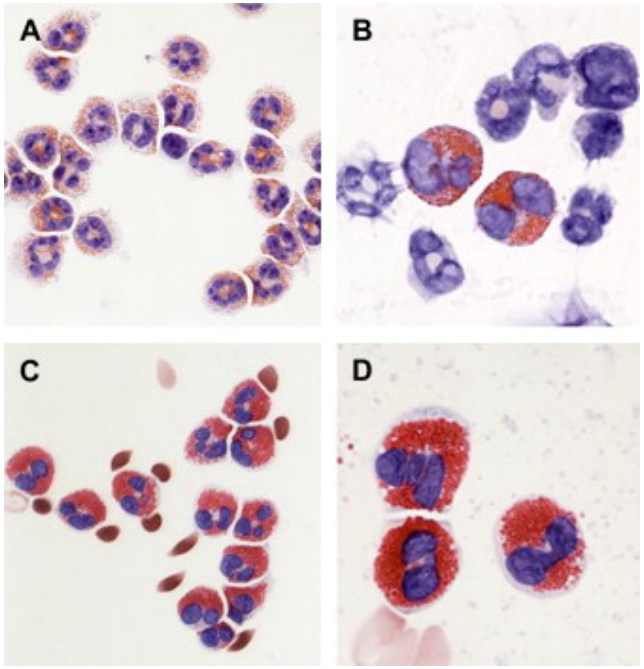


Fig. 1 Changes in bronchial RBM thickness in omalizumab responders (OR) and non-omalizumab responders (NOR) at baseline and after 12 and 36 months of anti-IgE treatment

Riccio *et al. Clin Transl Allergy (2017) 7:6*
DOI 10.1186/s13601-017-0143-1

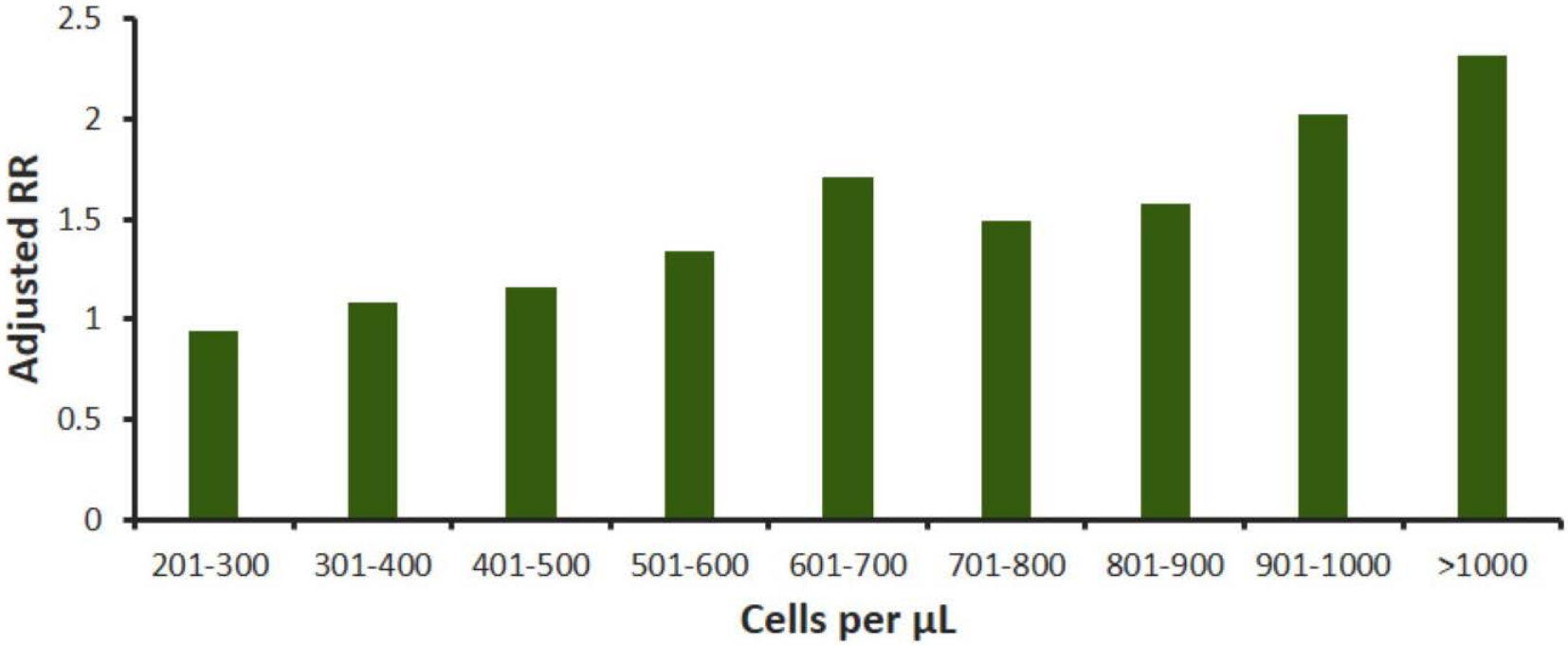
Interleukin-5

IL-5 is primarily produced by activated Th2 cells, but also Mast cells and eosinophils.
It promotes:



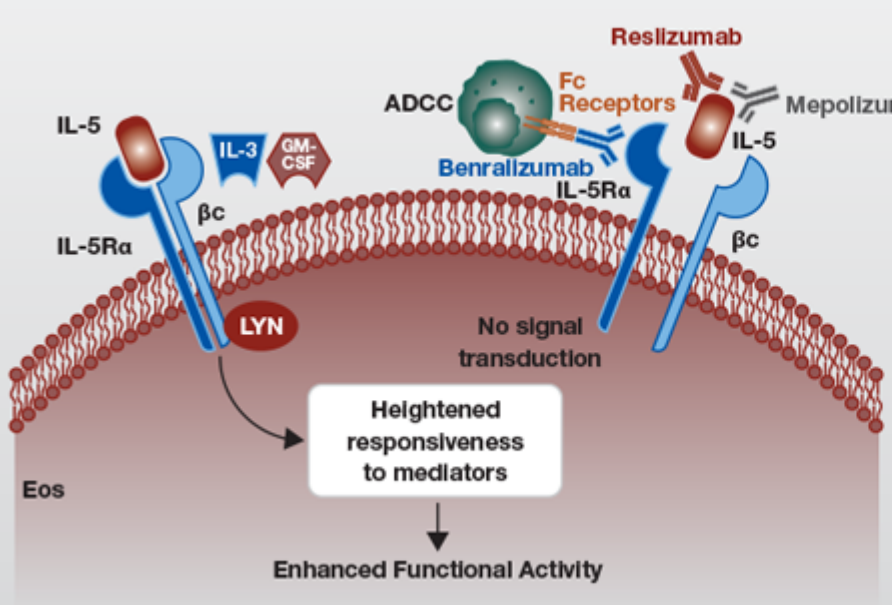
- eosinophil maturation
- eosinophil migration and chemotaxis
- eosinophil activation and survival

What is the relationship between blood eosinophils and severe asthma exacerbations ?



Pride DB, et al. Lancet Resp Med 2015

IL-5 pathways inhibition in severe eosinophilic asthma



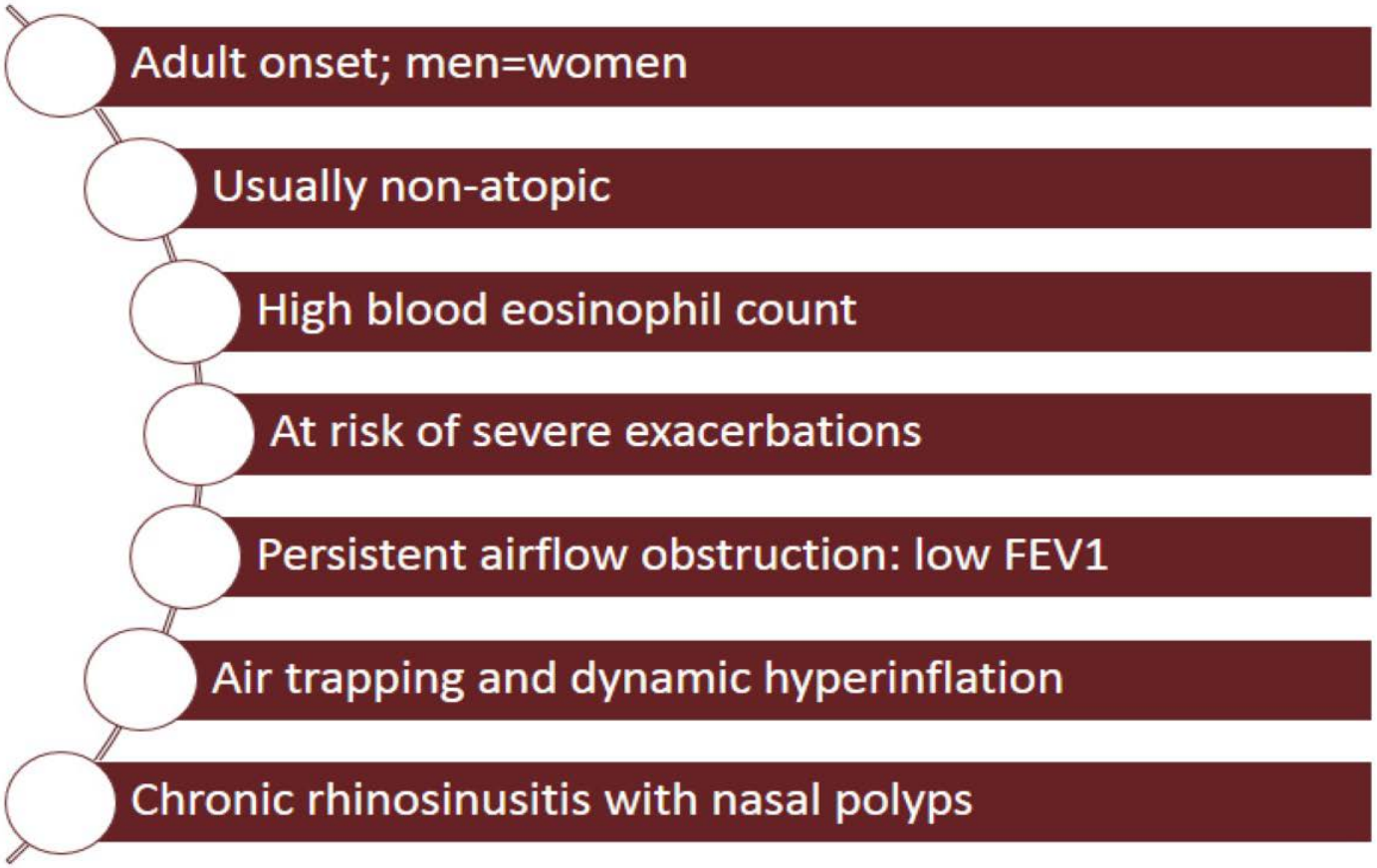
Eosinophils

- Major source of IL-5
- Critical role in pathogenesis and severity of asthma through action of IL-5
- Il-5 concentrations correlate with clinical features of asthma

Agent	Target/MOA
Mepolizumab	Binds to epitope of IL-5, blocks binding with IL-5Rα
Reslizumab	Binds to epitope of IL-5, blocks binding with IL-5Rα
Benralizumab	Inhibition of IL-5Rα activation, leading to enhanced antibody-dependent cell-mediated cytotoxicity

Varricchi G, et al. Curr Opin Allergy Clin Immunol 2016

Clinical profile of late-onset eosinophilic asthma



De Groot JC, et al. ERJ Open Res 2016

DREAM study: inclusion criteria

- Age 12-74 years
- Clinical diagnosis of asthma (refractory)
- History of two or more exacerbations / year
- **<u>Evidence of eosinophilic inflammation</u>**:

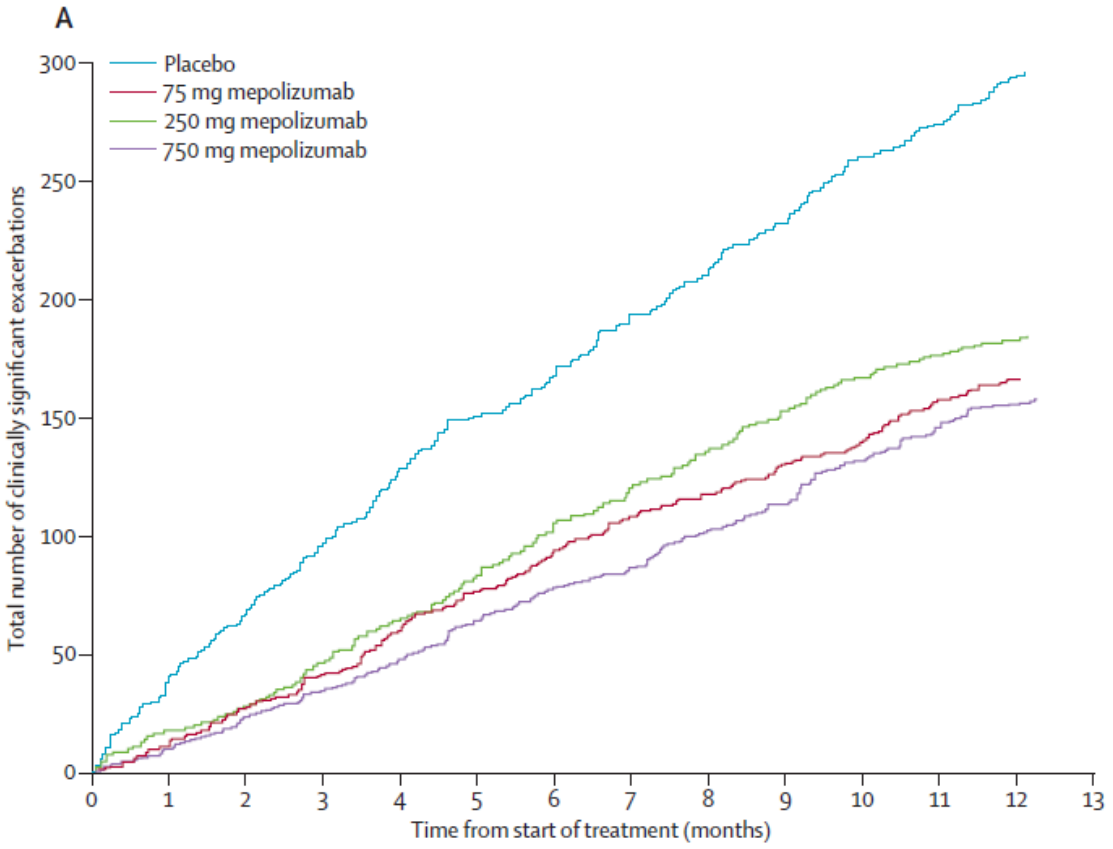
1) sputum eosinophil count ≥ 3%, *or*

2) blood eosinophil count ≥ 300/µL, *or*

3) FE_{NO} ≥ 50 ppb.

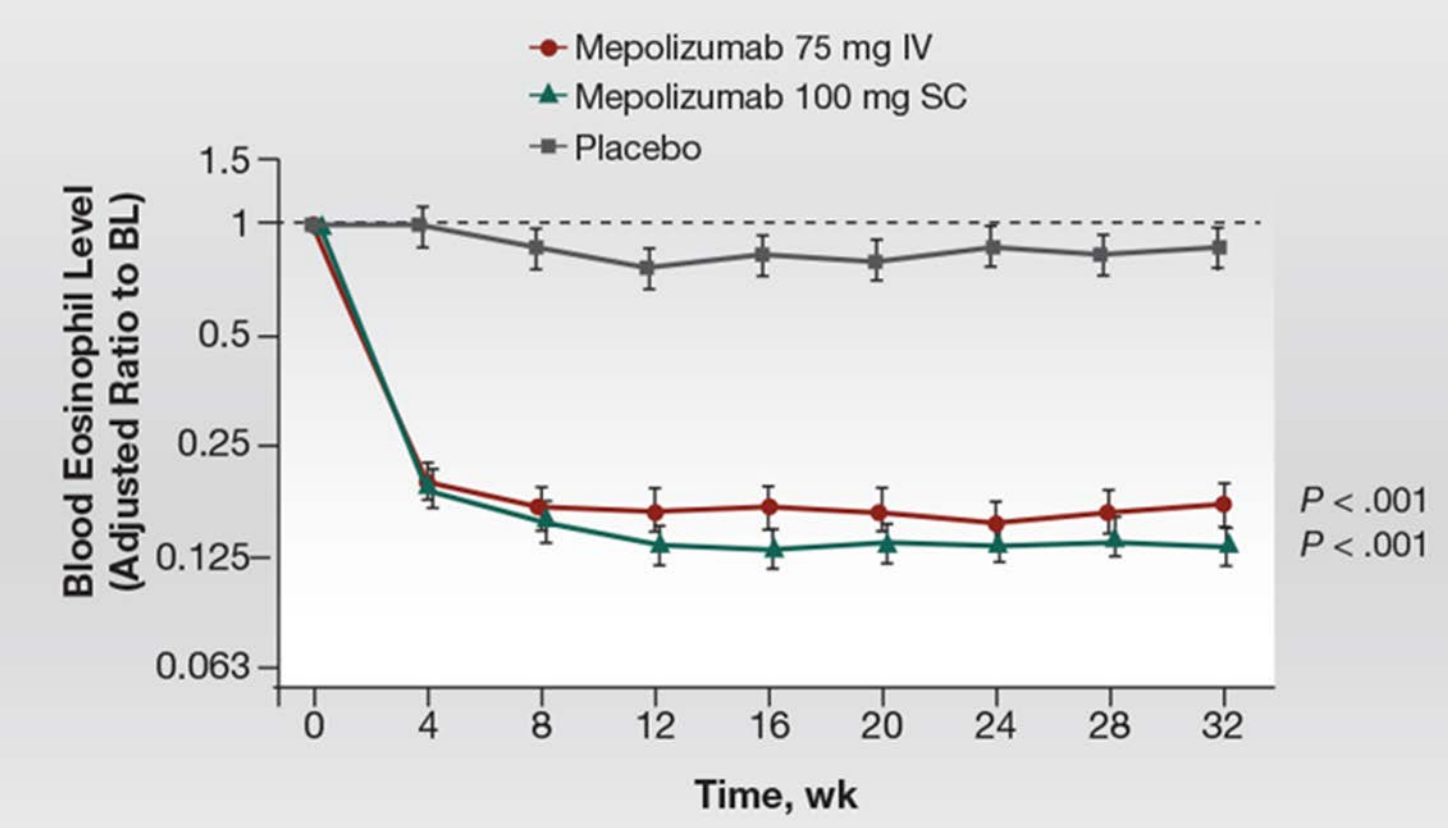
Pavord I. et al, Lancet 2012; 380: 651-659.

Mepolizumab in severe eosinophilic asthma: impact on exacerbations

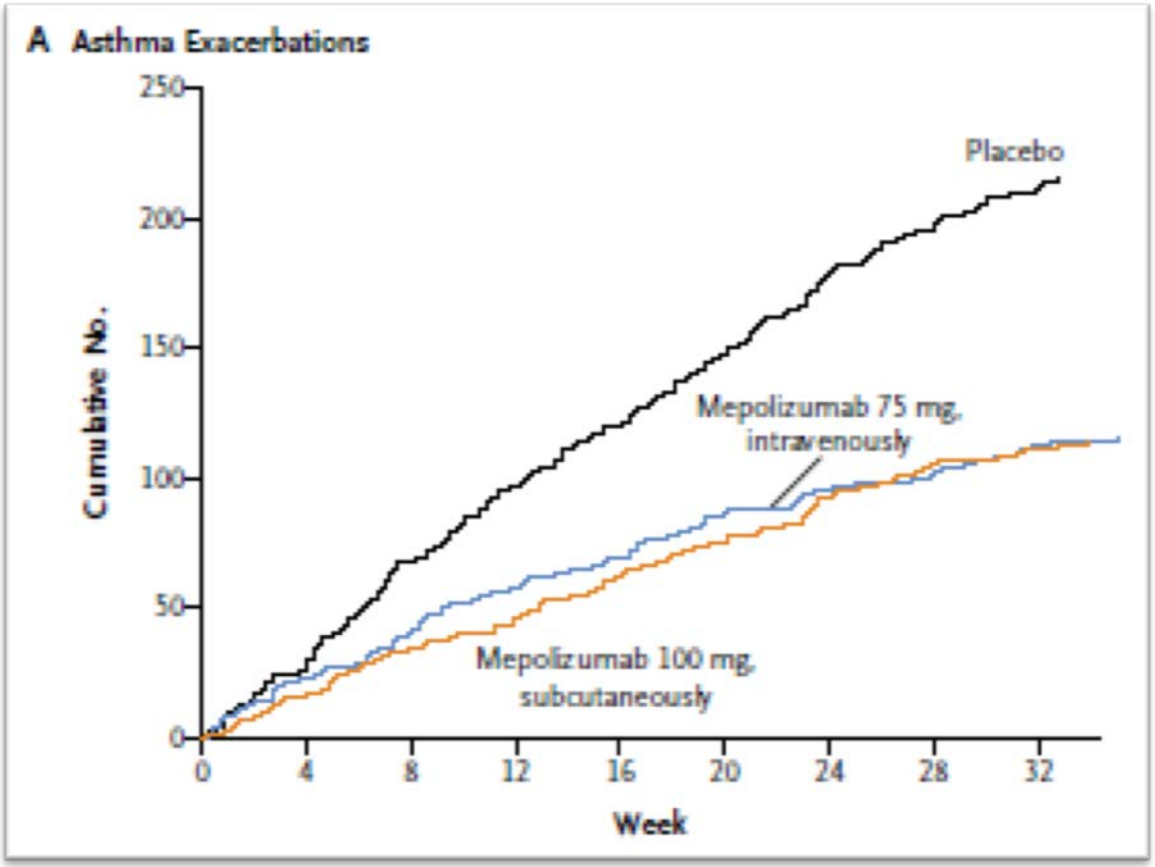


Pavord I. et al, Lancet 2012; 380: 651-659.

The effect of IL-5 targeted treatment on blood eosinophils levels: Mepolizumab

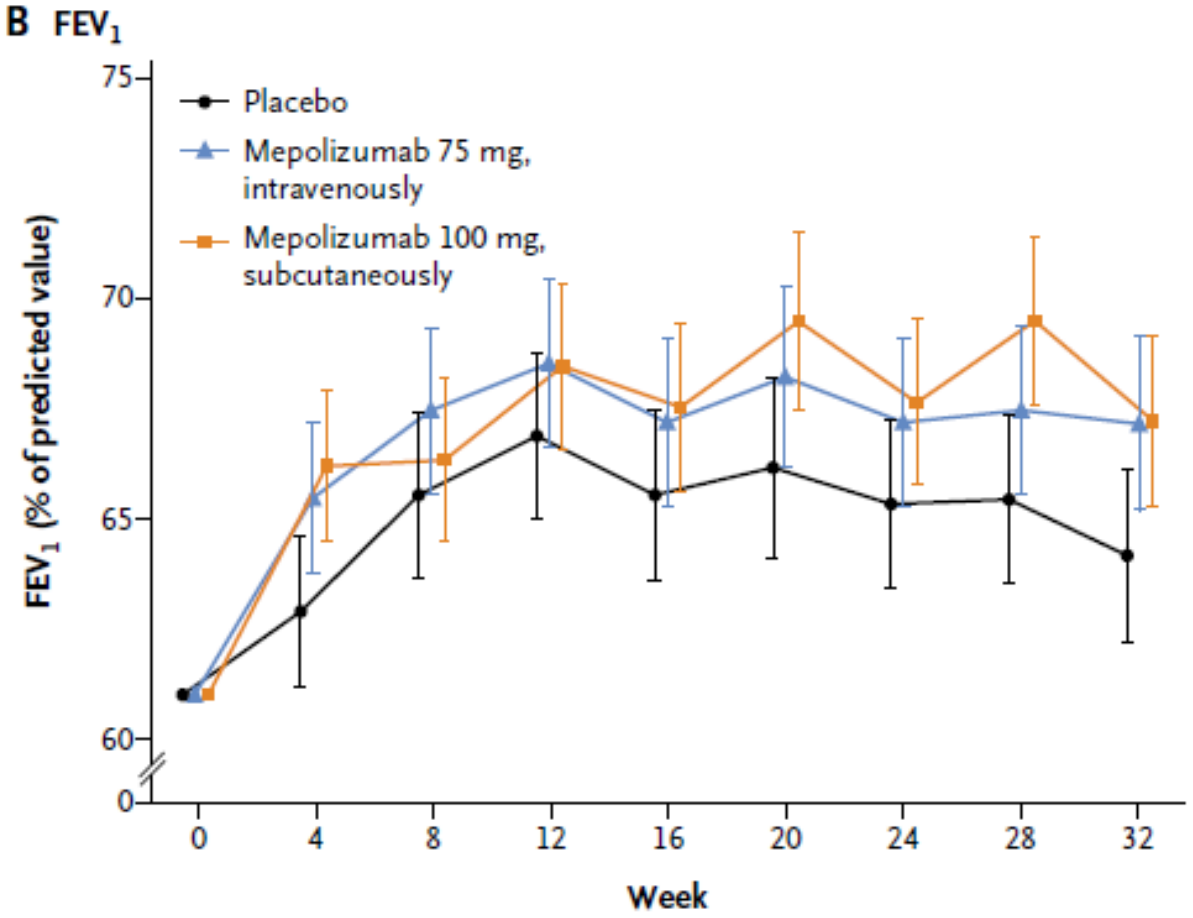


Ortega HG, et al. New Engl J Med 2014



The rate of exacerbations was reduced by **47 %** among patients receiving intravenous mepolizumab and by **53 %** among those receiving subcutaneous mepolizumab, as compared with those receiving placebo ($P<0.001$).

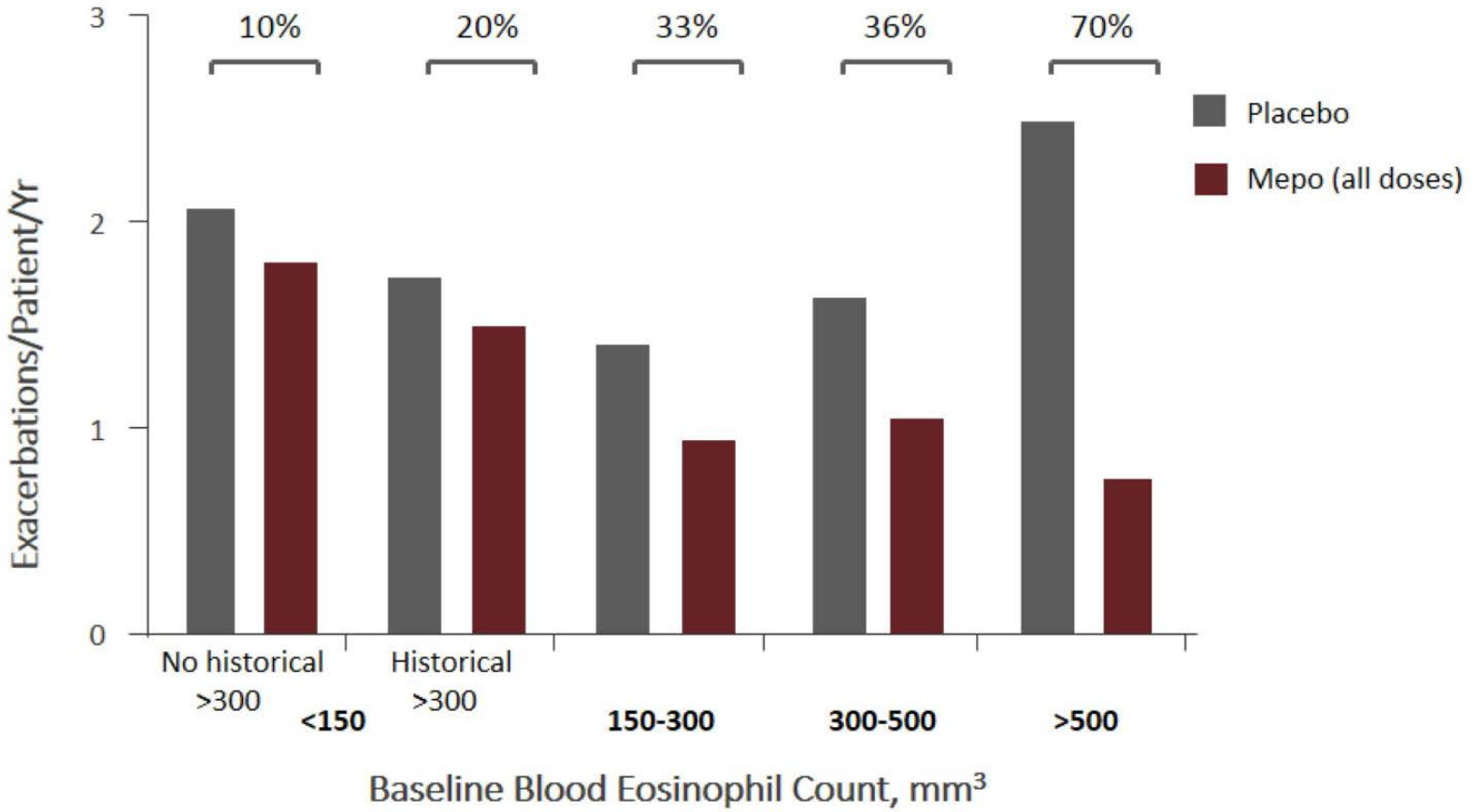
Ortega HG, et al. New Engl J Med 2014



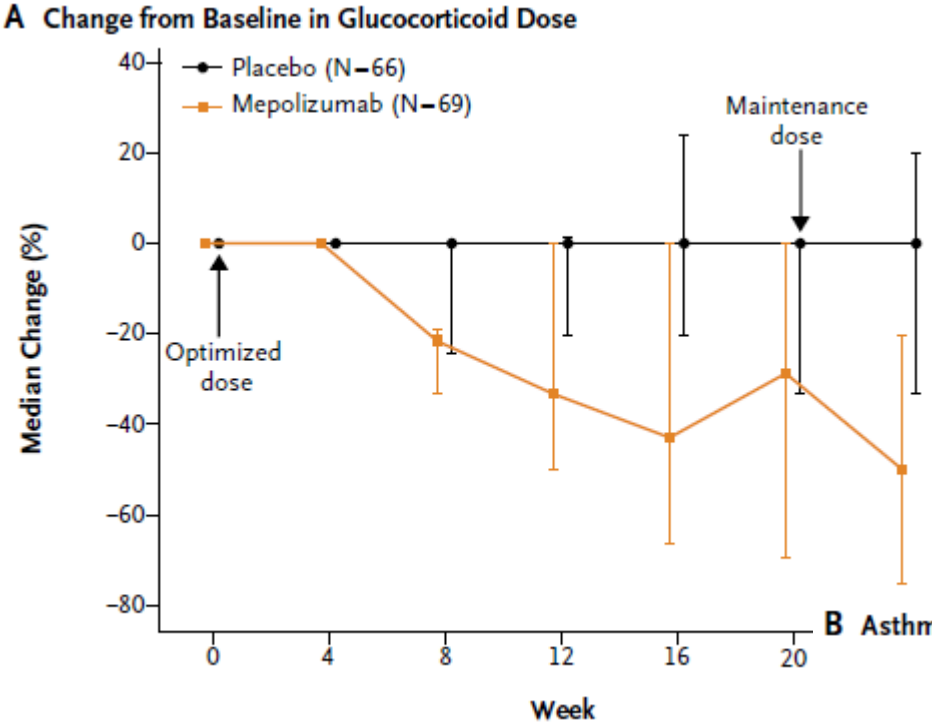
At week 32, the mean increase from baseline in FEV_1 was 100 ml greater in patients receiving intravenous mepolizumab than in those receiving placebo (P = 0.02) and **98 ml** greater in patients receiving subcutaneous mepolizumab than in those receiving placebo (P=0.03).

Ortega HG, et al. New Engl J Med 2014

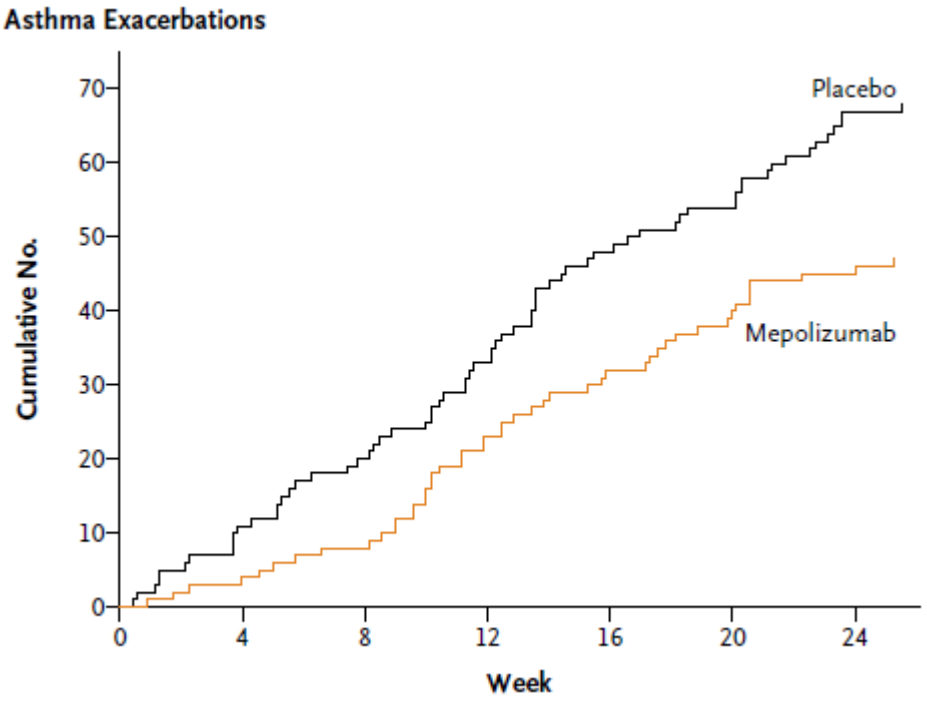
Exacerbation rate reduction with mepolizumab baseline blood eosiniphil count



Ortega HG, et al. New Engl J Med 2014



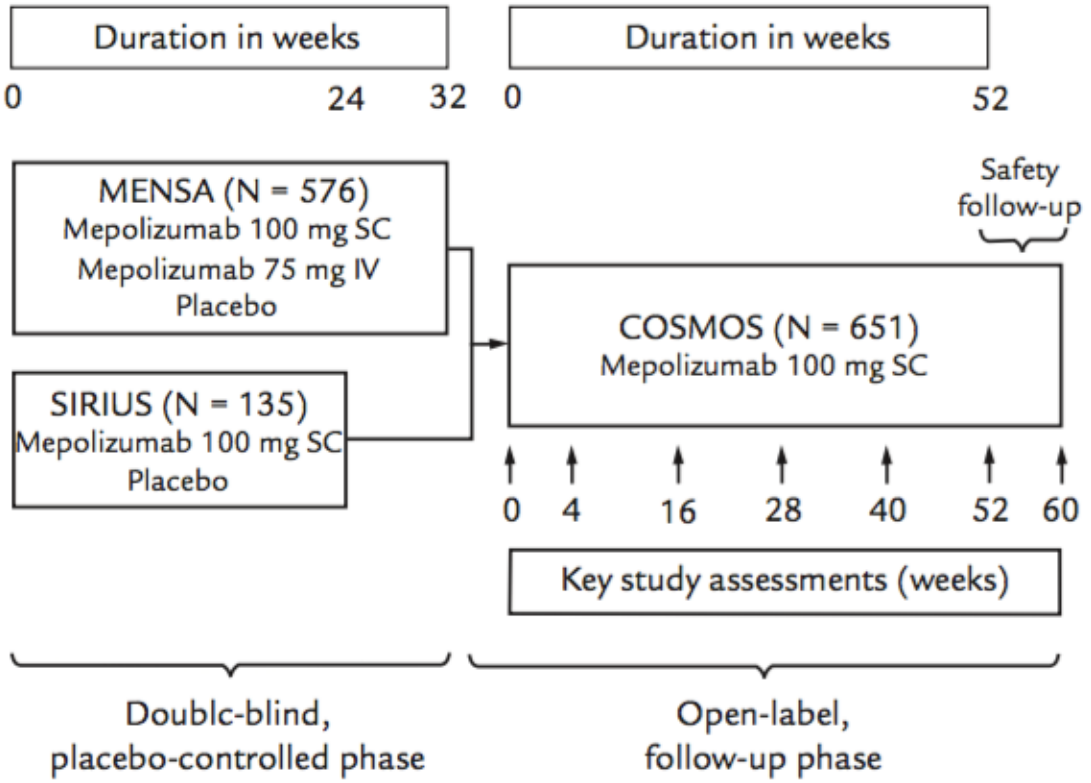
- 50 %



- 32 %

EH Bel, et al. New Engl J Med 2014

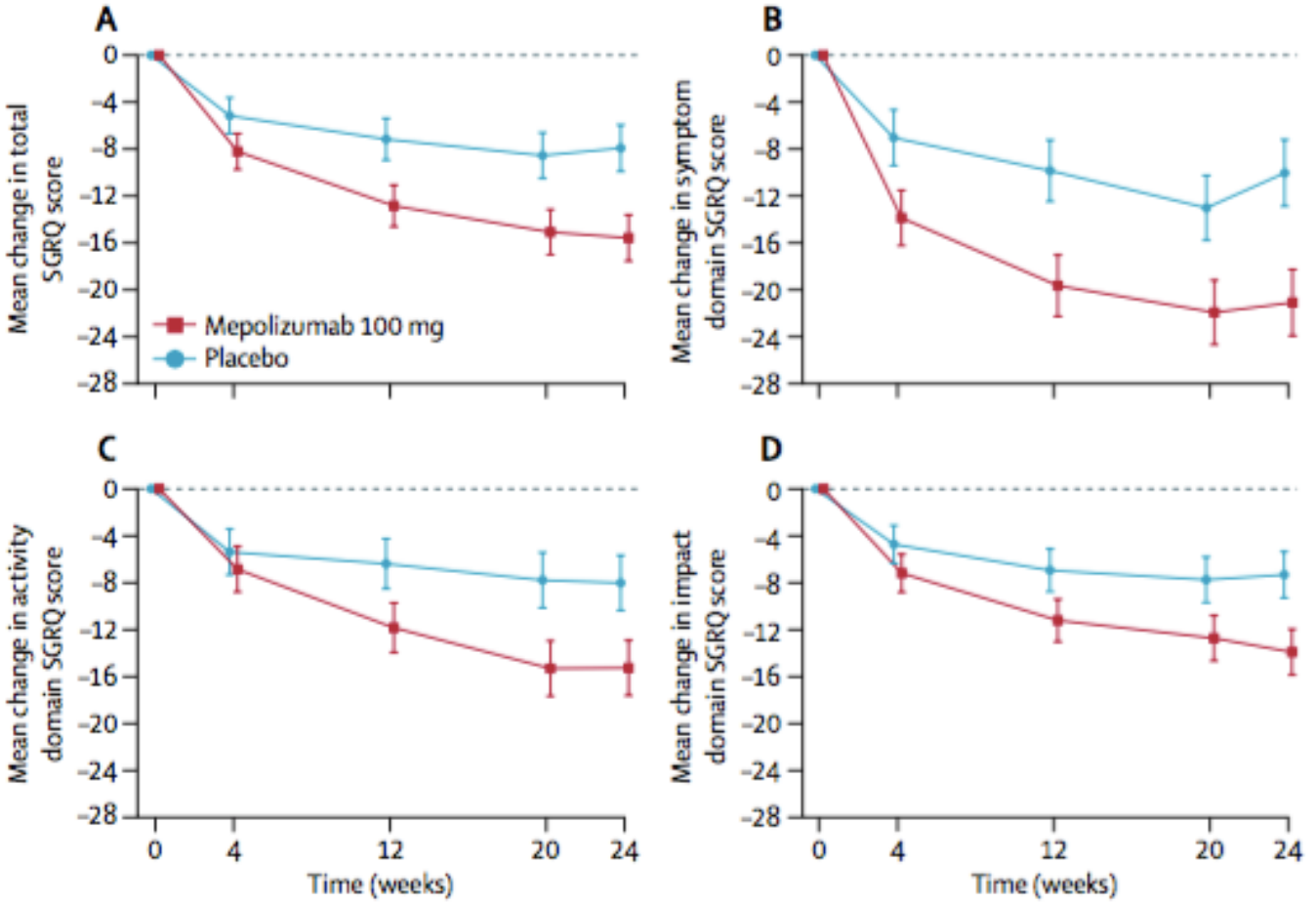
Long-Term Efficacy and Safety of Mepolizumab in Patients With Severe Eosinophilic Asthma



Implications: These data demonstrate a favorable safety profile of mepolizumab and indicate a durable and stable effect over time, supporting long-term treatment in patients with severe eosinophilic asthma.

Clinical Therapeutics 2016

Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA).



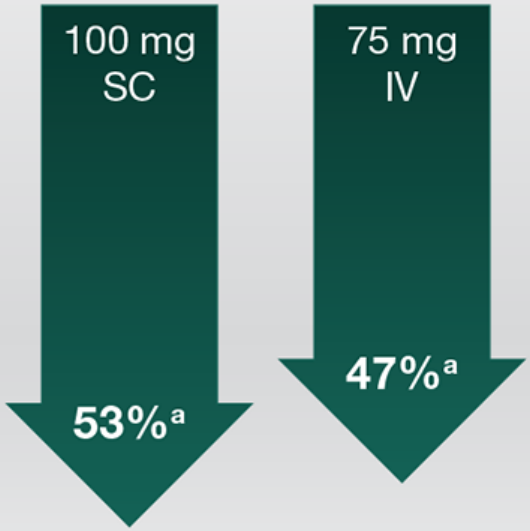
Chupp GL, et al. Lancet Resp Med 2017

Treatments Targeting IL-5: Effect on Exacerbations (Mepolizumab)

MENSA: Phase 3 RCT of mepolizumab vs placebo Q4W for 32 wk

- 576 patients with recurrent asthma exacerbations
- Evidence of eosinophilic inflammation (≥300 cells/μL)
- Inadequate control with high-dose ICS

Reduction in Exacerbations at 32 Wk Mepolizumab vs Placebo



[a] $P < .001$ vs placebo.

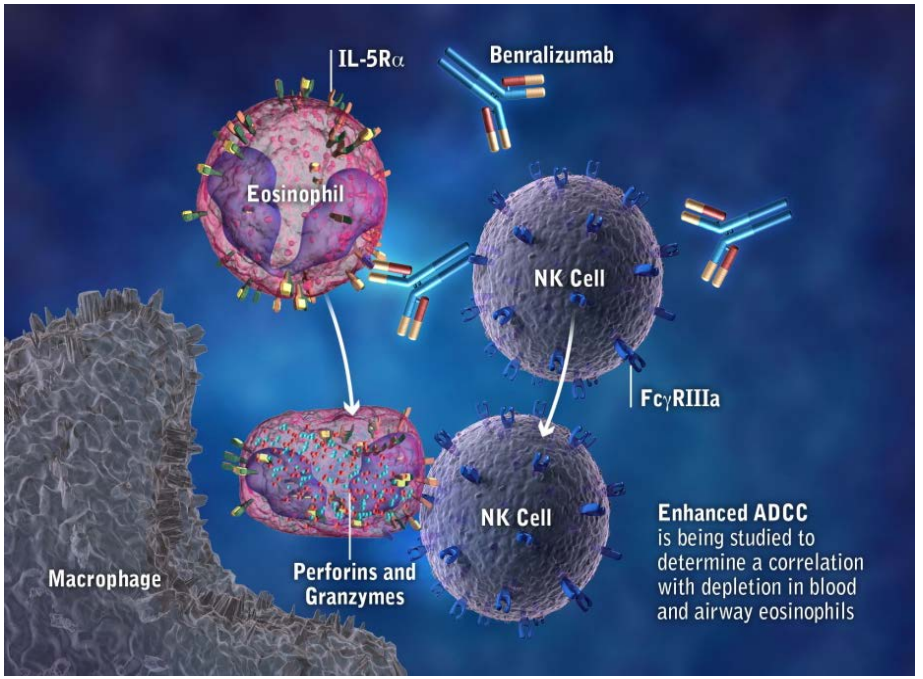
Benralizumab depletes eosinophils: how does it work?

Benralizumab depletes eosinophils in a different way from anti-IL-5 antibodies:

1) Binds with high specificity to IL-5Rα on eosinophils and basophils, then

2) Binds with increased affinity to Fc receptors on immune effector cells through the afucosylated (lack of fucose sugar residues) Fc region of benralizumab;

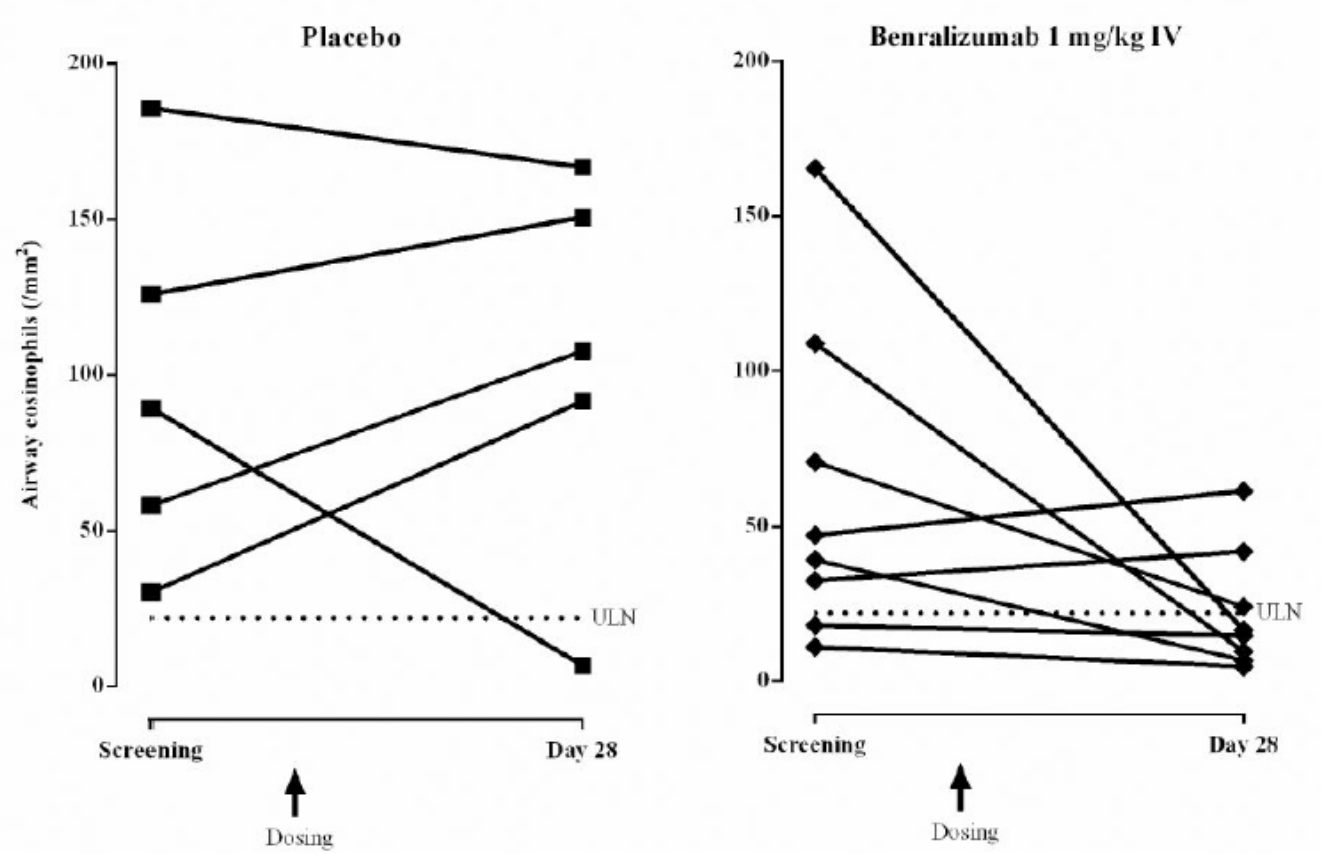
3) This results in increased ADCC and death of eosinophils and basophils via apoptosis (programmed cell death).



ADCC, antibody-dependent cell-mediated cytotoxicity; IL-5Rα, interleukin-5 receptor α; NK, natural killer

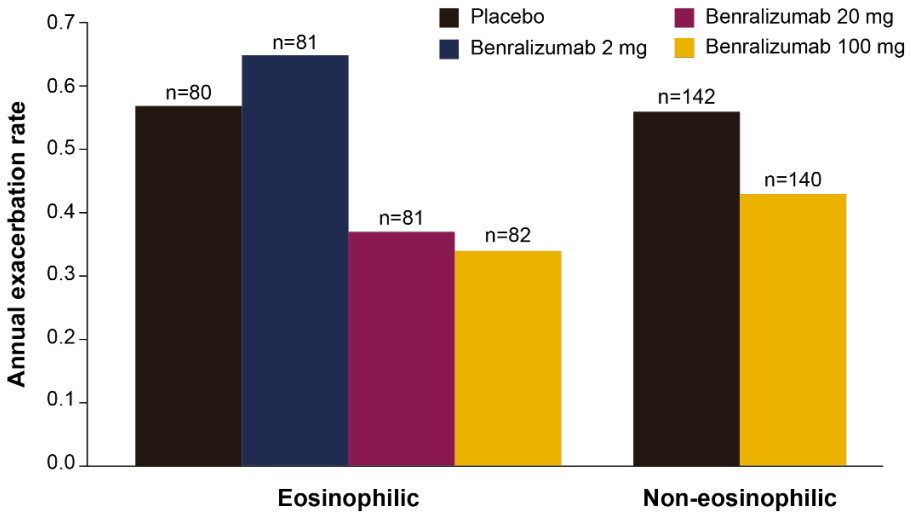
Kolbeck R et al. J Allergy Clin Immunol 2010

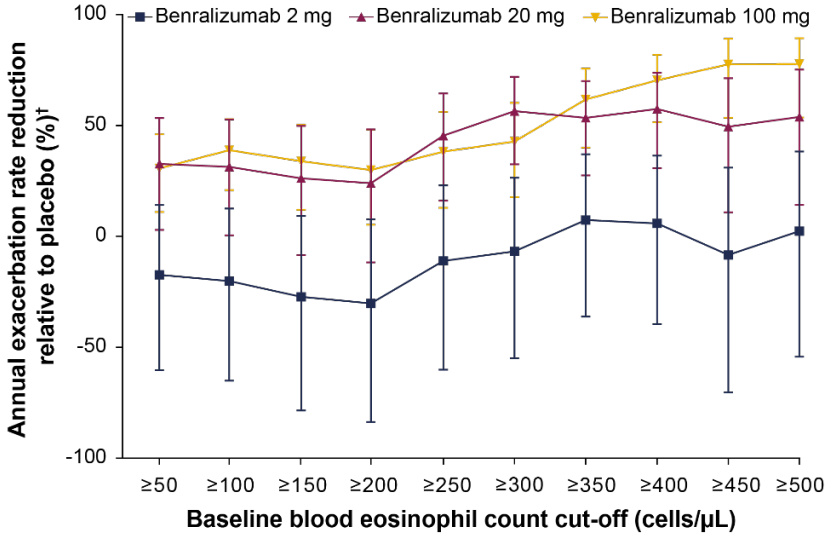
Effects of benralizumab on airway eosinophils in asthma with sputum eosinophilia



J Allergy Clin Immunol. 2013

Annual exacerbation rate





Treatment group	Benralizumab dose	AERR relative to placebo
Eosinophilic	2 mg	-9% (p=0.781)
	20 mg	36% (p=0.173)
	100 mg	41% (p=0.096*)
Non-eosinophilic	100 mg	22% (p=0.284)

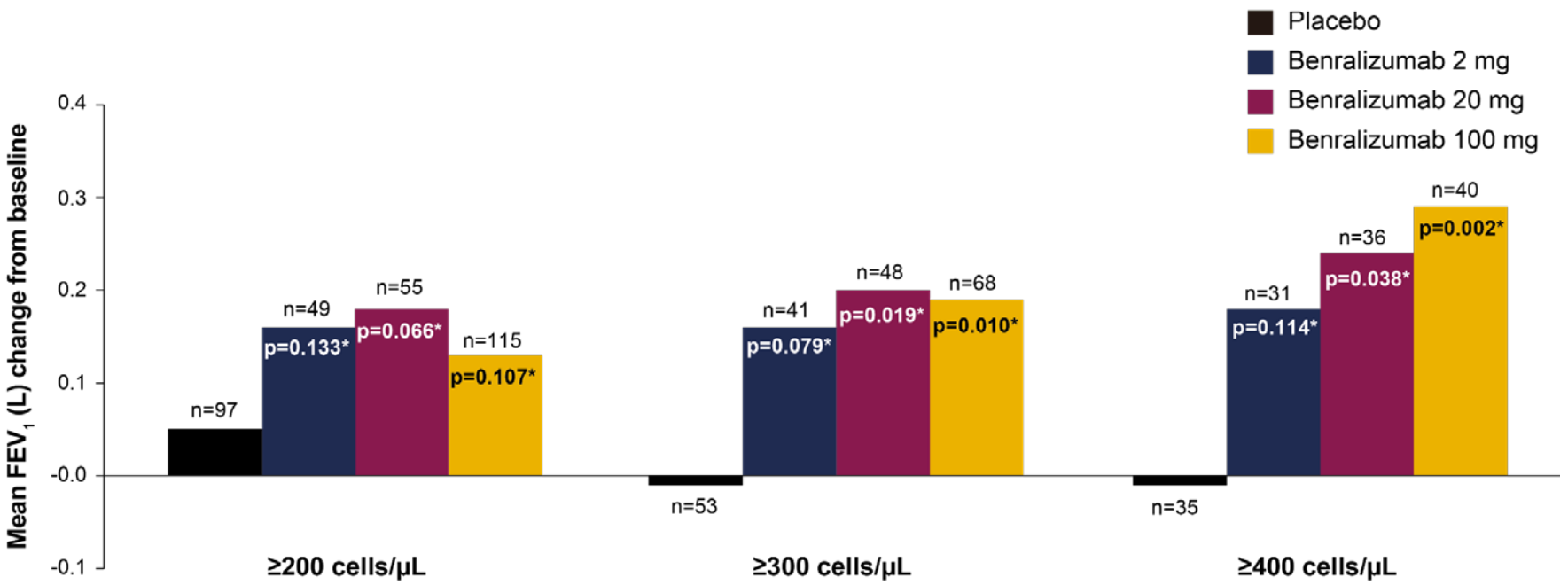
Blood eosinophils	n	AERR relative to placebo
≥300 cells/µL	Benralizumab 20 mg: n=70 Placebo: n=83	57% (p=0.015*)
	Benralizumab 100 mg: n=97 Placebo: n=83	43% (p=0.049*)
≥400 cells/µL	Benralizumab 100 mg: n=58 Placebo: n=52	70% (p=0.002*)

- **Benralizumab 100 mg significantly reduced AER relative to placebo**
  - **In eosinophilic patients (primary endpoint)**
  - **In patients with baseline blood eosinophils ≥300 and ≥400 cells/µL**

*Statistically significant (p<0.169)
†Data are expressed as mean (80% confidence interval)
AERR, annual exacerbation rate reduction; asthma exacerbation was defined as an increase in asthma symptoms that did not resolve after rescue medication and required treatment with systemic steroids for at least 3 days

Castro M, et al. Lancet Respir Med 2014;2:879–890
Castro M, et al. Presented at the Annual Meeting of the American Thoracic Society, San Diego, USA, 16–21 May 2014

Change from baseline in FEV_1 by baseline blood eosinophil count

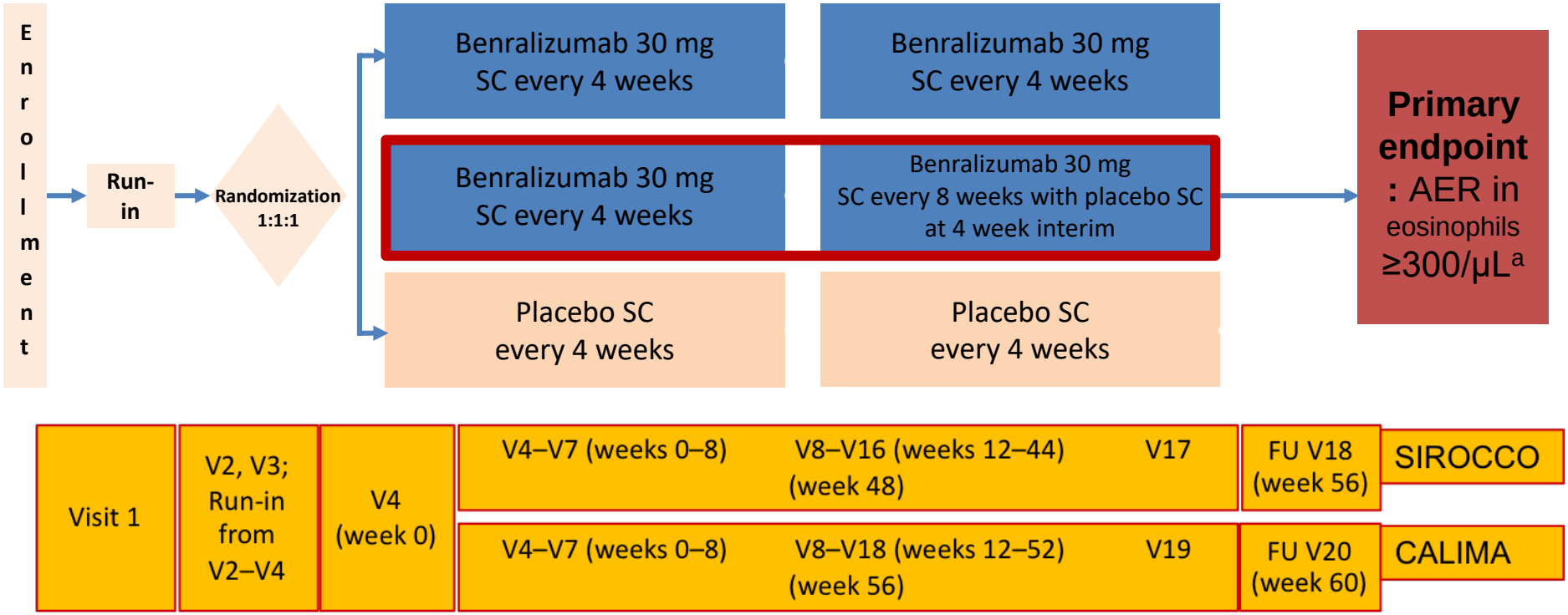


- In subgroups with blood eosinophil counts ≥200, ≥300 and ≥400 cells/µL all doses of benralizumab showed significant improvements in FEV_1 vs placebo

*Statistically significant ($p<0.169$) FEV_1, forced expiratory volume in 1 second

Castro M, et al. Annual Meeting of the American Thoracic Society, San Diego, 2014

SIROCCO and CALIMA Study Design: Benralizumab 30 mg SC Every 4 or 8 Weeks vs Placebo

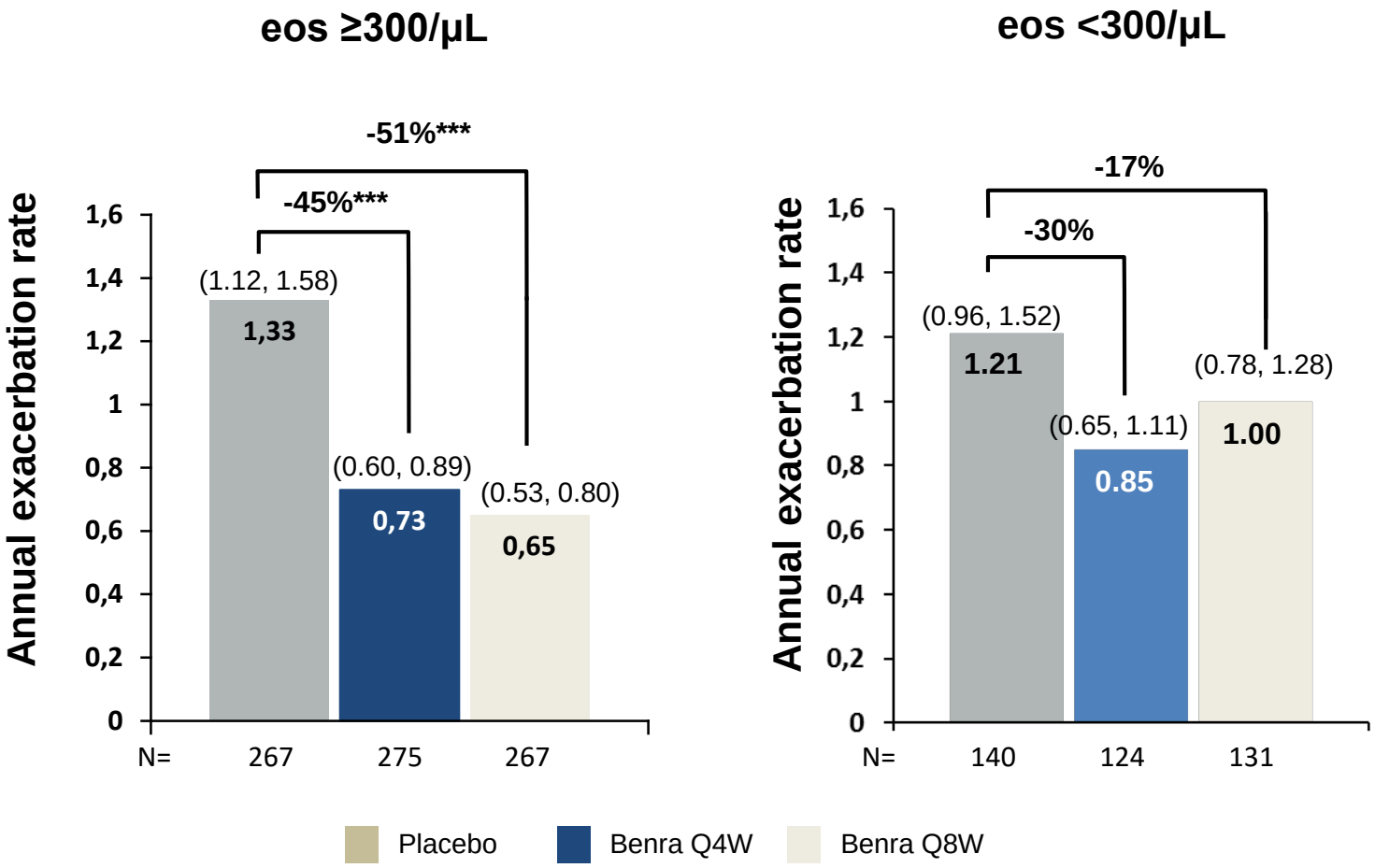


Randomized, double-blind, placebo-controlled study

- Planned 2:1 randomization ratio by eos (≥300/μL vs <300/μL)
- Stratified by ICS dose (high- and medium-dosage ICS, CALIMA only), region, age group, and baseline eosinophil

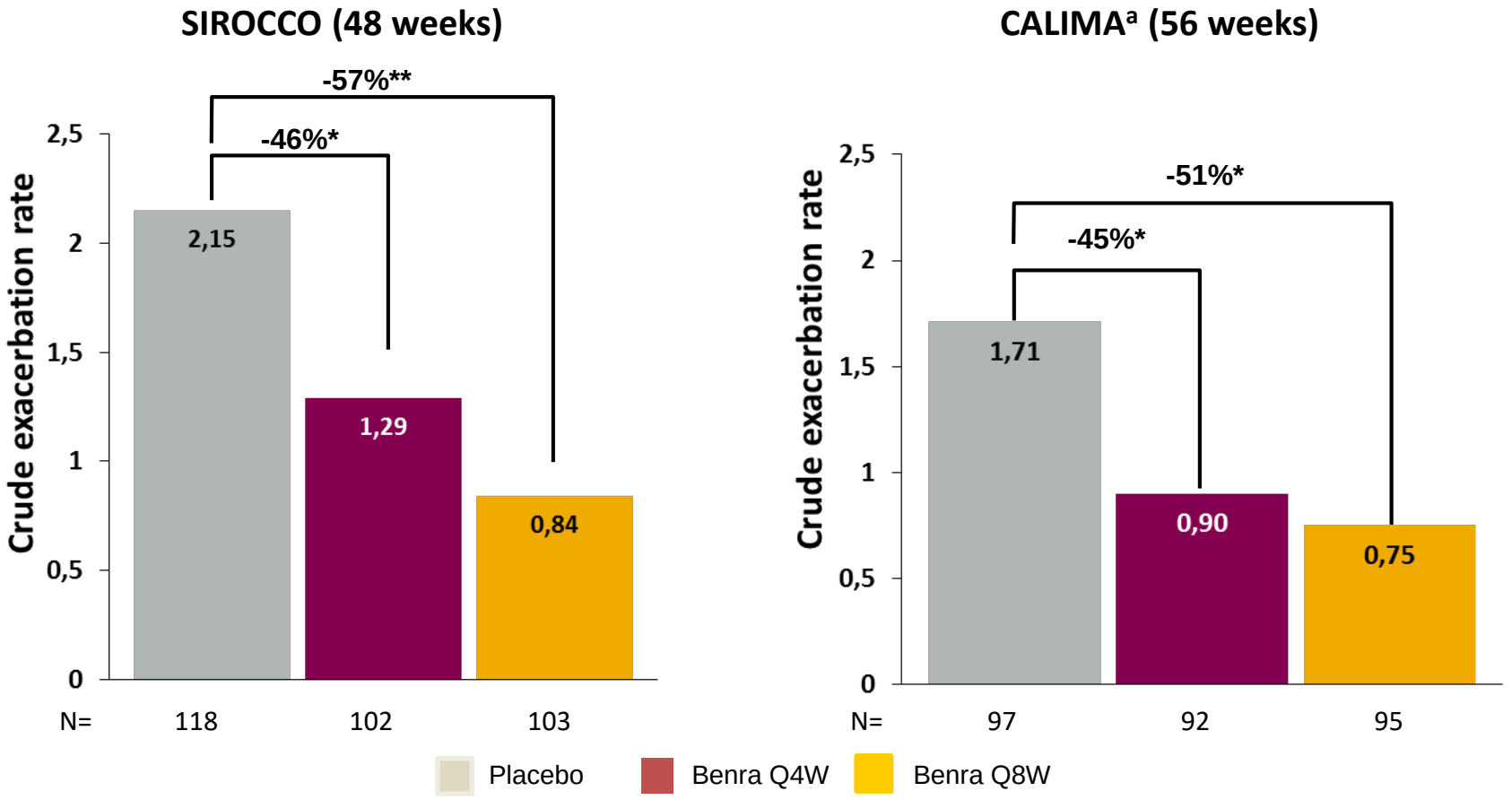
The Lancet 2016

SIROCCO Primary Efficacy Endpoint: Benralizumab Reduced the Annual Exacerbation Rate (AER) Compared with Placebo (FAS, eos ≥300/µL)



The Lancet 2016

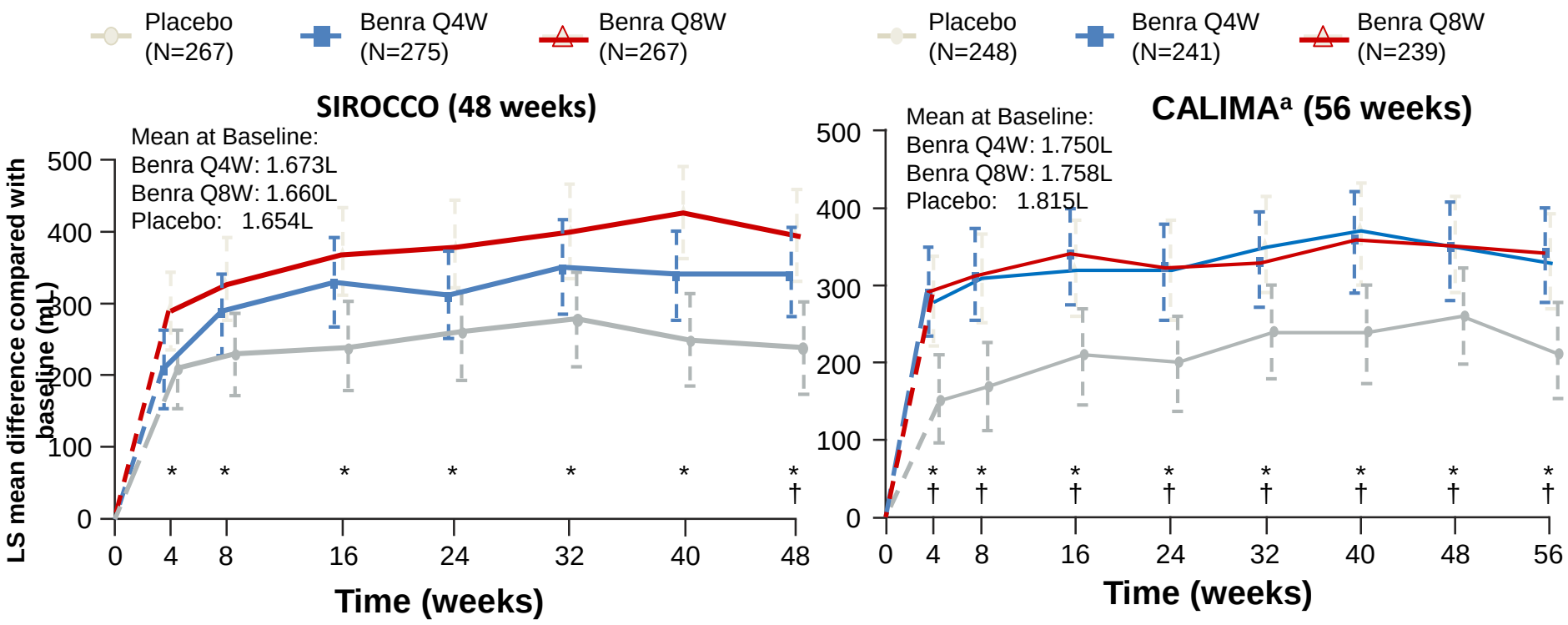
SIROCCO and CALIMA: AER in Patients with ≥3 Prior Exacerbations (eos ≥300/µL)



In both studies Benralizumab produced a similar magnitude reduction of exacerbation

The Lancet 2016

FEV_1 Improvements Were Seen After the First Dose and Maintained Throughout the Treatment Period (eos ≥300/µL)

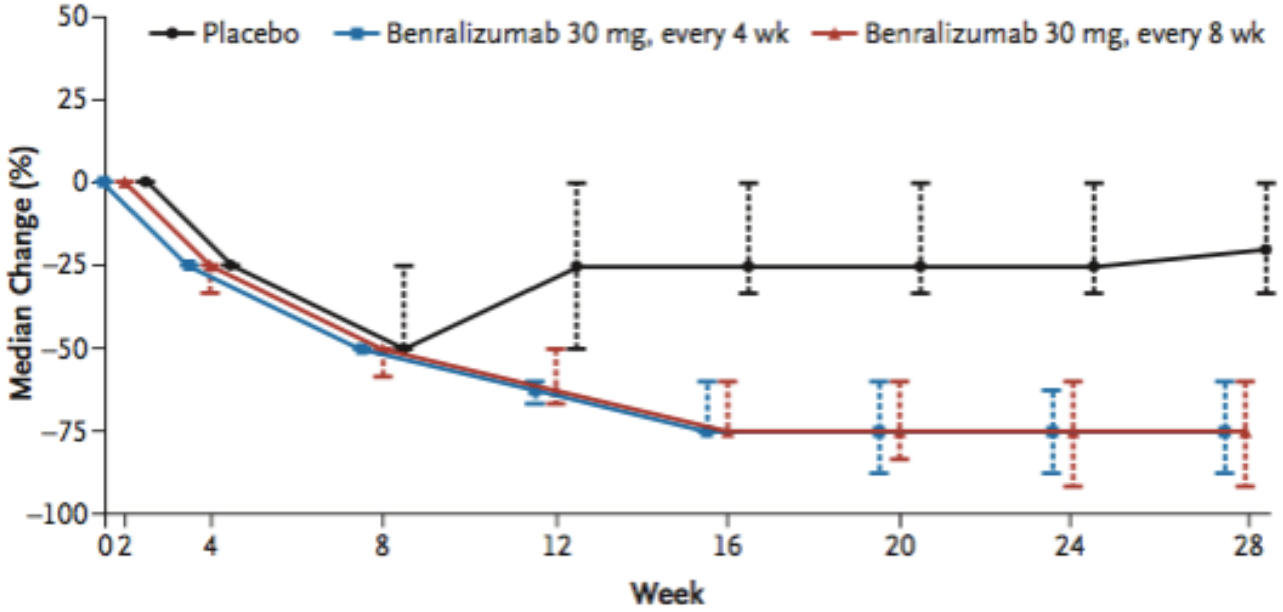


56/48 wks	Group LS MEANS	LS MEAN Difference (95% CI)	Group LS MEANS	LS MEAN Difference (95% CI)
Q4 – placebo	345 vs 239	106 (16, 198); *P*=0.022	340 vs 215	125 (37, 213); *P*=0.005
Q8 – placebo	398 vs 239	159 (68, 249); *P*=0.001	330 vs 215	116 (28, 204); *P*=0.010

The Lancet 2016

Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma

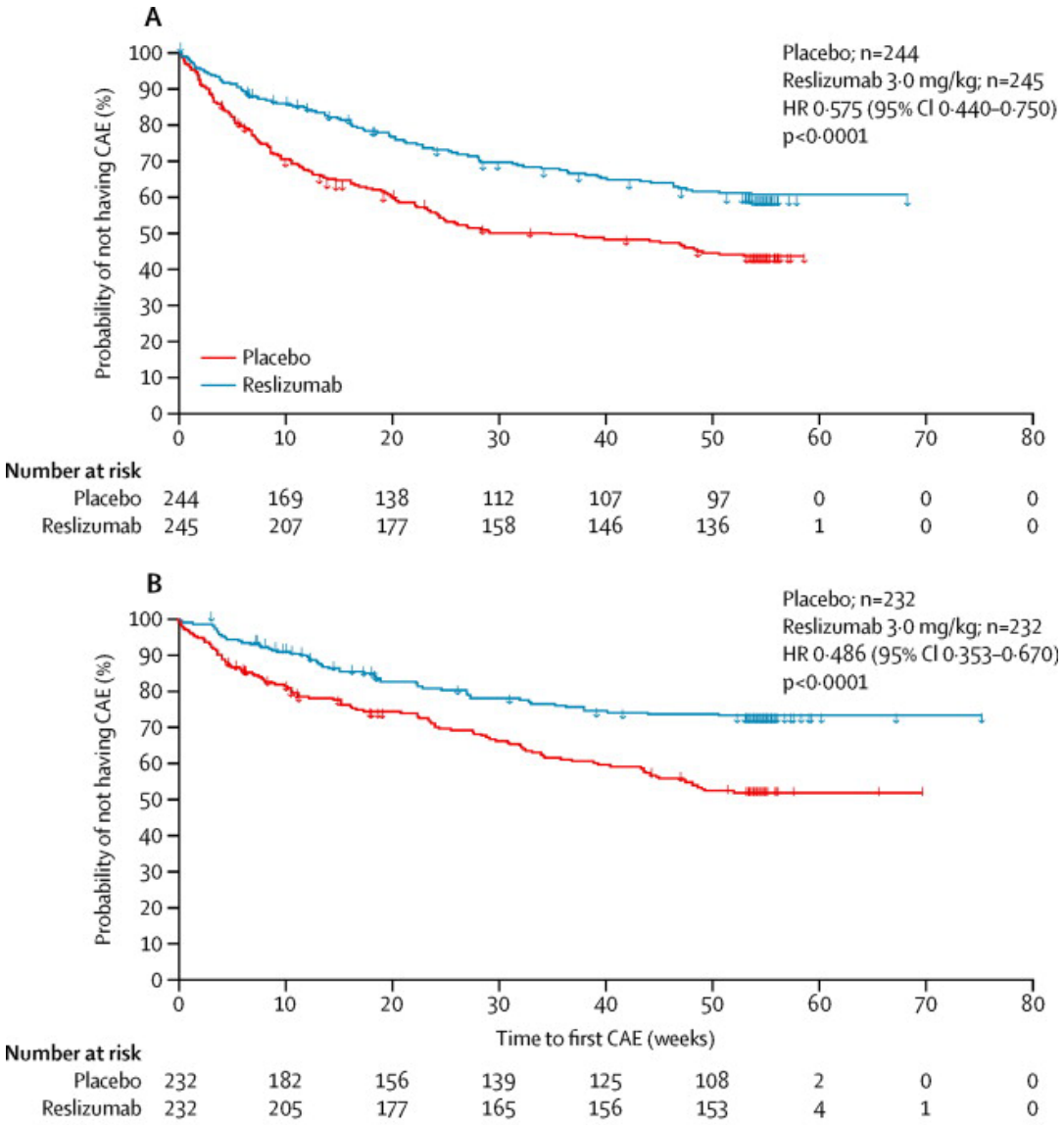
A Change from Baseline in Oral Glucocorticoid Dose



No. at Risk

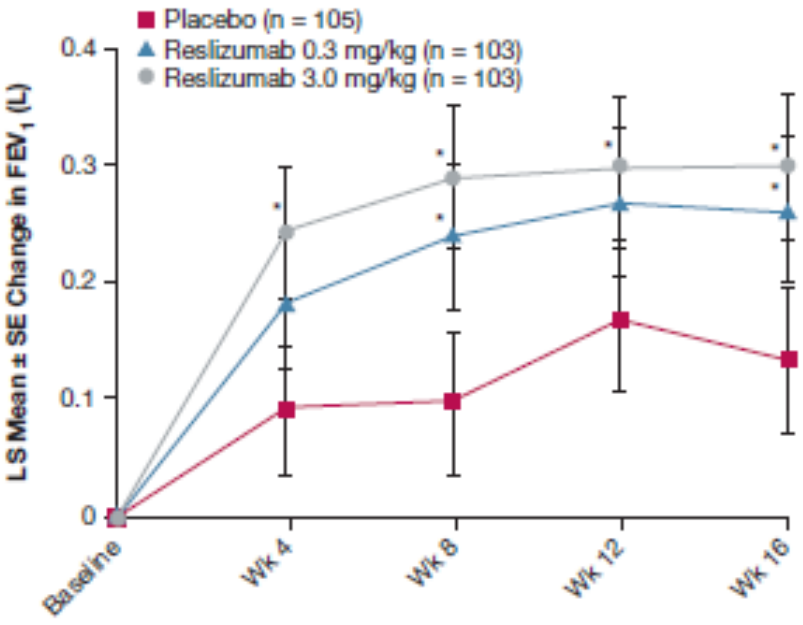
Benralizumab 30 mg, every 4 wk	72	70	70	69	69	68	66	68
Benralizumab 30 mg, every 8 wk	70	72	67	69	69	66	69	68
Placebo	74	75	73	74	74	73	73	72

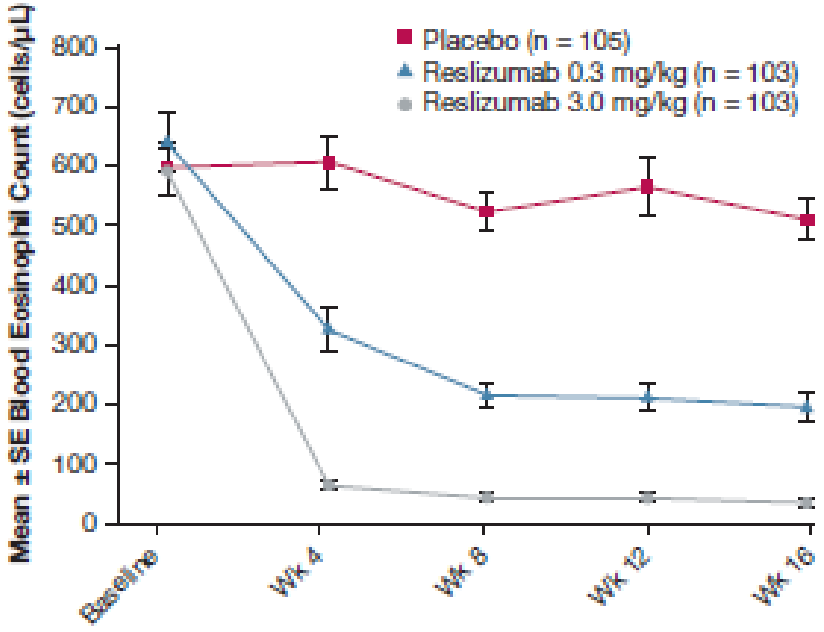
New Engl J Med 2017



Mario Castro et al. Lancet Resp Med 2015

Reslizumab for Inadequately Controlled Asthma with Elevated Blood Eosinophil Levels

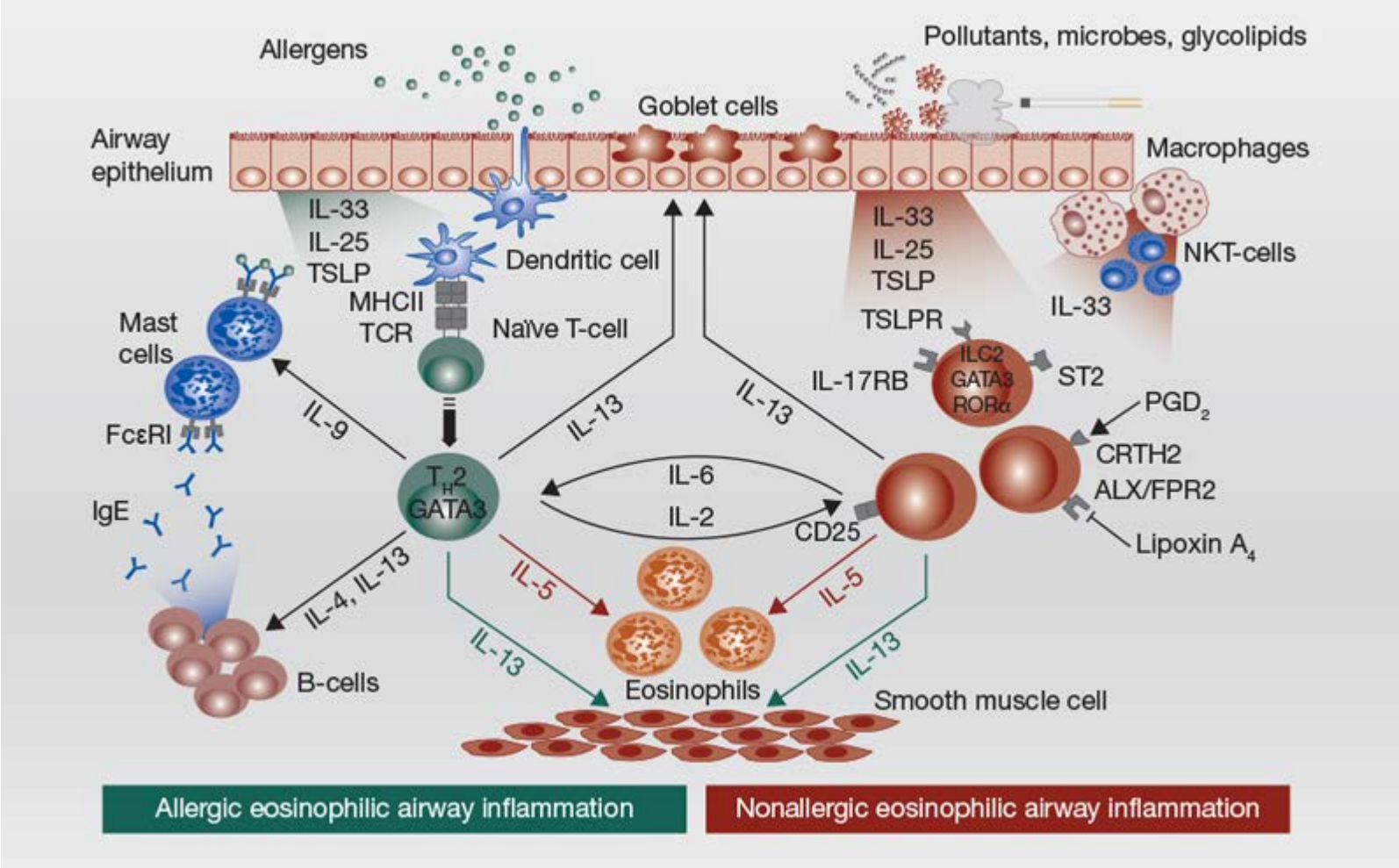




blood eosinophil levels > 400 cells/µL.

Bjermer L, et al. Chest 2016

Multiple mediators contribute to eosinophilic (Type 2) airway inflammation



De Groot JC. ERJ Open Research 2015

T cell cytokines are key mediators of eosinophilia in patients with asthma

Cytokine	Effect
IL-4	• Increases production of IgE • Increases number of T_H2 cells
IL-5	• Stimulates bone marrow production • Increases number of eosinophils
IL-9	• Increases number of mast cells
IL-13 (from T cells, mast cells, basophils, and eosinophils)	• Increases production of IgE • Induces airway remodelling
IL-17	• Increases neutrophil number • Induces production of cytokines by airway epithelium

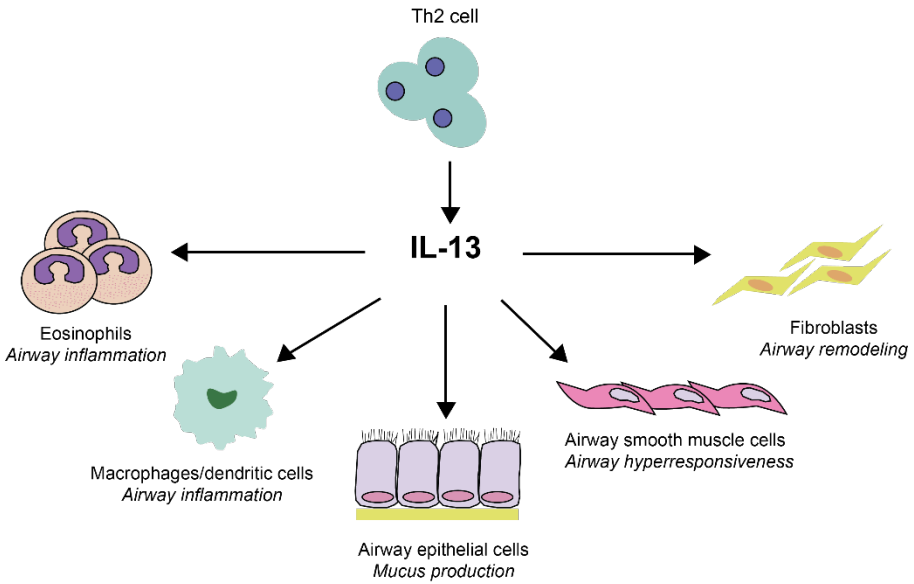
IL-4, IL-5, and IL-13 induce eosinophilia and are key drivers of airway inflammation

Parulekar AD, et al. Curr Opinion Pulm Med 2016

IL-13: A central mediator in asthma

The pleiotropic cytokine IL-13 is a central mediator implicated in the key pathological features of asthma[1]

- Promotes airway hyperresponsiveness in humans and animals[2–5]
- Smooth-muscle proliferation *in-vitro* and in animals[4,6–8]
- Increased mucus production in humans, *in-vitro*, and in animals[2,4,9,10]



IL-13 shares some of the same functions as IL-4; however, only IL-13 stimulates subepithelial fibrosis and directly induces airway hyperresponsiveness independent of IgE and eosinophils[11]

1. Corren J. Curr Allergy Asthma Rep 2013;13:415–420; 2. Grünig G, et al. Science 1998;282:2261–2263; 3. Chiba Y, et al. Am J Respir Cell Mol Biol 2009; 40:159–167; 4. Zhu Z, et al. J Clin Invest 1999;103:779–788; 5. Gauvreau GM, et al. Am J Respir Crit Care Med 2011; 183: 1007–1014; 6. Chiba Y, et al. Pharmacol Rep 2012;64:454–458; 7. Bossé Y, et al. Int Arch Allergy Immunol 2008;146:138–148; 8. Bansal G, et al. Free Radic Biol Med 2012;52:1552–1559; 9. Kondo M, et al. Allergol Int 2006;55:329–336; 10. Alevy Y, et al. J Clin Invest 2012;122:4555–4568; 11. Corren J. Curr Opin Pulm Med 2011;17:29–33

Periostin as a biomarker for IL-13

Periostin (encoded by *POSTN*) is a matricellular protein belonging to the fasciclin family[1]

Periostin may play a key role in asthma pathophysiology:

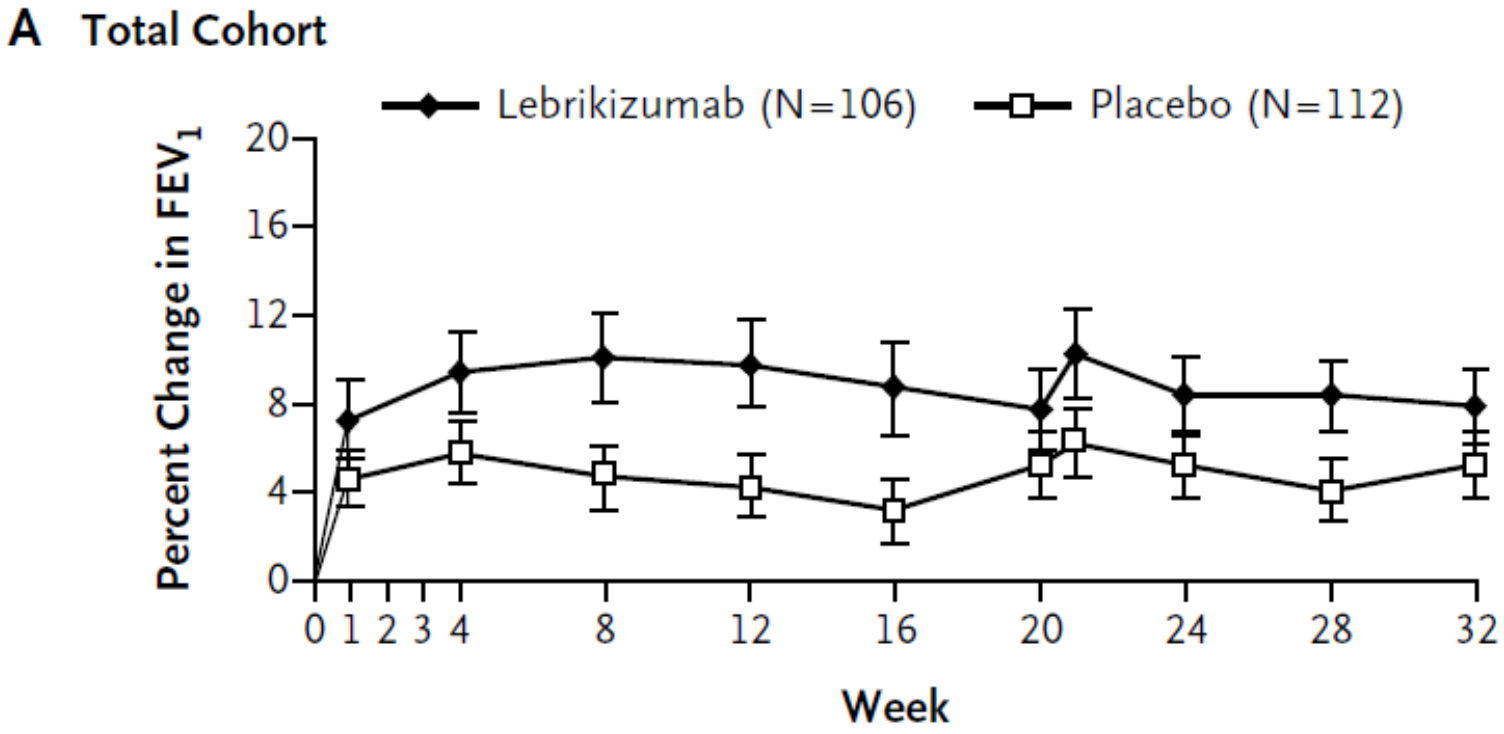
- Periostin may promote airway pathological changes in response to Th2 cytokines[2,3]
- Periostin secretion by bronchial epithelial cells induced by IL-13[2–5]
  - Serum periostin levels may reflect IL-13 pathway activation[2,6,7]
  - Serum periostin levels may predict response to tralokinumab[7]

Periostin is measured using a simple blood test[7]

Current Phase 3 studies will determine the relative predictive value of periostin for response to tralokinumab in asthma[8,9]

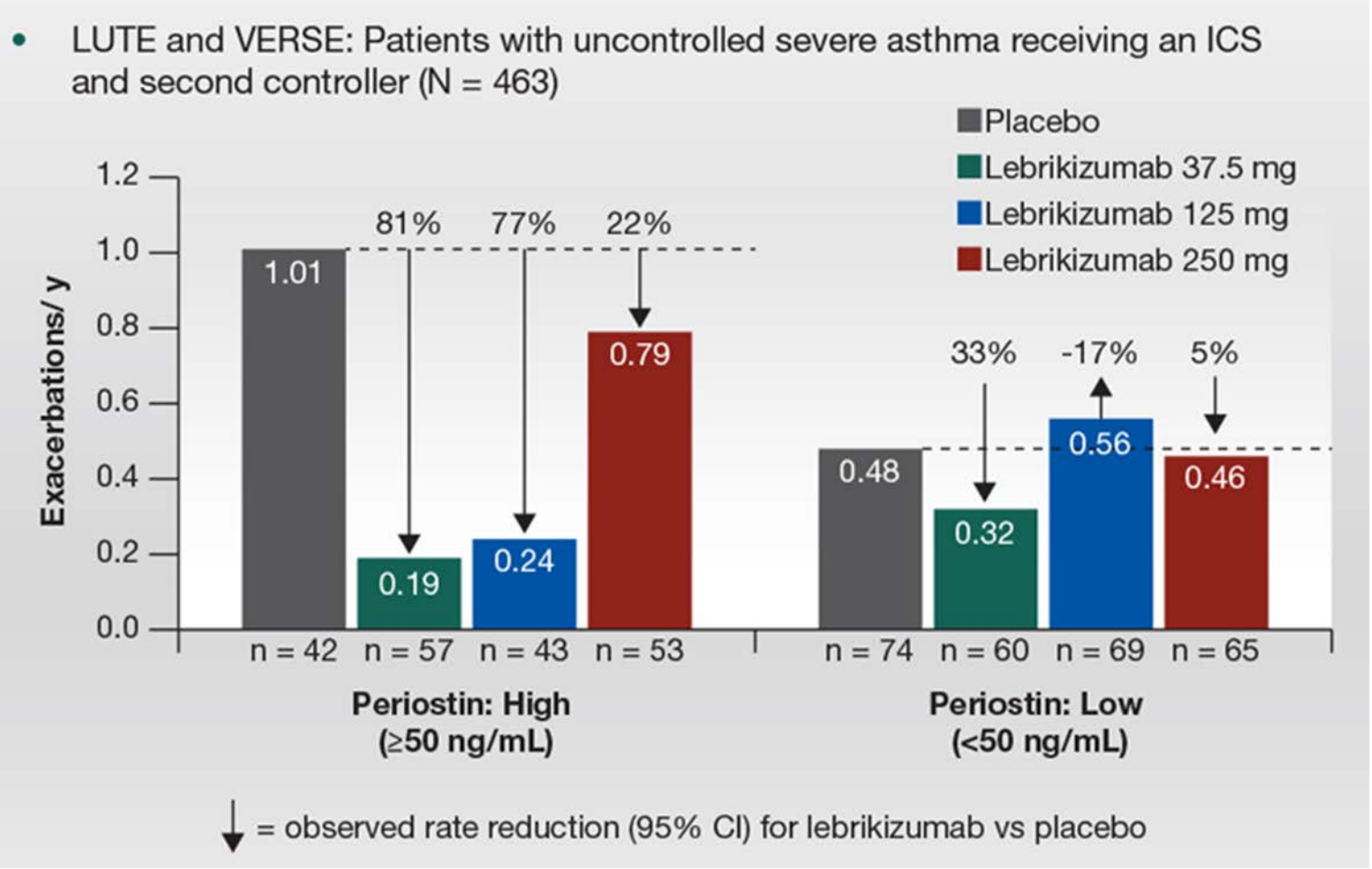
1. Hamilton DW. J Cell Commun Signal 2008;2: 9–17; 2. Woodruff P, et al. Proc Natl Acad Sci U S A 2007;104:15858–15863; 3. Jia G, et al. J Allergy Clin Immunol 2012;130:647–654; 4. Sidhu SS, et al. Proc Natl Acad Sci U S A 2010;107:14170–14175; 5. Corren J. Curr Allergy Asthma Rep 2013;13:415–420; 6. Piper E, et al. Eur Respir J 2013;41:330–338; 7. Brightling CE, et al. Am J Respir Crit Care Med 2014;189:A6670; 8. http://clinicaltrials.gov/show/NCT02161757, accessed July 25, 2014; 9. http://clinicaltrials.gov/show/NCT02194699, accessed July 25, 2014

Anti-IL-13 lebrikizumab in severe asthma



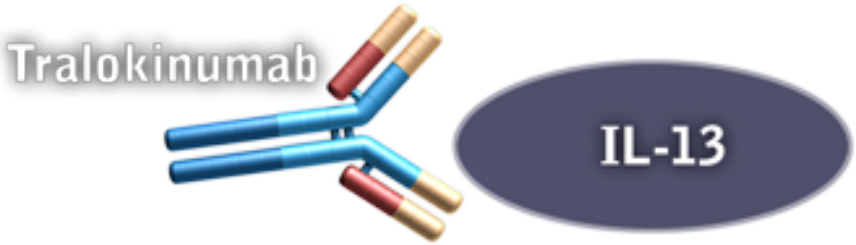
Corren J. et al, NEJM 2011; 1088-98.

Lebrikizumab in moderate-to-severe asthma: pooled data from two randomised placebo-controlled studies



Hanania NA, et al. Thorax 2015;70:748–756

Overview Tralokinumab



- An investigational human monoclonal antibody that specifically binds to IL-13 to prevent its interaction with the IL-13 receptor[1]
- In development in asthma as a q2w SC formulation[2]
- In Phase 3 development for asthma and Phase 2 for the treatment of idiopathic pulmonary fibrosis

May R, et al. Br J Pharmacol 2012;166:177–193

Treatments Targeting IL-13: Lebrikizumab and Tralokinumab

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

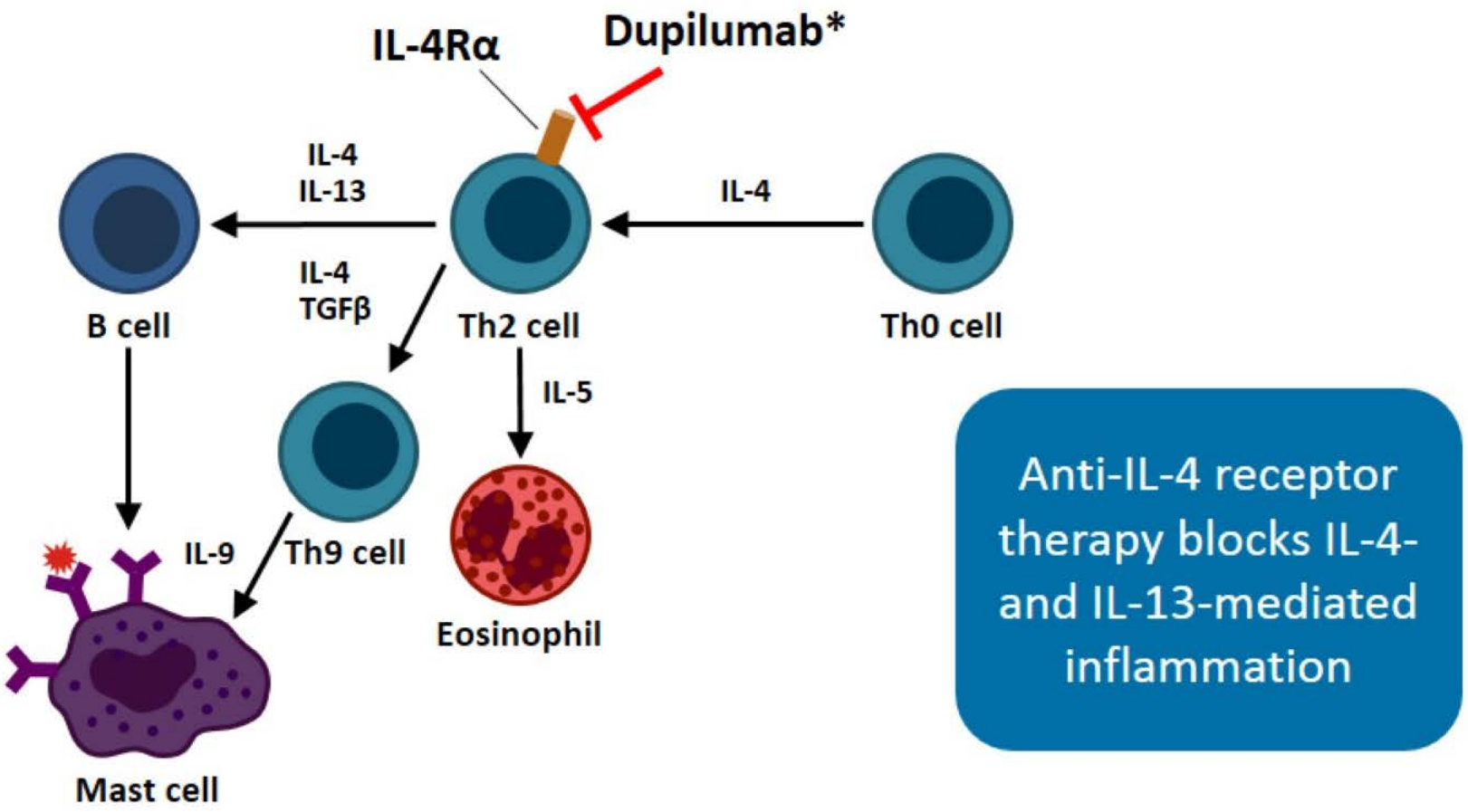
Nicola A Hanania, Phillip Korenblat, Kenneth R Chapman, Eric D Bateman, Petr Kopecky, Pierluigi Paggiaro, Akihito Yokoyama, Julie Olsson, Sarah Gray, Cecile T J Holweg, Mark Eisner, Charles Asare, Saloumeh K Fischer, Kun Peng, Wendy S Putnam, John G Matthews

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

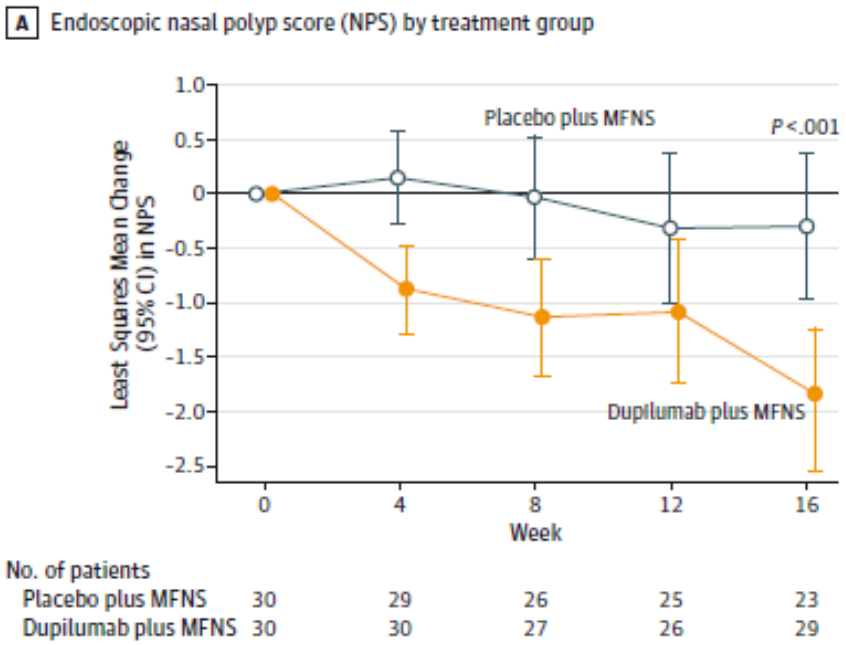
No consistent significant reduction in asthma exacerbations[1,2]

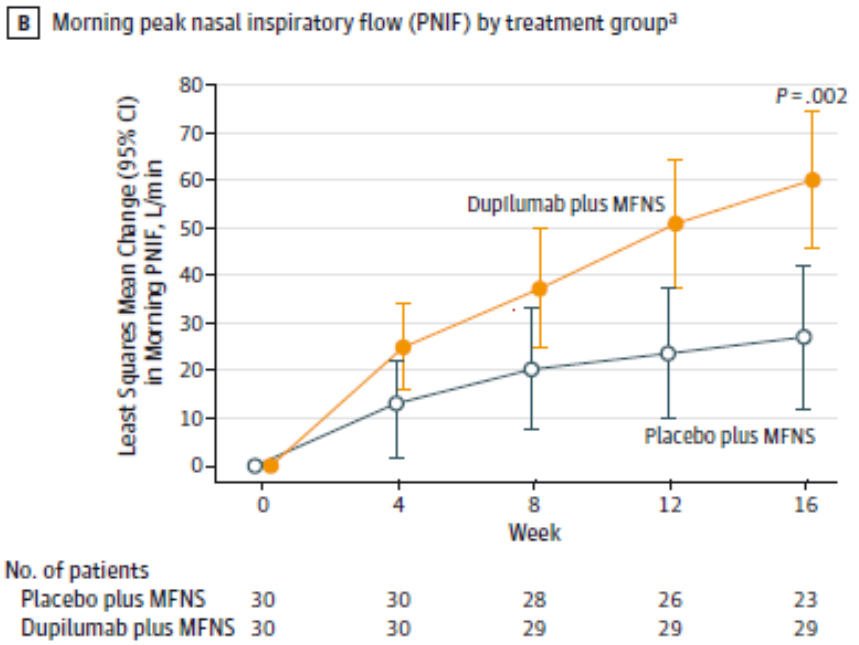
Anti IL-4/IL-13 Therapy



Hambly N, et al. Curr Opinion Pulm Med 2014

Effect of Subcutaneous Dupilumab on Nasal Polyp Burden in Patients With Chronic Sinusitis and Nasal Polyposis



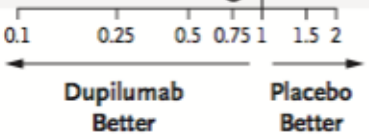


Bachert C, et al. JAMA 2016

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

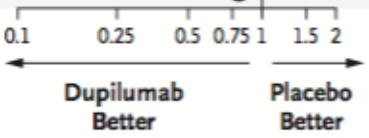
A Dupilumab, 200 mg Every 2 Wk, vs. Matched Placebo

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)



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)



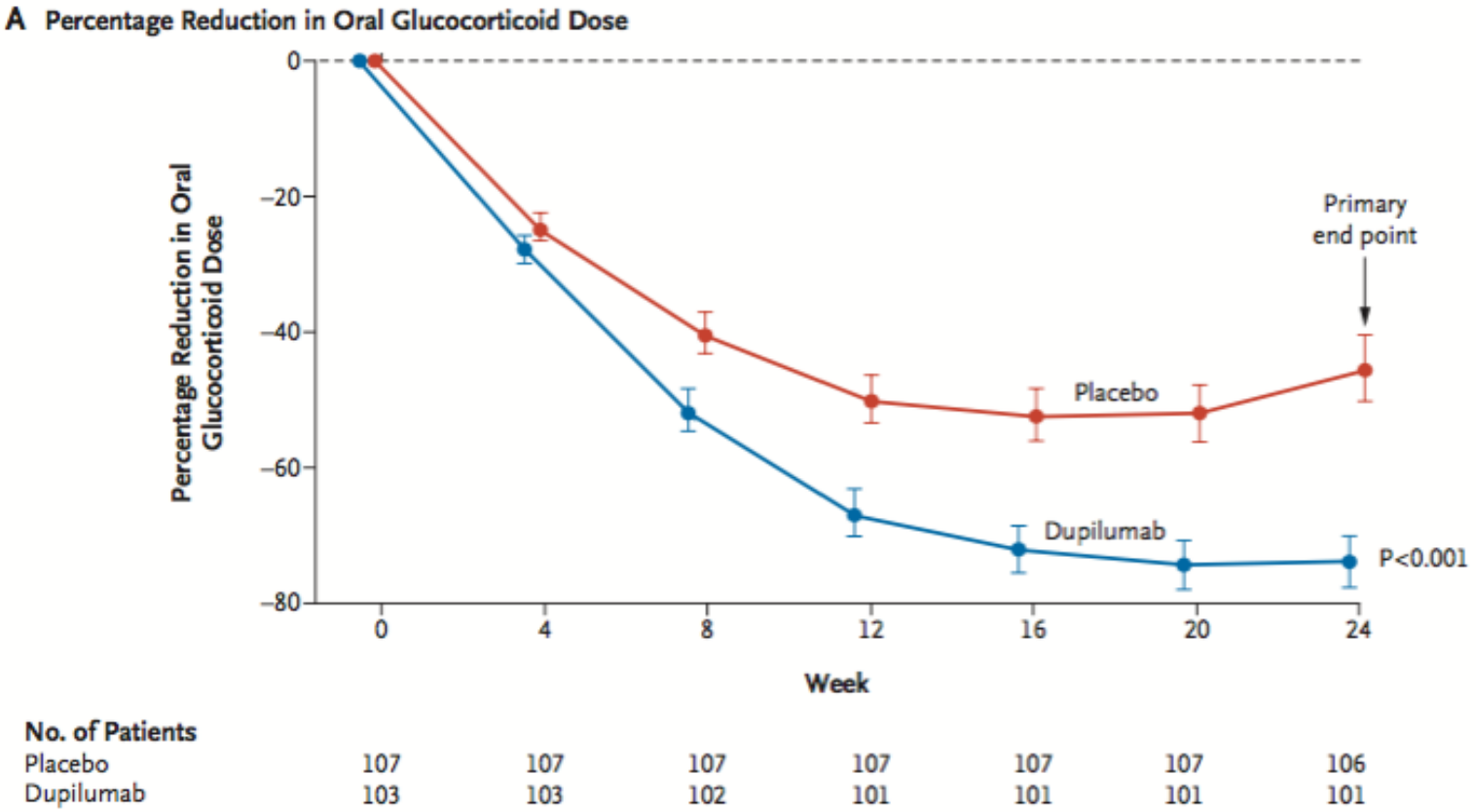
Castro M, et al. New Engl J Med 2018

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

Most of the observed elevations in eosinophil counts were laboratory findings without clinical consequences or associated adverse events. The increase in blood eosinophil counts is consistent with the hypothesis that dupilumab blocks interleukin-4 and interleukin-13 function in eosinophil survival, activation, and recruitment to tissues but not egress from bone marrow, which is influenced by interleukin-5. As a result, it has been speculated that initial treatment with dupilumab may result in a transient increase in circulating blood eosinophil counts.[20]

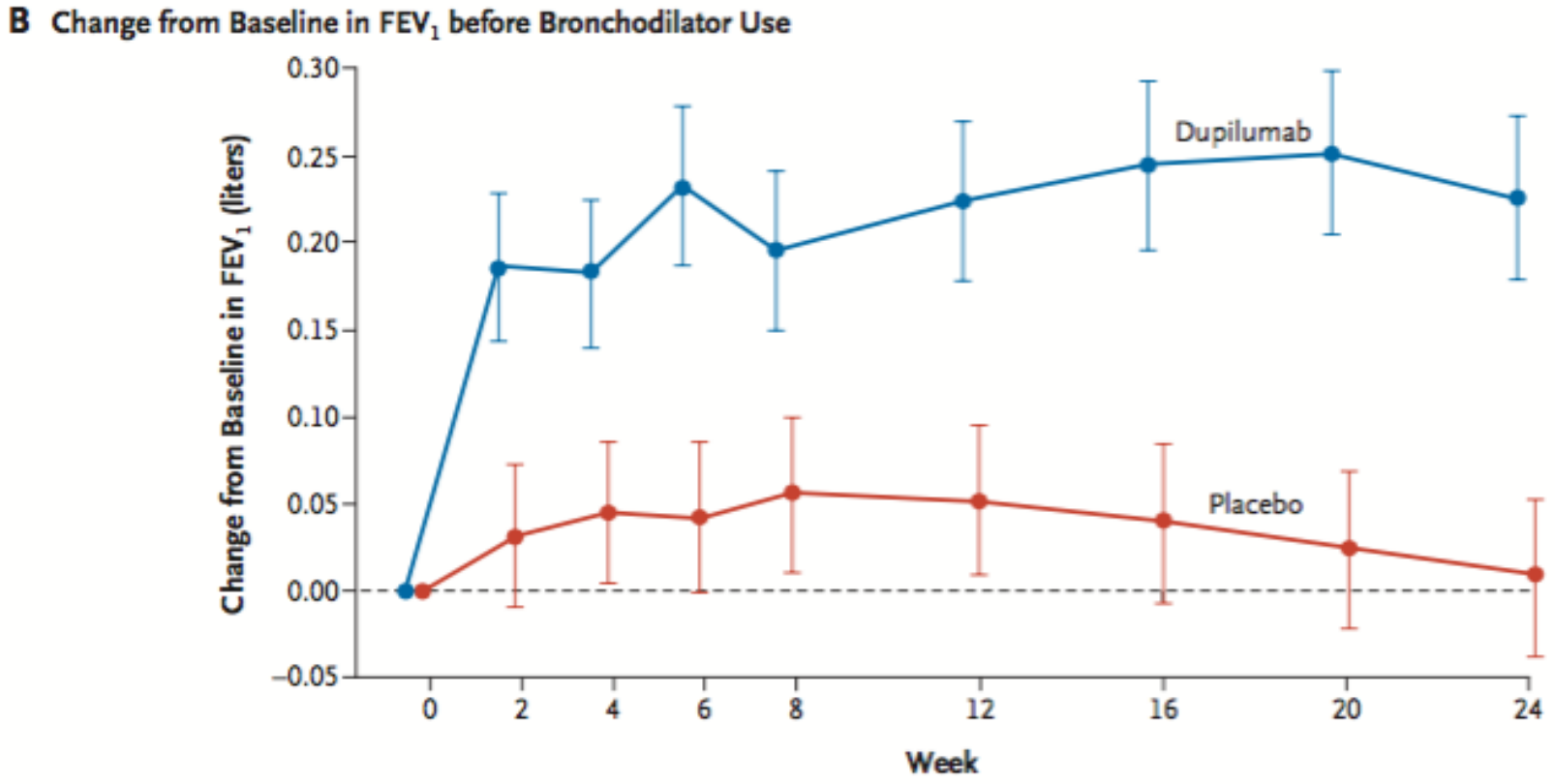
Castro M, et al. New Engl J Med 2018

Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma



Rabe K, et al. New England J Med 2018

Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma



Rabe K, et al. New England J Med 2018

Which Biologic? IL-5–Targeting Therapy

Which Patient?

- Raised blood eosinophil count
- Frequent exacerbations

Agent	IL-5 mAb		IL-5 Rα
	Mepolizumab[1]	Reslizumab[2]	Benralizumab[3-5,a]
Efficacy	← Broadly similar effects[1-4] →		
			More acute depletion of eosinophils[5]
Dosing	SC Q4W	IV Q4W	SC Q4W or Q8W

[a] Not approved for use as of June 2017.

Reference(s): 1. Ortega HG et al; MENSA Investigators. *N Engl J Med*. 2014;371:1198-1207.
2. Castro M et al. *Lancet Respir Med.* 2015;3:355-366.
3. FitzGerald JM et al; CALIMA Study Investigators. *Lancet.* 2016;388:2128-2141.
4. Bleecker ER et al; SIROCCO Study Investigators. *Lancet.* 2016;388:2115-2127.
5. Tan LD et al. *J Asthma Allergy.* 2016;9:71-81.

Which Biologic? Anti-IgE Therapy

Which Patient?
- Allergy-based asthma
- Blood eosinophils not necessarily raised

Agent	Omalizumab	
Efficacy	Despite no head-to-head studies, seems to be less effective against exacerbations than IL-5–targeting therapies[1-5]	
Safety	Good safety profile[6]	
Dosing	SC Q2W or Q4W; Based on IgE levels and body weight	Narrow patient population due to dosing restrictions

Reference(s): 1. Ortega HG et al; MENSA Investigators. *N Engl J Med.* 2014;371:1198-1207.
2. Castro M et al. *Lancet Respir Med.* 2015;3:355-366.
3. FitzGerald JM et al; CALIMA Study Investigators. *Lancet.* 2016;388:2128-2141.
4. Bleecker ER et al; SIROCCO Study Investigators. *Lancet.* 2016;388:2115-2127.
5. Busse W et al. *J Allergy Clin Immunol*. 2001;108:184-190.
6. Abraham I et al. *Allergy*. 2016;71:593-610.

Conclusioni

1.Gli anticorpi monoclonali sono un approccio versatile e promettente

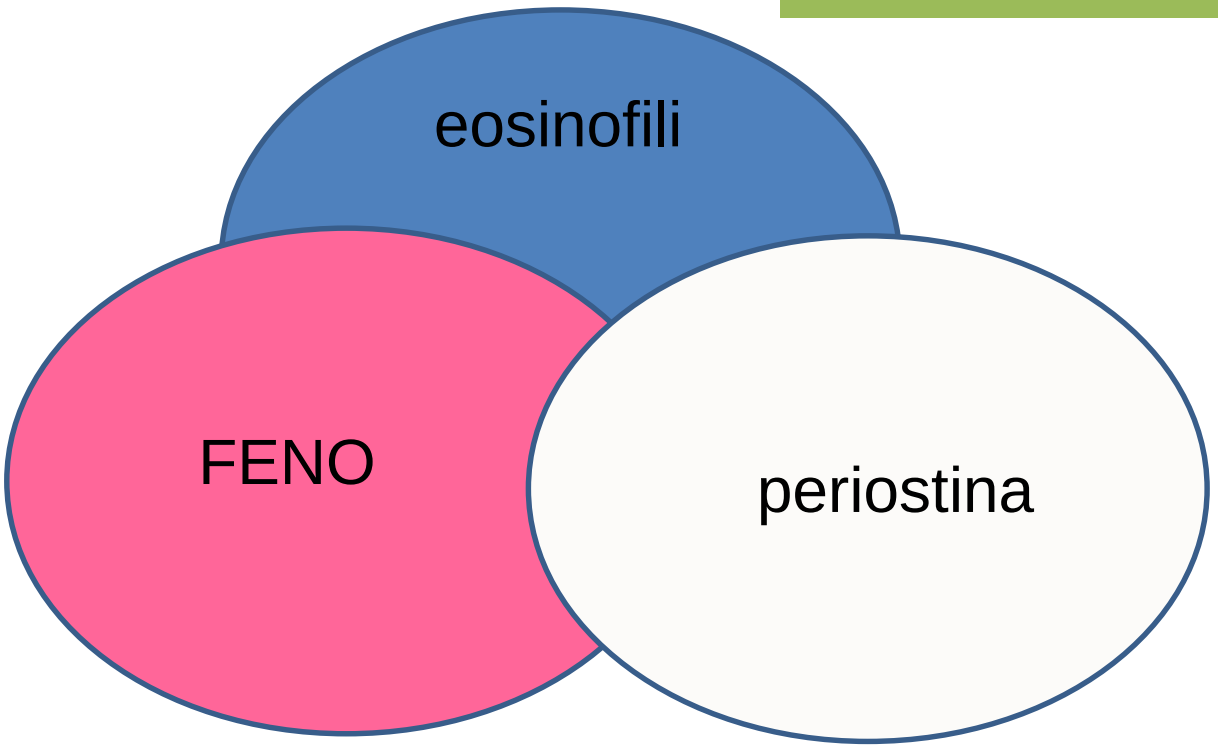
2.I trial sino ad ora conclusi hanno dimostrato un buon profilo di tollerabilità

3.I mediatori e le citochine hanno azioni largamente overlapping: il blocco selettivo di uno di essi è spesso clinicamente poco rilevante.

4.I “biologici” sono il paradigma della terapia fenotipo-orientata

Overlap dei biomarcatori di Tipo 2: qual è il miglior approccio ?

- Abbiamo bisogno di tutti i marcatori ?
- Qual è il miglior biomarcatore ?
- E' più utile un biomarcatore composito ?



Come determinare se il Paziente ha realmente asma refrattaria al trattamento

Paziente non controllato con una alta dose di ICS

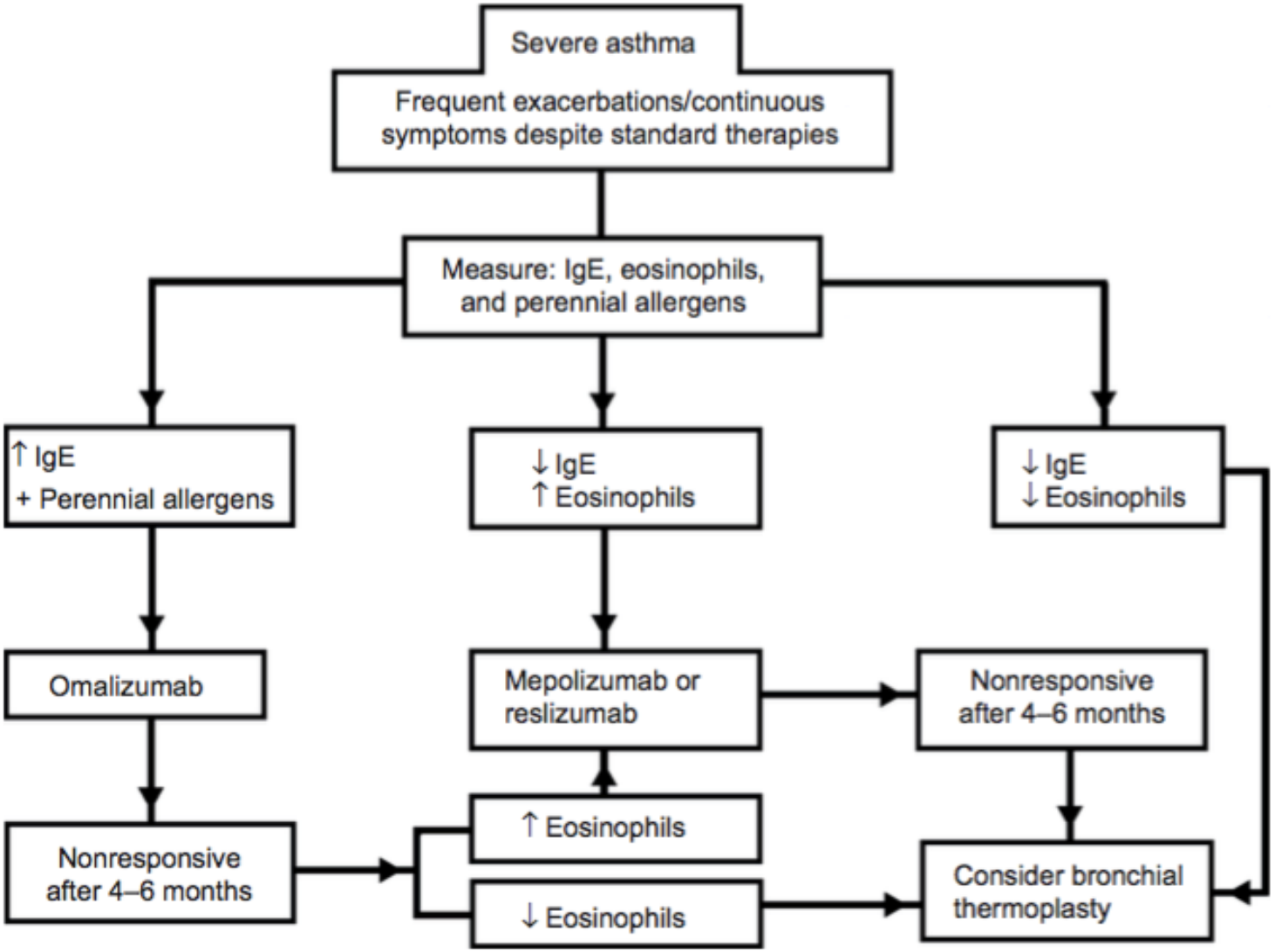
Verifica le comorbidità

Assicurati che abbia una buona:

- Aderenza ai farmaci
- Tecnica inalatoria
- Conoscenza della malattia

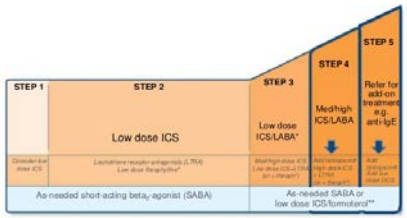
Verifica Biomarcatori che possono guidare il trattamento:

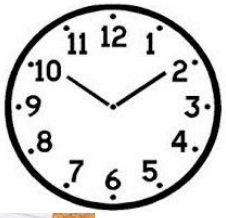
- IgE
- Eosinofili
- FENO



Maselli DJ, et al. J of Asthma 2016

Il Paziente ideale per un biologico





Ossido nitrico eosinofili

GINA step 4 o step 5

aderente al trattamento

appropriato profilo del biomarcatore

Ricorrenti esacerbazioni