

# ***Il Futuro della Medicina Personalizzata: Nuove Evidenze e Prospettive Future***

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**SOD IMMUNOALLERGOLOGIA  
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**XXX CONGRESSO NAZIONALE S.I.A.A.I.C.  
6-9 APRILE 2017 - FIRENZE**

# Asthma Treatment: Concepts evolution

**BIOLOGICAL AGENTS**  
(Anti-IgE; anti-IL-5)

«Precision Medicine»

**PHENOTYPE**

«One size fit all»

Ongoing therapy; extrafine ICS

**DISTAL  
INFLAMMATION**

CCS/LABA  
Anti-leukotrienes

**ONGOING  
INFLAMMATION**

Inhaled CSS as  
«Cornestone»  
treatment

**REMODELING**

Short-acting  
B2 agonists

**INFLAMMATION**

**BRONCHOSPASM**

1975

1980

1990

2000

2010



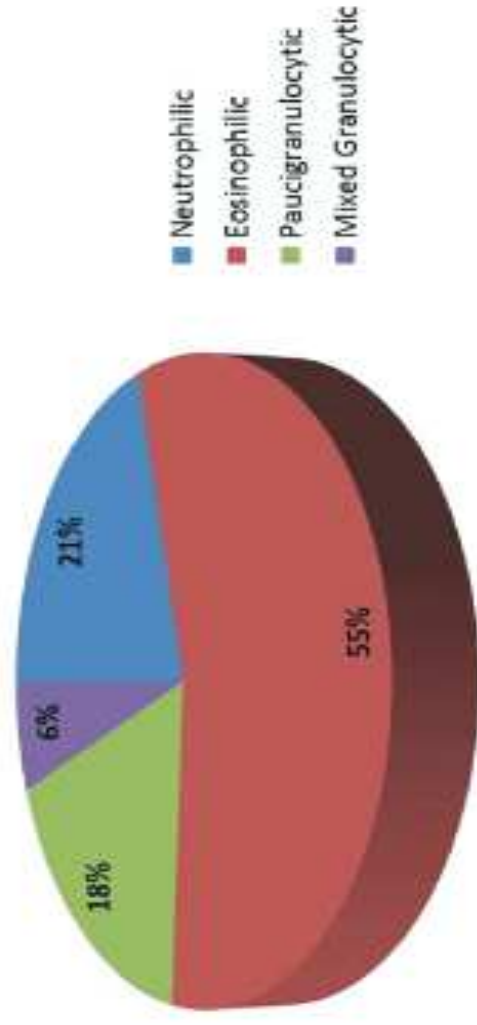
**Why should we use an anti-eosinophilic  
strategy in severe asthma ?**

# Heterogeneity of phenotypes in severe asthmatics. The Belgian Severe Asthma Registry (BSAR)

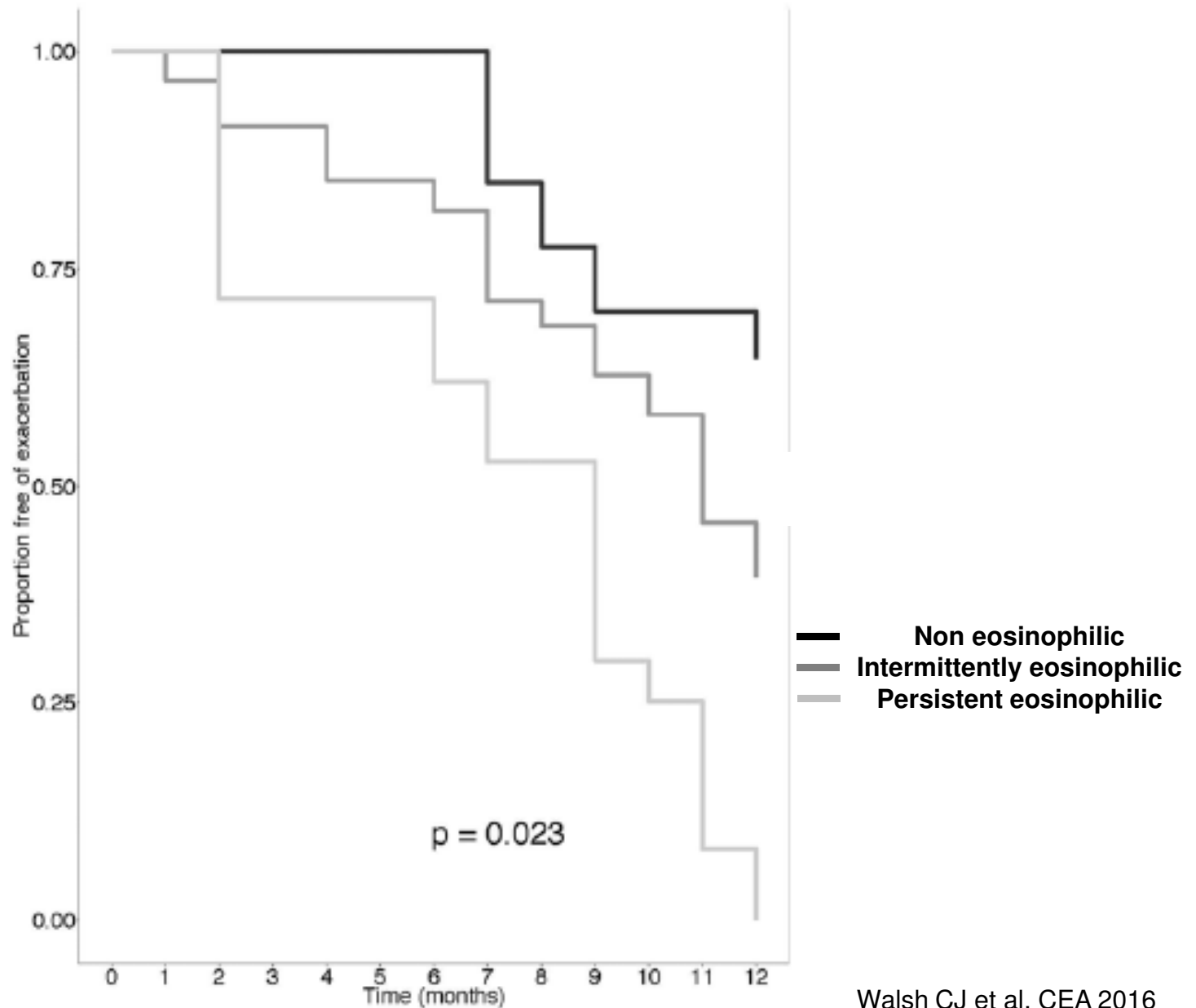
F. Schleich <sup>a,\*</sup>, G. Brusselle <sup>b</sup>, R. Louis <sup>a</sup>, O. Vandenplas <sup>c</sup>,  
A. Michils <sup>d</sup>, C. Pilette <sup>e</sup>, R. Peche <sup>f</sup>, M. Manise <sup>a</sup>, G. Joos <sup>b</sup>



Inflammatory Phenotypes

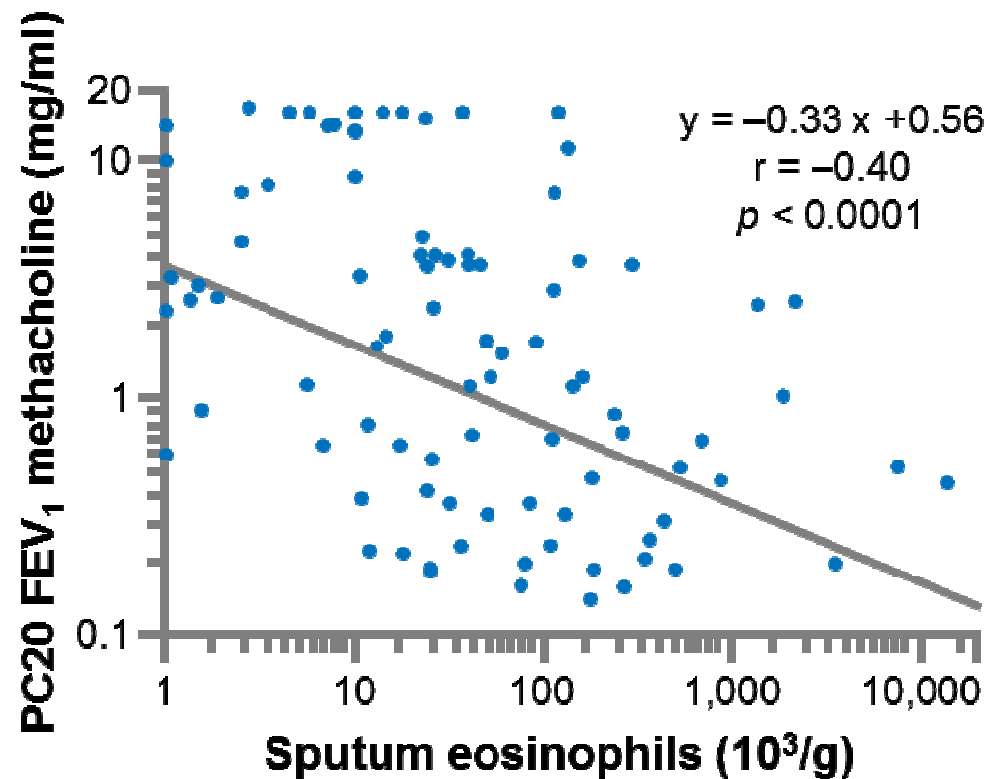


# Exacerbation risk in severe asthma is stratified by inflammatory phenotype using Longitudinal measures of sputum eosinophils.

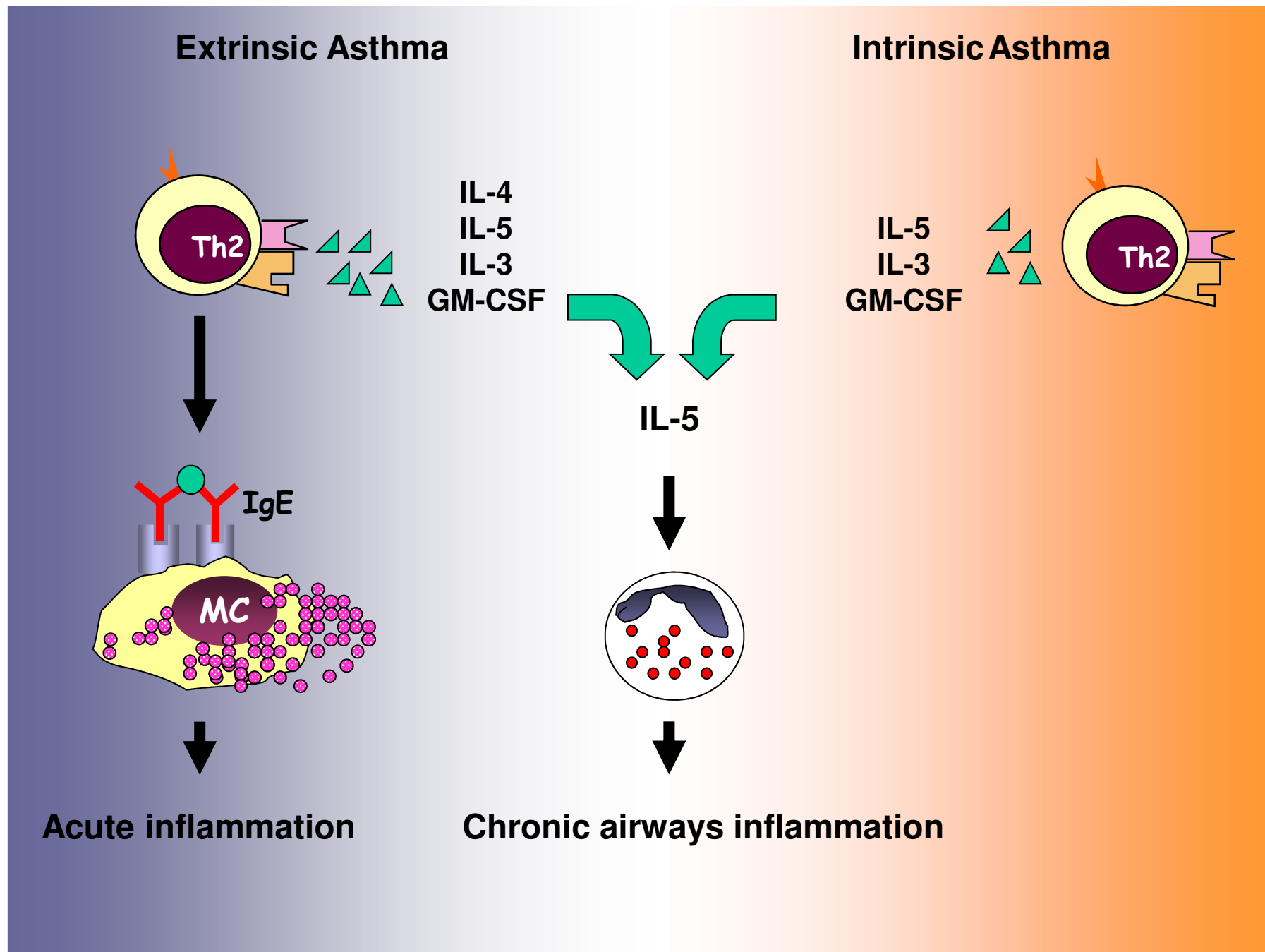


# Lung eosinophils and impaired lung function

Elevated sputum eosinophil counts are associated with decreased lung function (FEV<sub>1</sub>) assessed by bronchial hyperresponsiveness tests<sup>1</sup>

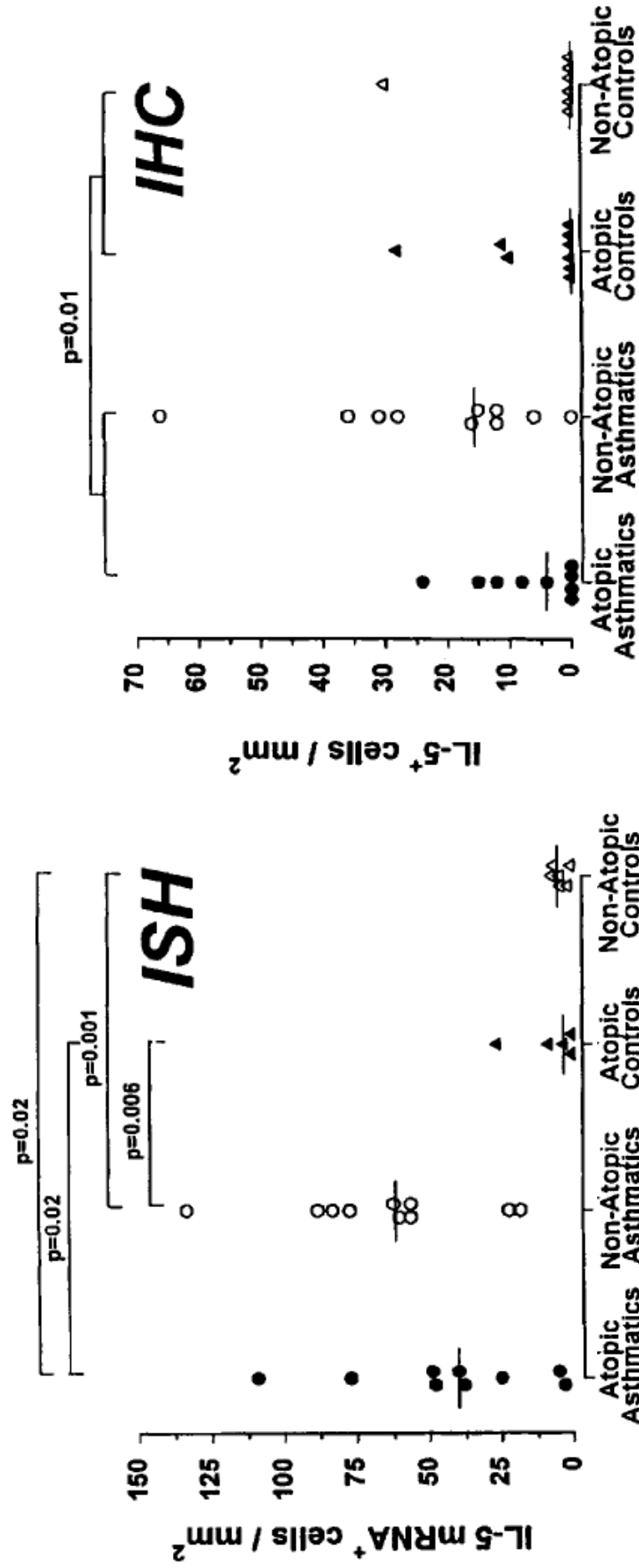


FEV<sub>1</sub> = forced expiratory volume in 1 second.  
1. Louis R, *et al. Allergy* 2002; 57:907-912.

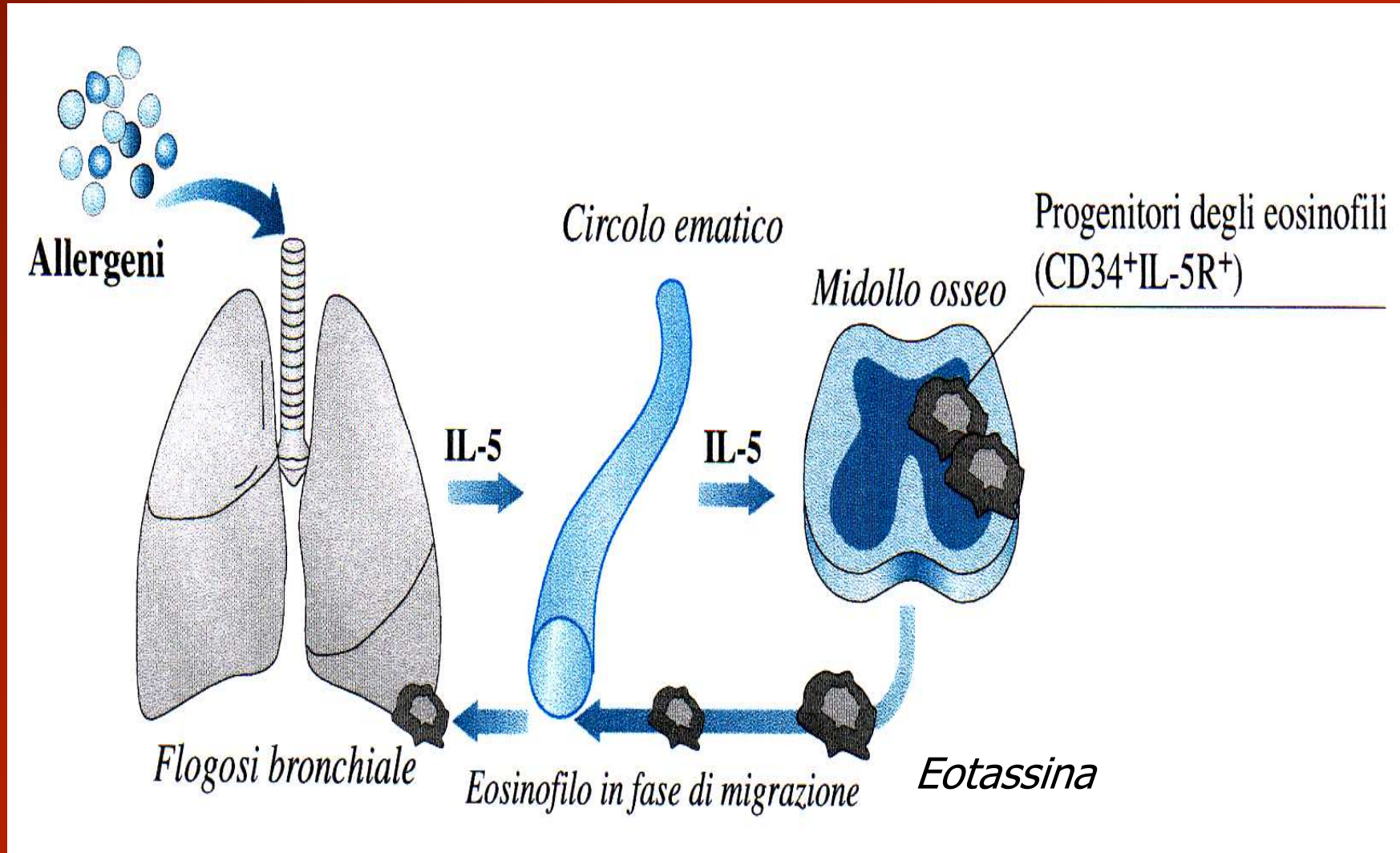




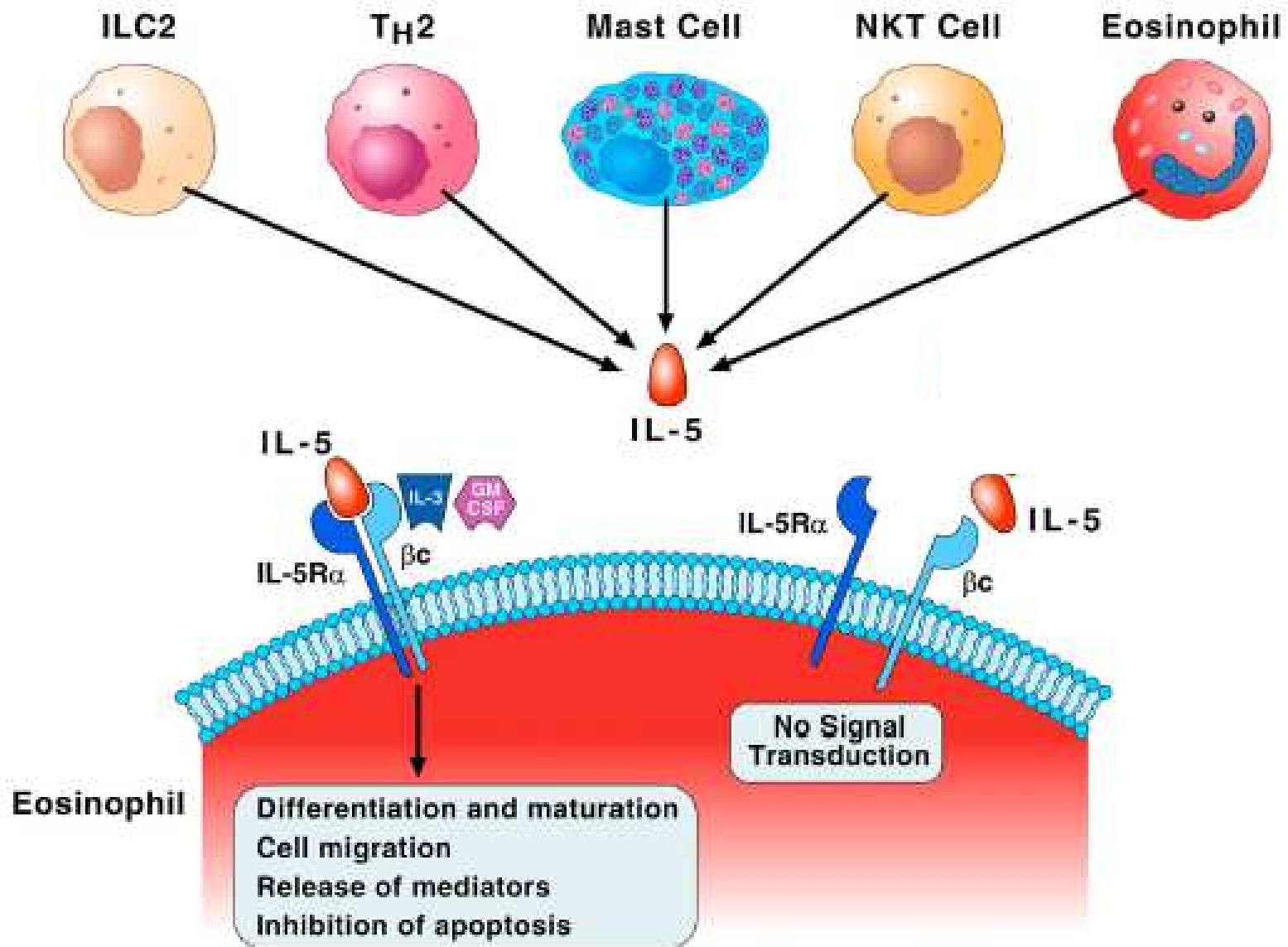
# IL-4 and IL-5 mRNA and Protein in Bronchial Biopsies from Patients with Atopic and Nonatopic Asthma: Evidence Against "Intrinsic" Asthma Being a Distinct Immunopathologic Entity



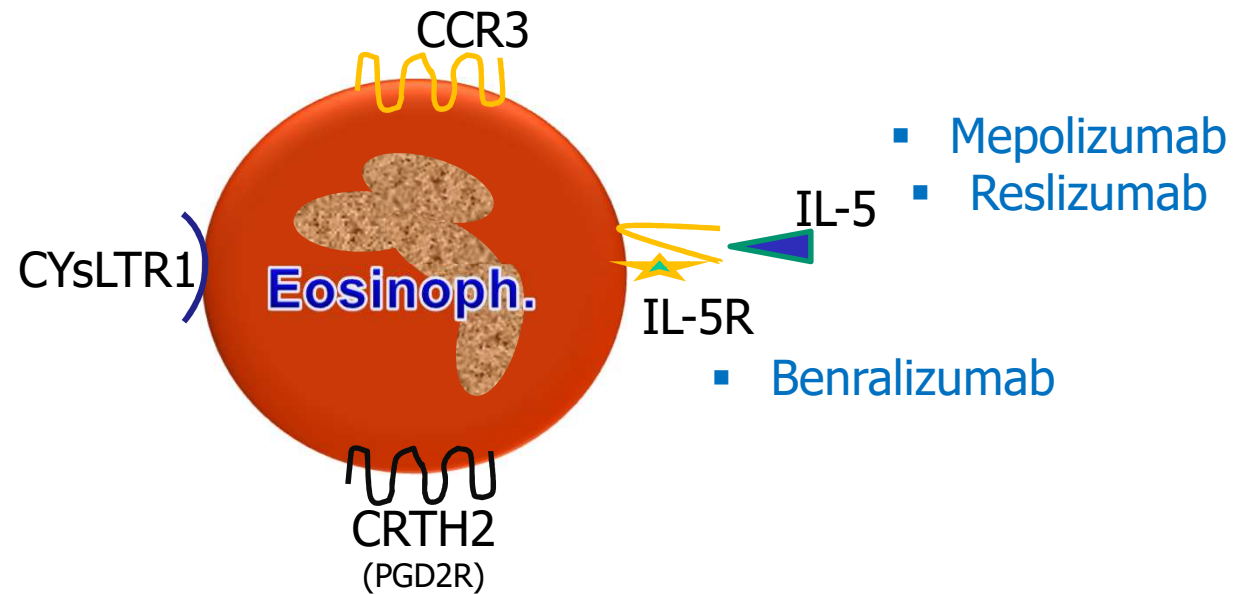
# MIGRAZIONE POLMONARE DEGLI EOSINOFILI



# SEVERAL CELLS PRODUCE IL-5

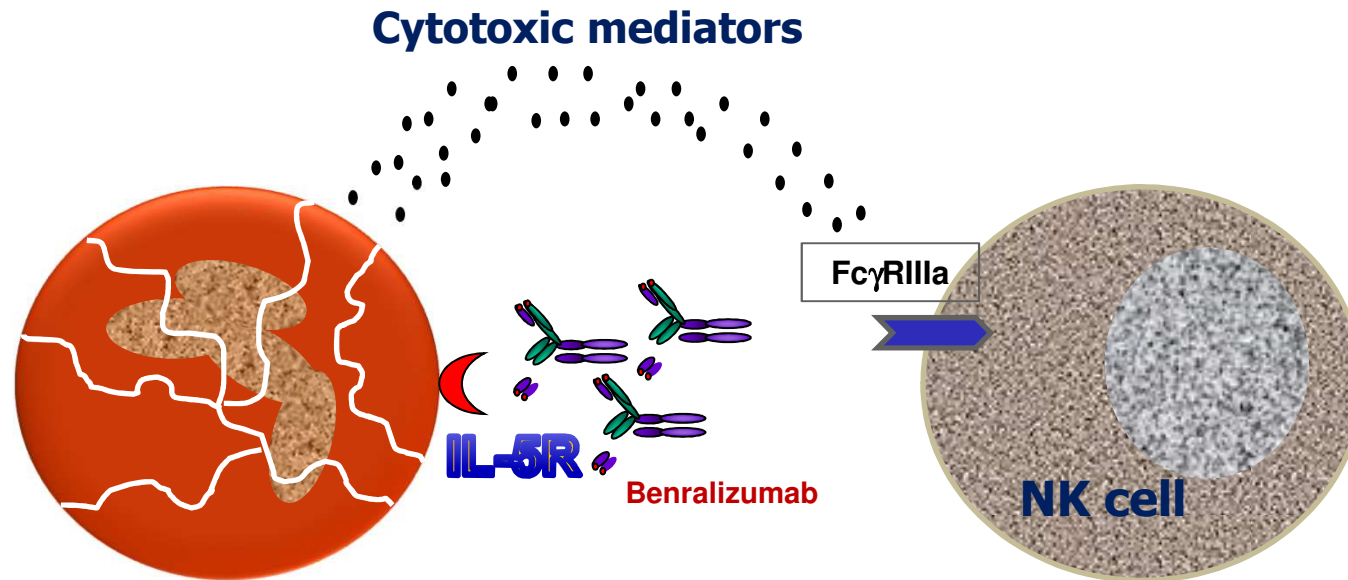


# EOSINOPHIL (IL-5 PATHWAY) AS TARGET



# IL-5-receptor: A KEY TARGET

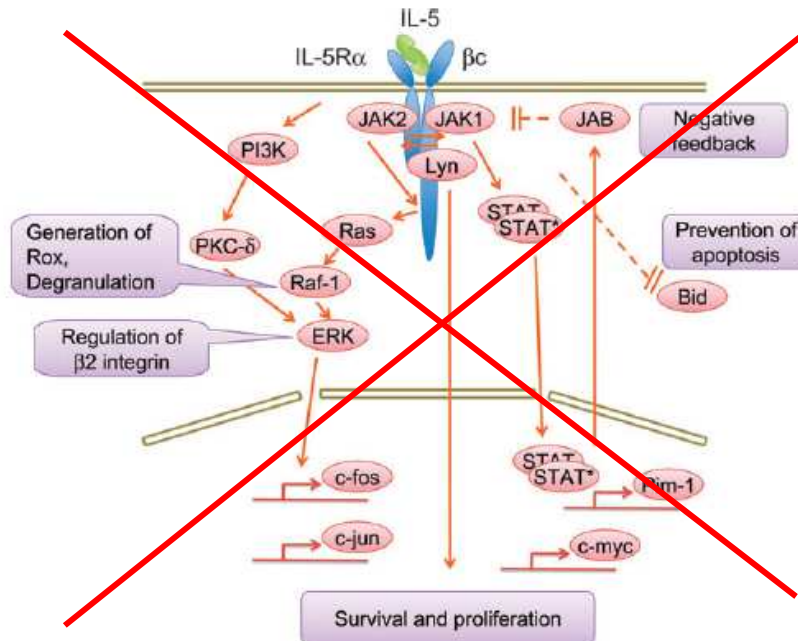
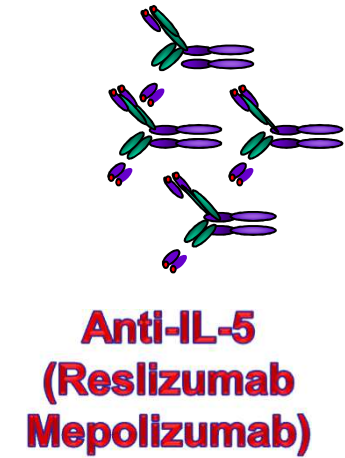
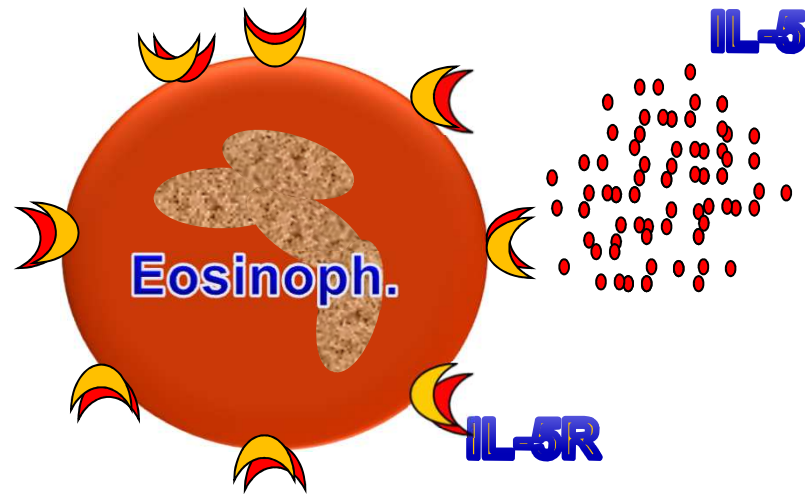
**BENRALIZUMAB: IgG1k anti-IL-5R $\alpha$  chain**



## Mechanisms of action:

- Neutralizing activity of IL-5 by blocking IL-5-receptor
- Eosinophil/basophil apoptosis (ADCC) not inducing degranulation
- Low expression of IL-5R do not abrogate ADCC

# IL-5: TARGET FOR BIOLOGICAL AGENTS



**How can we identify a candidate  
for anti-IL-5 treatment ?**

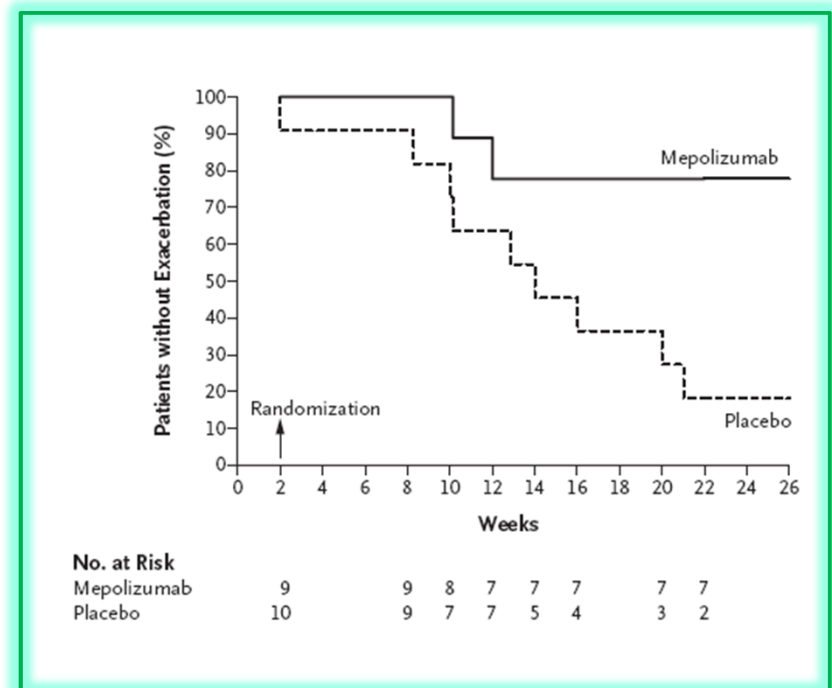
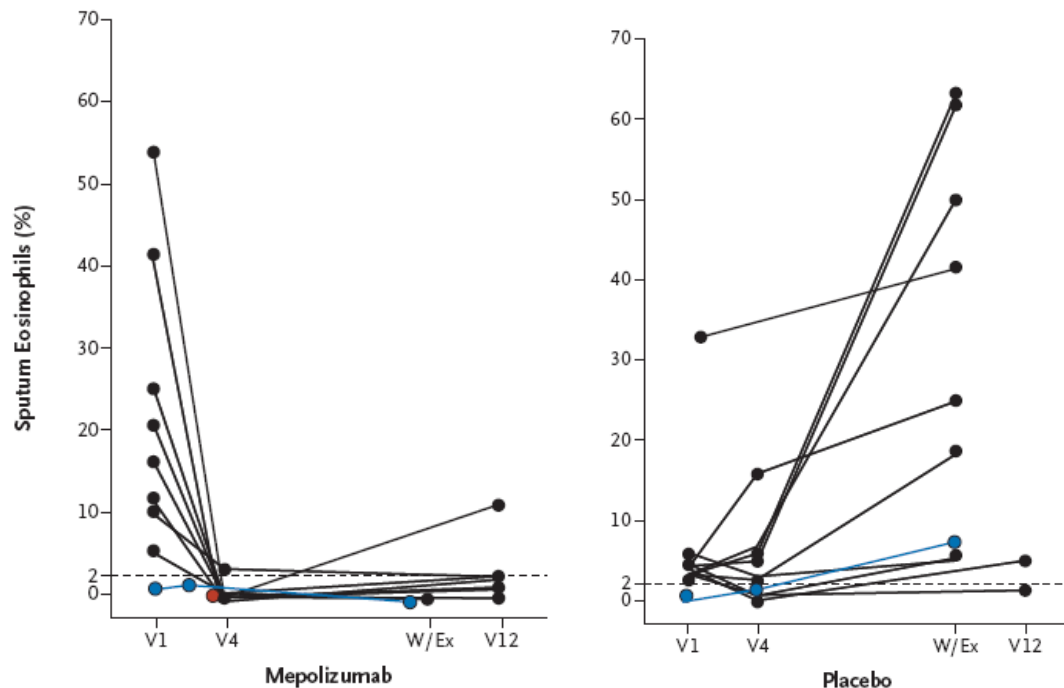


**What is the real eosinophilic phenotype ?**



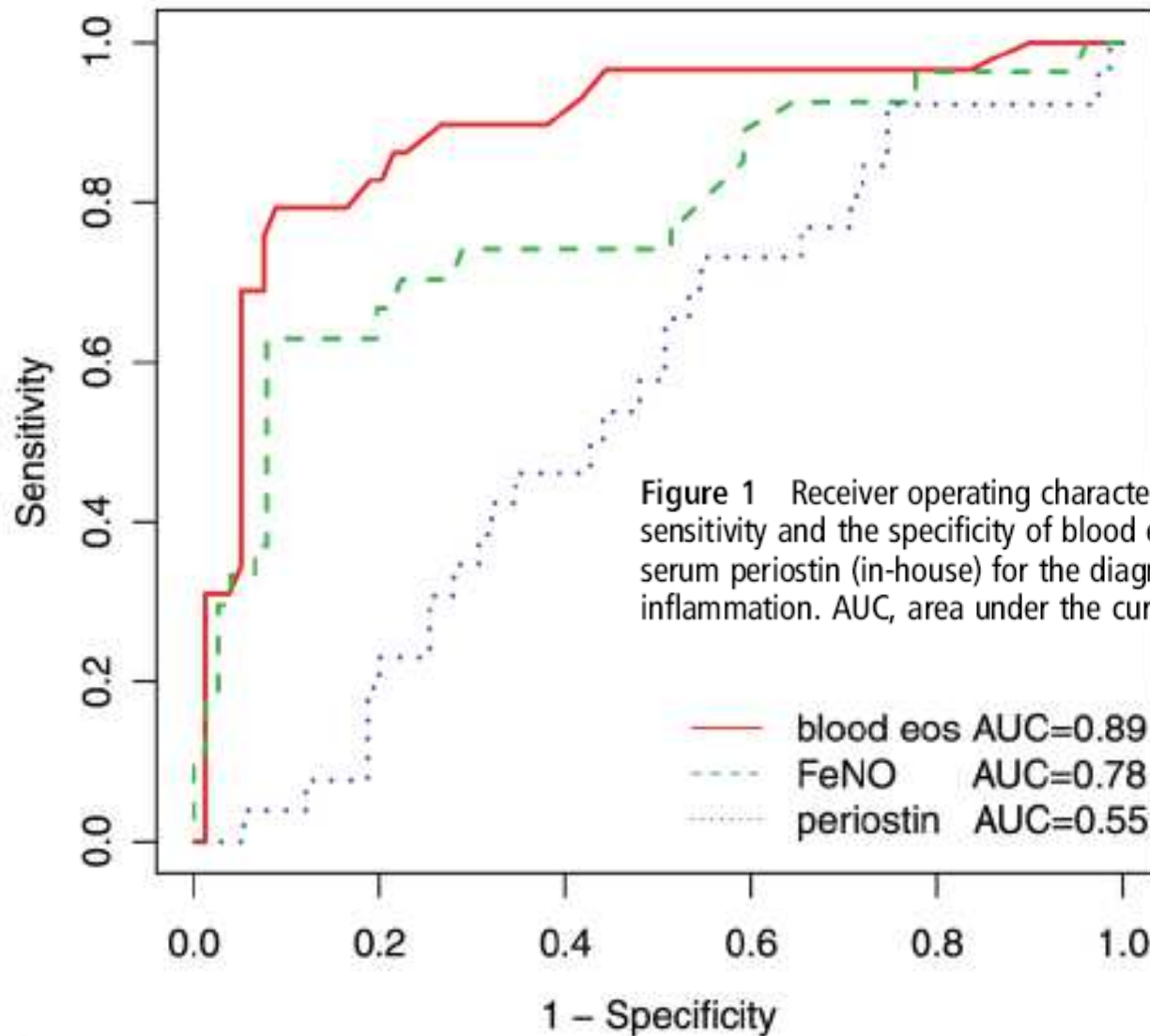
# Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia

Parameswaran Nair, M.D., Ph.D., Marcia M.M. Pizzichini, M.D., Ph.D., et al.





# Sensitivity and Specificity (ROC Curve) of Different Biomarkers for the Diagnosis of Eosinophilic Inflammation



**Figure 1** Receiver operating characteristics curve analyses of the sensitivity and the specificity of blood eosinophils (eos),  $FE_{NO}$  and serum periostin (in-house) for the diagnosis of eosinophilic inflammation. AUC, area under the curve.

**What is the key question?**

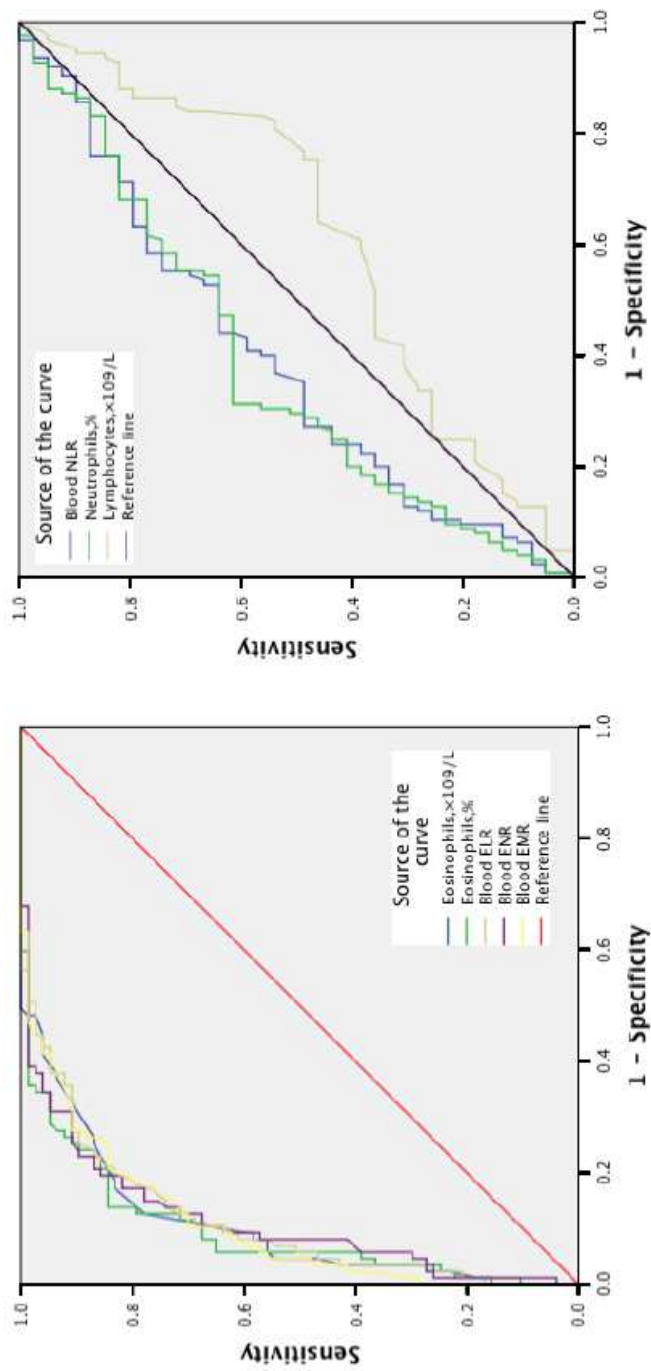
**What are the mutual relationships between blood and sputum eosinophils?**

**What is the cut-off point ?**

**Several studies on the diagnostic accuracy of blood eosinophils to assess eosinophilic airway inflammation have demonstrated conflicting results**

# Summary ROC curve analyses of blood parameters for predicting inflammatory phenotype

	Area under the curve (AUC)	P-value	95% Confidence interval		Cut-off point	Sensitivity, %	Specificity, %	PPV, %	NPV, %
			Lower boundary	Upper boundary					
<b>Predicting eosinophilic asthma (sputum eosinophil count of <math>\geq 3\%</math>)</b>									
Eosinophils ( $\times 10^9/L$ )	0.898	0.000	0.851	0.945	0.26	83.1	82.8	81.0	84.7
Eosinophils, %	0.907	0.000	0.862	0.953	2.70	92.2	75.8	75.5	92.3
Blood ELR	0.892	0.000	0.843	0.940	0.10	89.6	74.4	75.8	88.9
Blood ENR	0.891	0.000	0.840	0.941	0.05	89.6	77.0	77.5	89.3
Blood EMR	0.898	0.000	0.853	0.943	0.26	98.7	49.4	63.3	97.7
<b>Predicting neutrophilic asthma (sputum neutrophil count <math>\geq 61\%</math>)</b>									
Neutrophils, %	0.623	0.020	0.519	0.728	61.52	61.5	63.2	38.1	81.7
Lymphocytes ( $\times 10^9/L$ )	0.385	0.031	0.277	0.493	2.54	65.9	48.0	23.8	85.2
Blood NLR	0.612	0.035	0.508	0.715	1.74	76.9	41.6	29.1	85.3
Blood ENR	0.406	0.076	0.303	0.508					
Blood PLR	0.587	0.103	0.483	0.690					



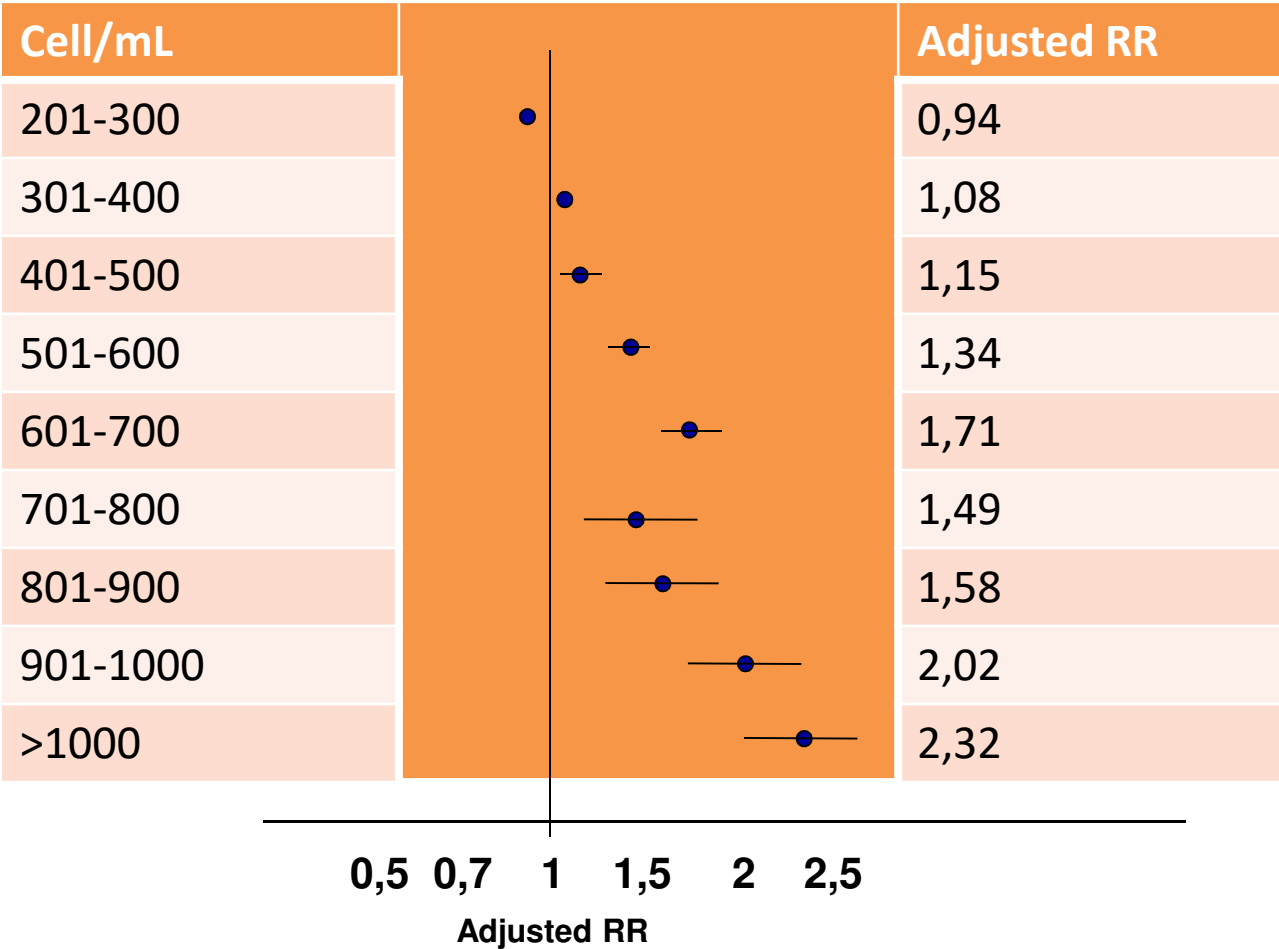
# Elevated blood eosinophils are associated with elevated sputum eosinophils

Increasing the blood eosinophil cut-off value increases the positive predictive value for sputum eosinophilia<sup>1</sup>

Blood eosinophil cut-off (cells/ $\mu$ l)	Predictive value (%)
$\geq 150$	45.2
$\geq 300$	65.6
$\geq 450$	89.2

**High blood eosinophil cut-off values are predictive of high sputum eosinophil counts<sup>1</sup>**

# What is the Relationship of Blood Eosinophils to Severe Asthma Exacerbations ?

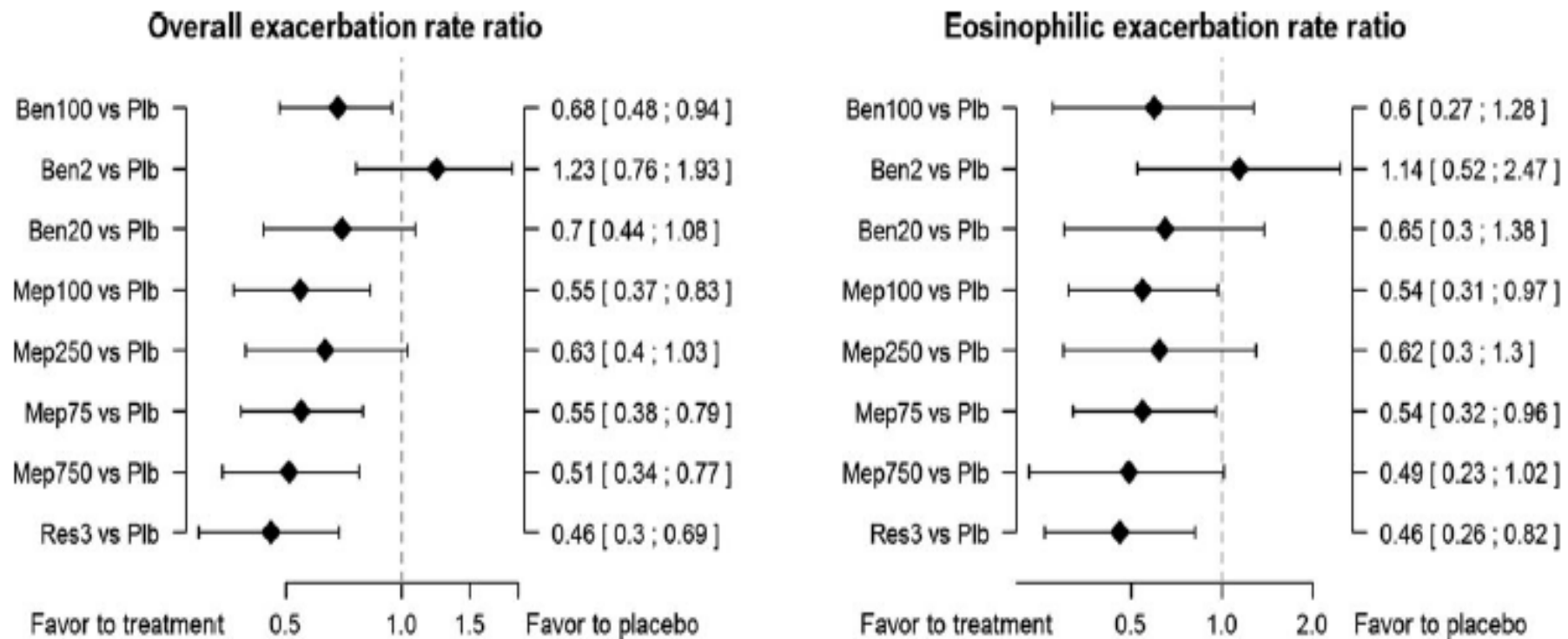


# Selection Biomarkers Employed for Targeted Asthma Therapies

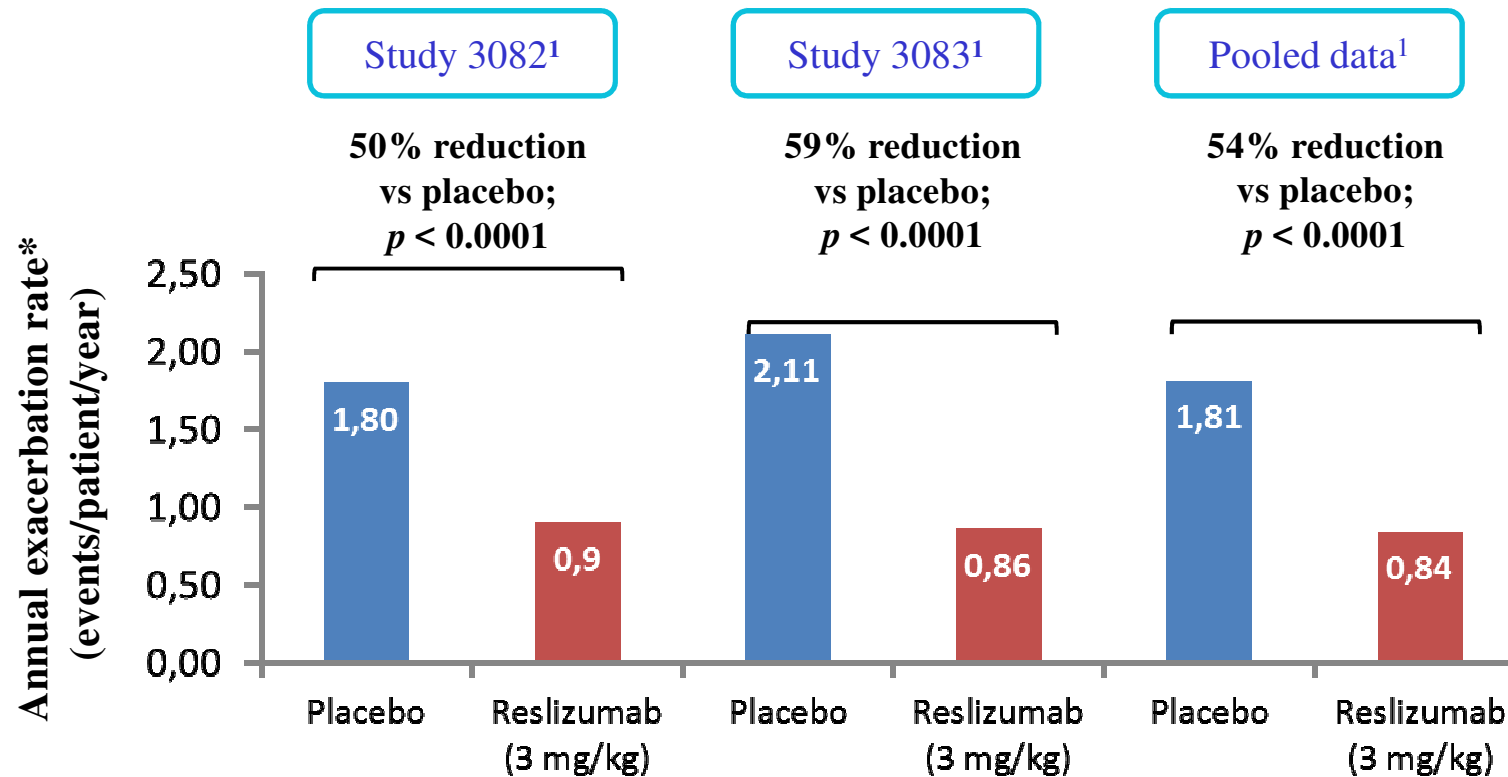
		Selection biomarkers				
Target	Drug	Blood eosinophils	Sputum eosinophils	FeNO	Periostin	IgE Other
IL-5	Mepolizumab	150/ $\mu\text{L}$ <sup>57-59,60</sup>	3% <sup>55,56</sup>			57
	Reslizumab	400/ $\mu\text{L}$ <sup>61-63</sup>	3% <sup>60</sup>			
	Benralizumab	300/ $\mu\text{L}$ <sup>64-67</sup>	2% <sup>65</sup>	50 ppb + PBE <sup>64</sup>		
IgE	Omalizumab	300/ $\mu\text{L}$ <sup>68</sup> 260/ $\mu\text{L}$ <sup>69</sup>		$\geq 19.5$ ppb <sup>69</sup>	50 ng/mL <sup>69,70</sup>	
	Lebrikizumab	300/ $\mu\text{L}$ <sup>70</sup> +Periostin high <sup>72</sup>		30 ppb <sup>70,72</sup>	Median <sup>70</sup> 50 ng/mL <sup>71,72</sup>	70 CCL13, CCL17, YKL-40, CEA <sup>70</sup>
	Tralokinumab					Sputum IL-13, <sup>73</sup> serum DPP-4 <sup>74</sup>
IL-4R $\alpha$	Dupilumab	300/ $\mu\text{L}$ <sup>76</sup>			Median <sup>67</sup>	
CRTH2	Fevipiprant		2% <sup>77</sup>			
CXCR2	AZD5069					Blood neutrophils <sup>78</sup>
IL-17R $\alpha$	Brodalumab	5% <sup>79</sup>		23 ppb <sup>79</sup>		

# Comparison of anti-interleukin-5 therapies in patients with severe asthma: global and indirect meta-analyses of randomized placebo-controlled trials

Y. Cabon<sup>1</sup>, N. Molinari<sup>1,2</sup>, G. Marin<sup>1</sup>, I. Vachier<sup>3</sup>, A. S. Gamez<sup>3</sup>, P. Chanez<sup>4</sup> and A. Bourdin<sup>2,3</sup>



# Reduced Clinical Exacerbation Rates vs Placebo

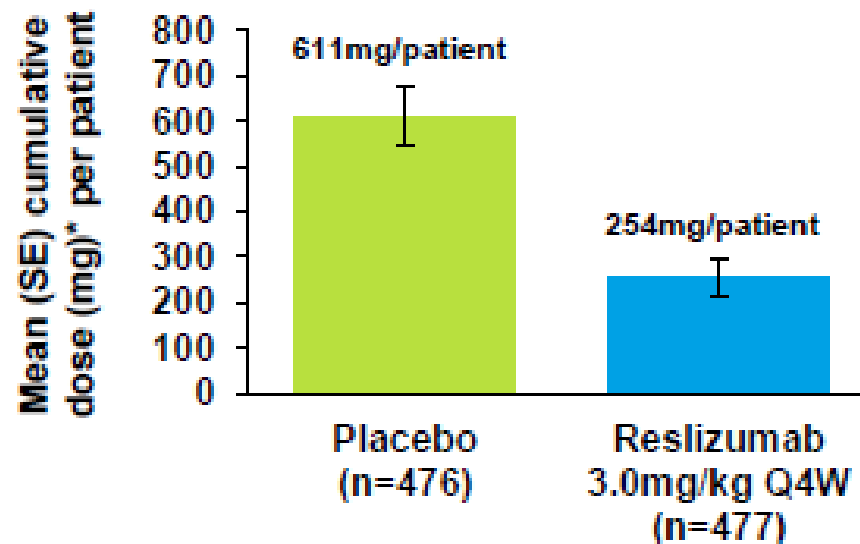


**Reslizumab significantly reduced the annual exacerbation rate in patients with inadequately controlled asthma and active eosinophilic airway inflammation<sup>1</sup>**



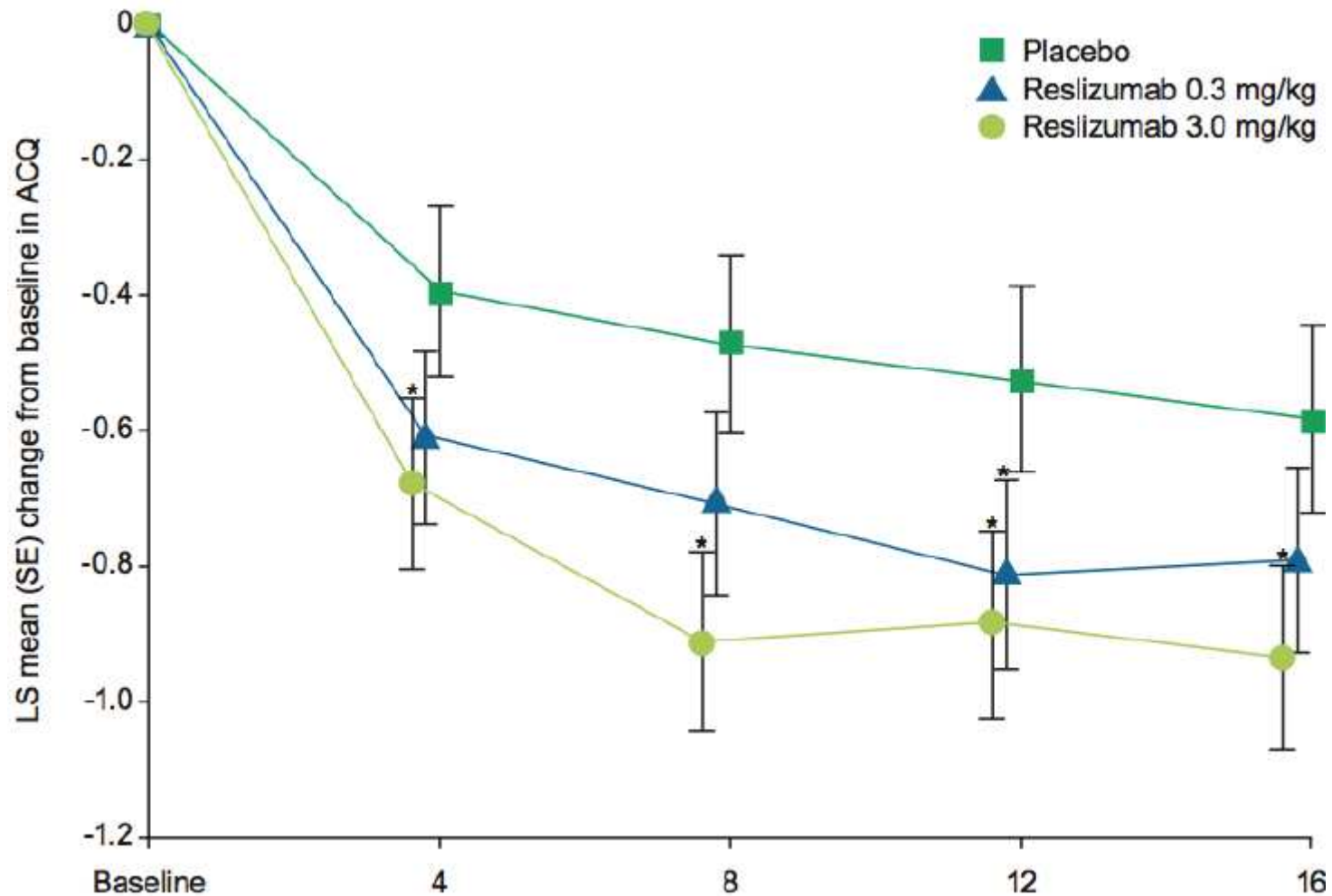
# Reslizumab on Rescue Systemic Corticosteroid Use in Patients With Asthma and Elevated Blood Eosinophils

	Placebo (n=476)	Reslizumab (n=477)
OCS prescribed* (%)	48%	29%
New prescriptions per patient. (mean n)	1.0 (p<0.0001)	0.5 (p<0.0001)
Tot rescue OCS	611 mg/patient (p<0.0001)	254 mg/patient (p<0.0001)



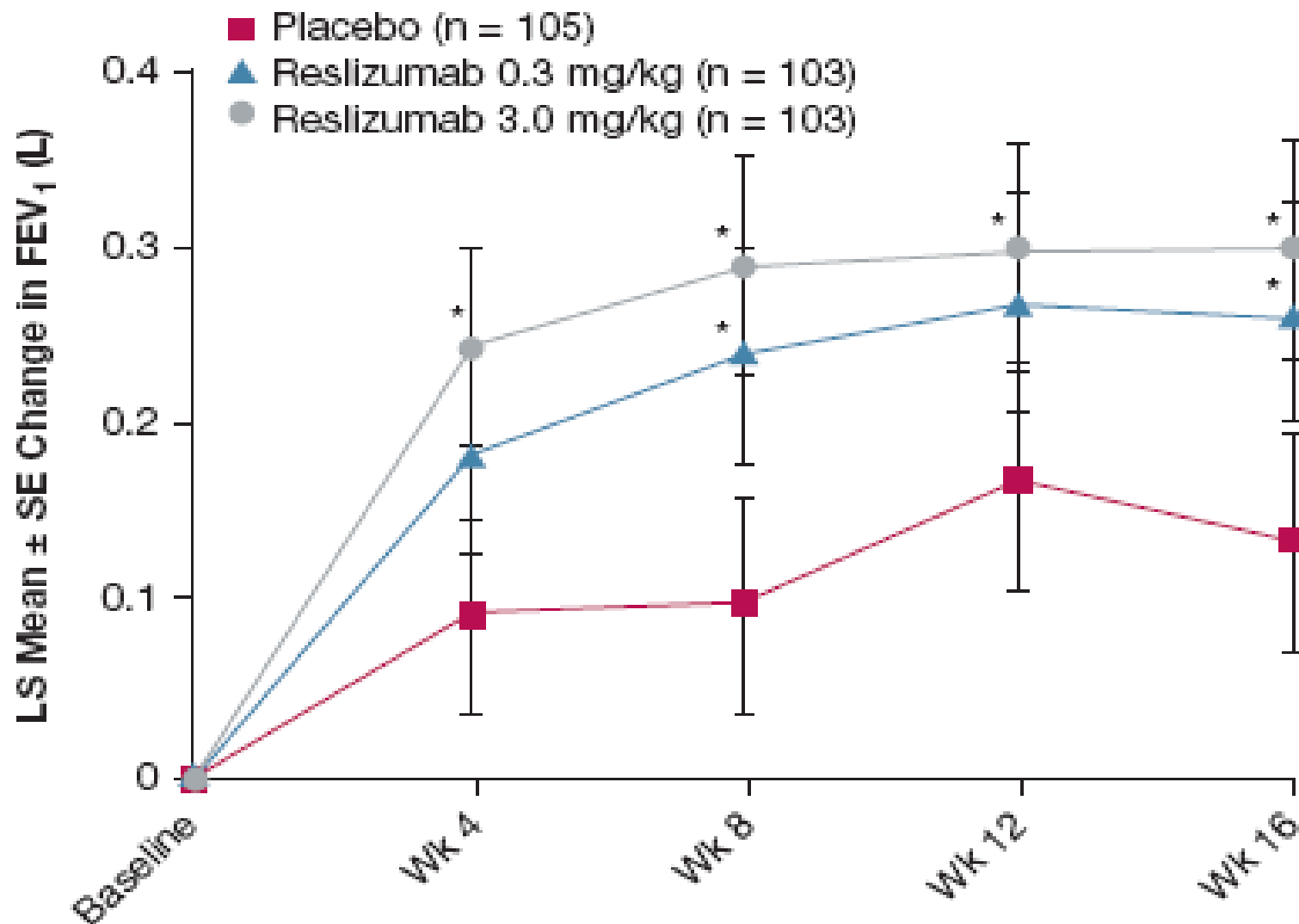
# Reslizumab for Inadequately Controlled Asthma With Elevated Blood Eosinophil Levels

*Leif Bjermer, et al.*



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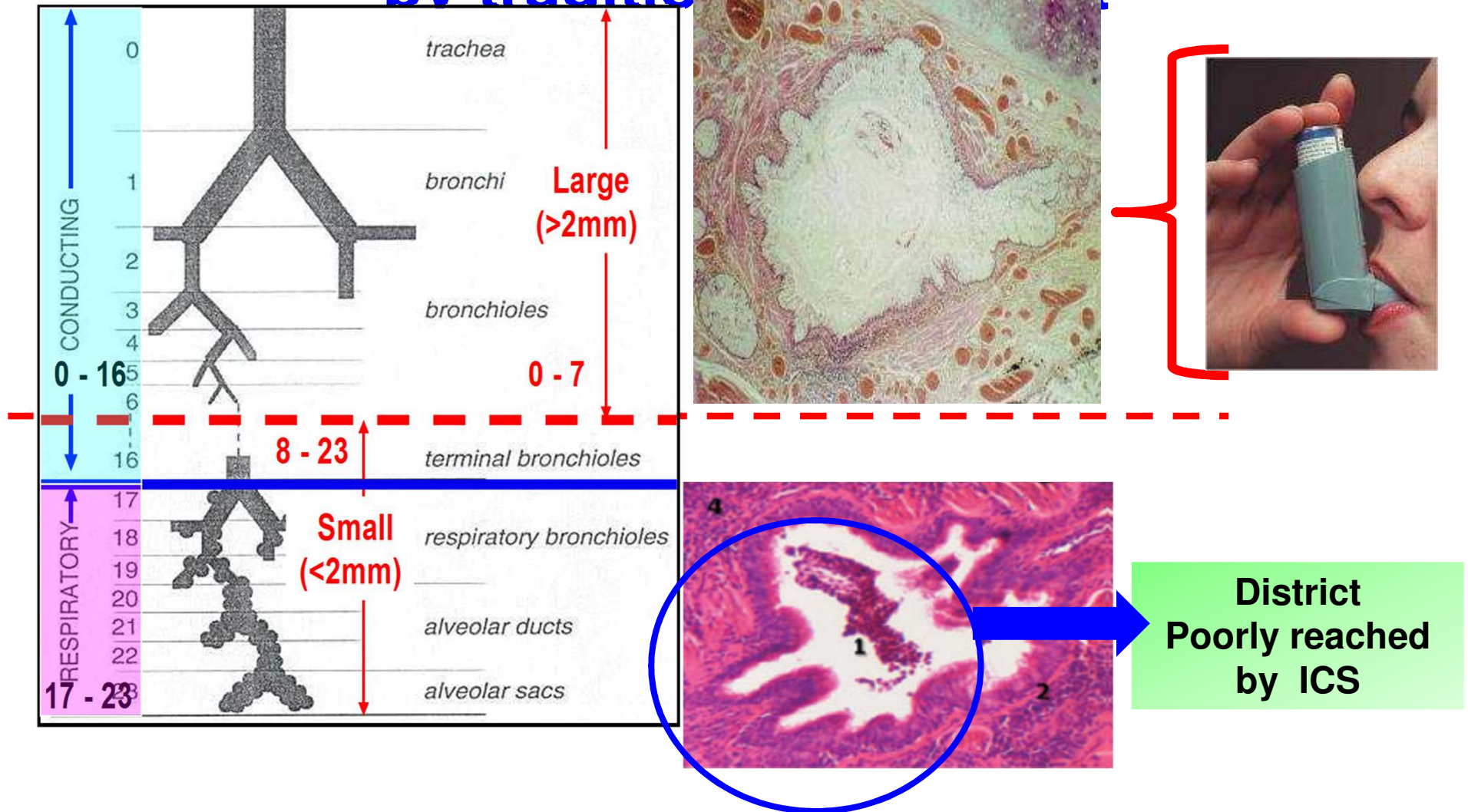
Leif Bjermer, et al.

**e-Table 2 | Efficacy Endpoints Over 16 Weeks (All Measures Included)**

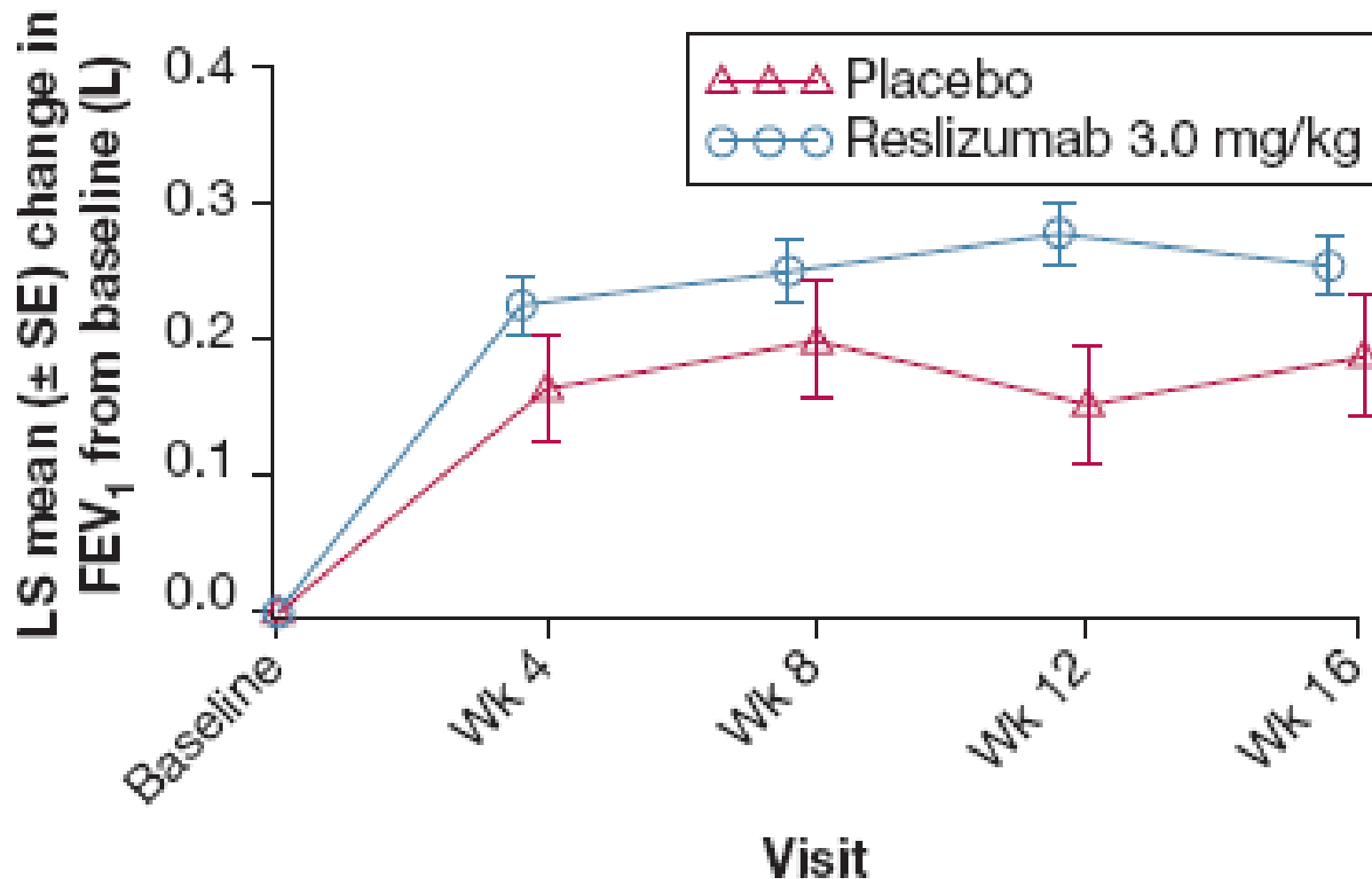
Variable	Placebo	Reslizumab 0.3 mg/kg	Reslizumab 3.0 mg/kg
FEV <sub>1</sub> , L (primary endpoint)			
n	103	101	102
LS mean (SE)	0.127 (0.0547)	0.238 (0.0553)	0.286 (0.0546)
Δ (95% CI) <sup>a</sup>		0.111 (0.012, 0.211)	<u>0.159</u> (0.060, 0.258)
P value		.0283	.0018
FVC, L			
n	103	101	102
LS mean (SE)	0.173 (0.0610)	0.217 (0.0620)	0.302 (0.0610)
Δ (95% CI) <sup>a</sup>		0.044 (-0.062, 0.150)	<u>0.129</u> (0.023, 0.235)
P value		.4147 <sup>b</sup>	.0173 <sup>b</sup>
FEF <sub>25-75%</sub> , L/s			
n	103	101	102
LS mean (SE)	-0.142 (0.1342)	-0.117 (0.1360)	0.091 (0.1342)
Δ (95% CI) <sup>a</sup>		0.025 (-0.214, 0.263)	<u>0.233</u> (-0.006, 0.471)
P value		.8400 <sup>b</sup>	.0559 <sup>b</sup>

# Small airway inflammation is poorly controlled

by traditional treatment

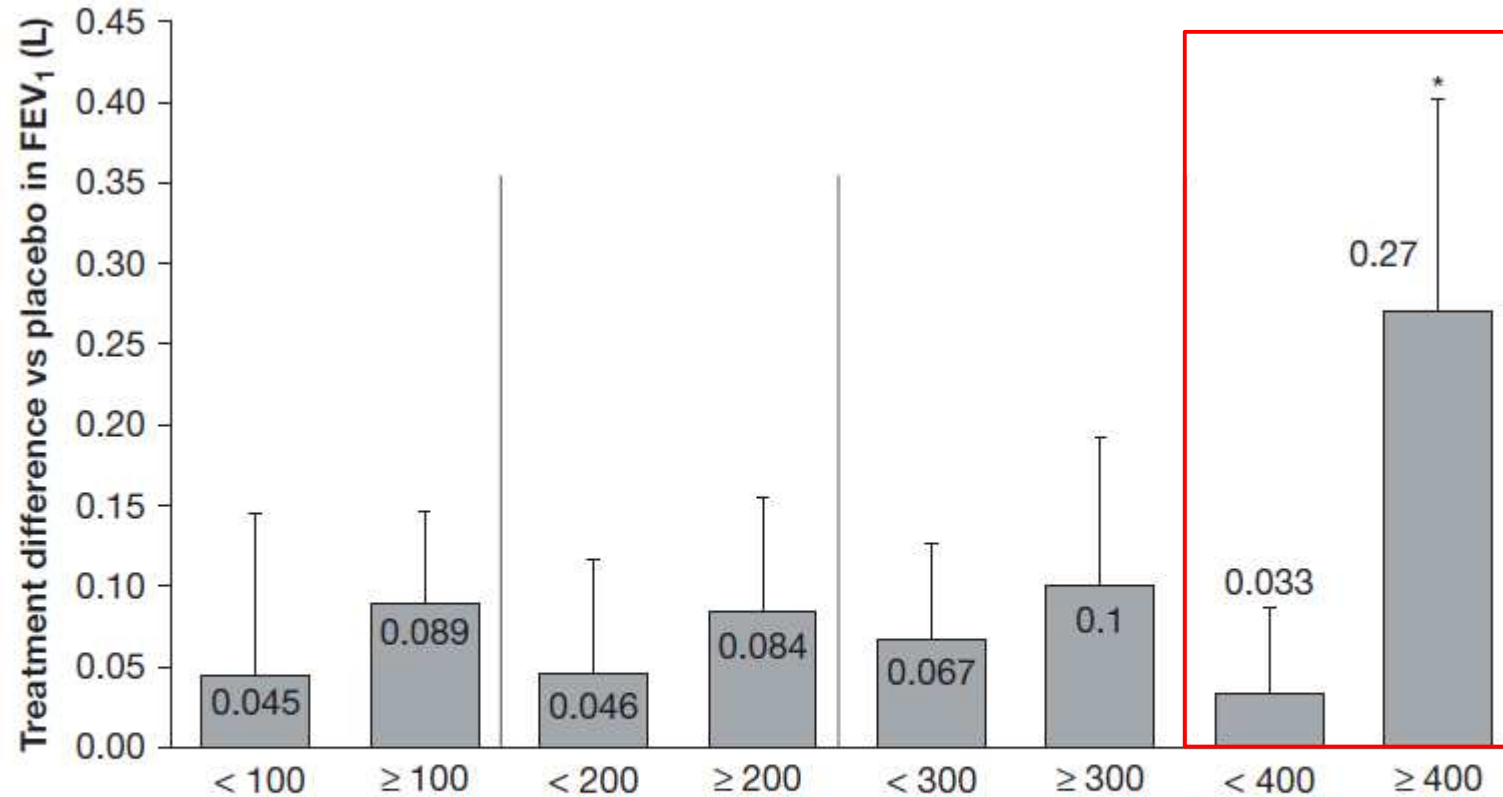


**Reslizumab treatment in patients unselected for eosinophil count produced only modest effects on FEV<sub>1</sub> compared to placebo (68 ml)**



# Lung function: Reslizumab improved FEV<sub>1</sub>

Reslizumab significantly improved FEV<sub>1</sub> in patients with blood eos ≥ 400 cells/μL

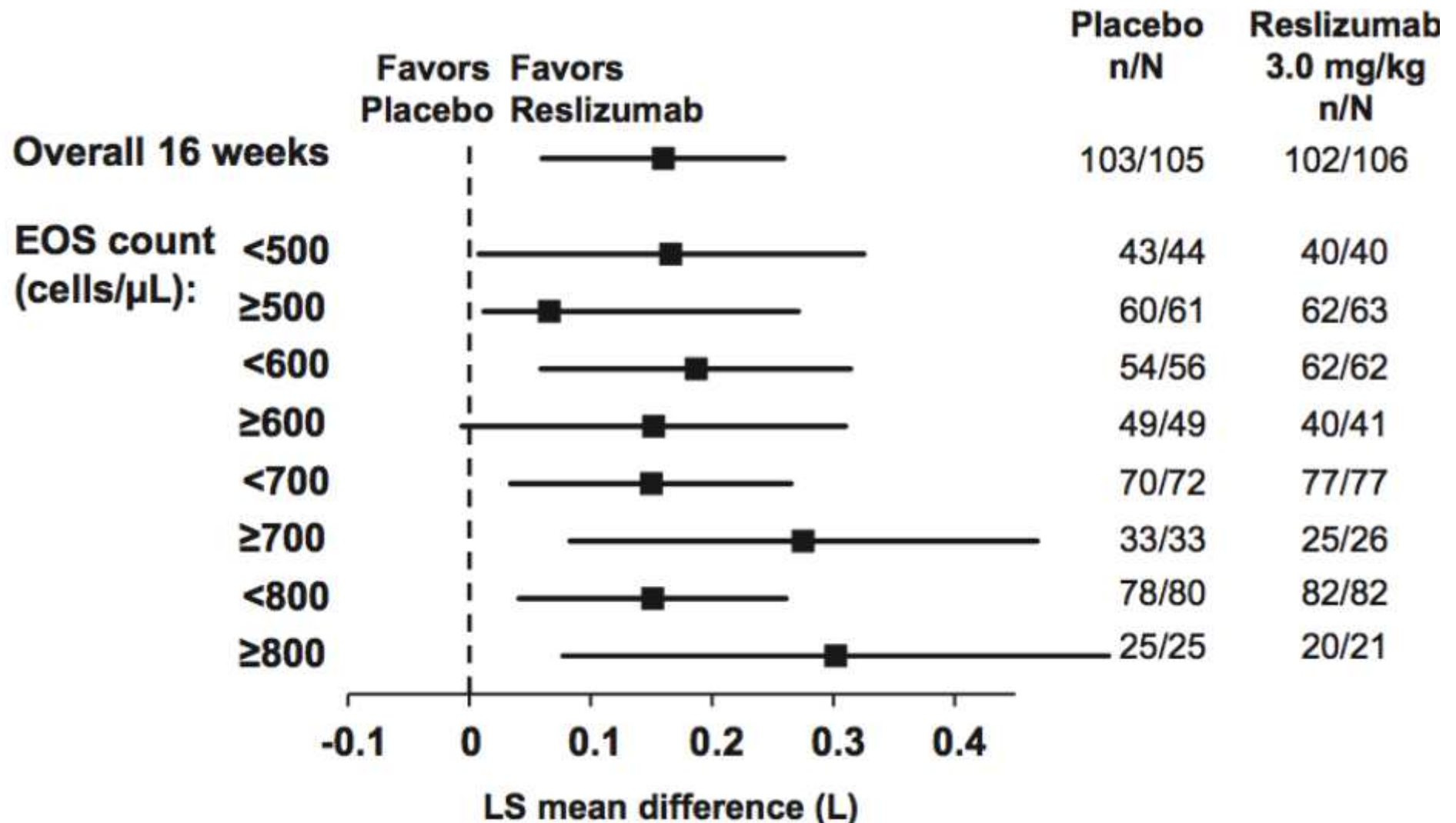


	Baseline eosinophils count strata (cells/μL)							
	< 100	≥ 100	< 200	≥ 200	< 300	≥ 300	< 400	≥ 400
Placebo	n = 16	n = 65	n = 37	n = 44	n = 54	n = 27	n = 68	n = 13
Reslizumab	n = 62	n = 282	n = 158	n = 186	n = 239	n = 105	n = 275	n = 69
P value	.6537	.1202	.5122	.2401	.2579	.2818	.5422	<b>.0436</b>



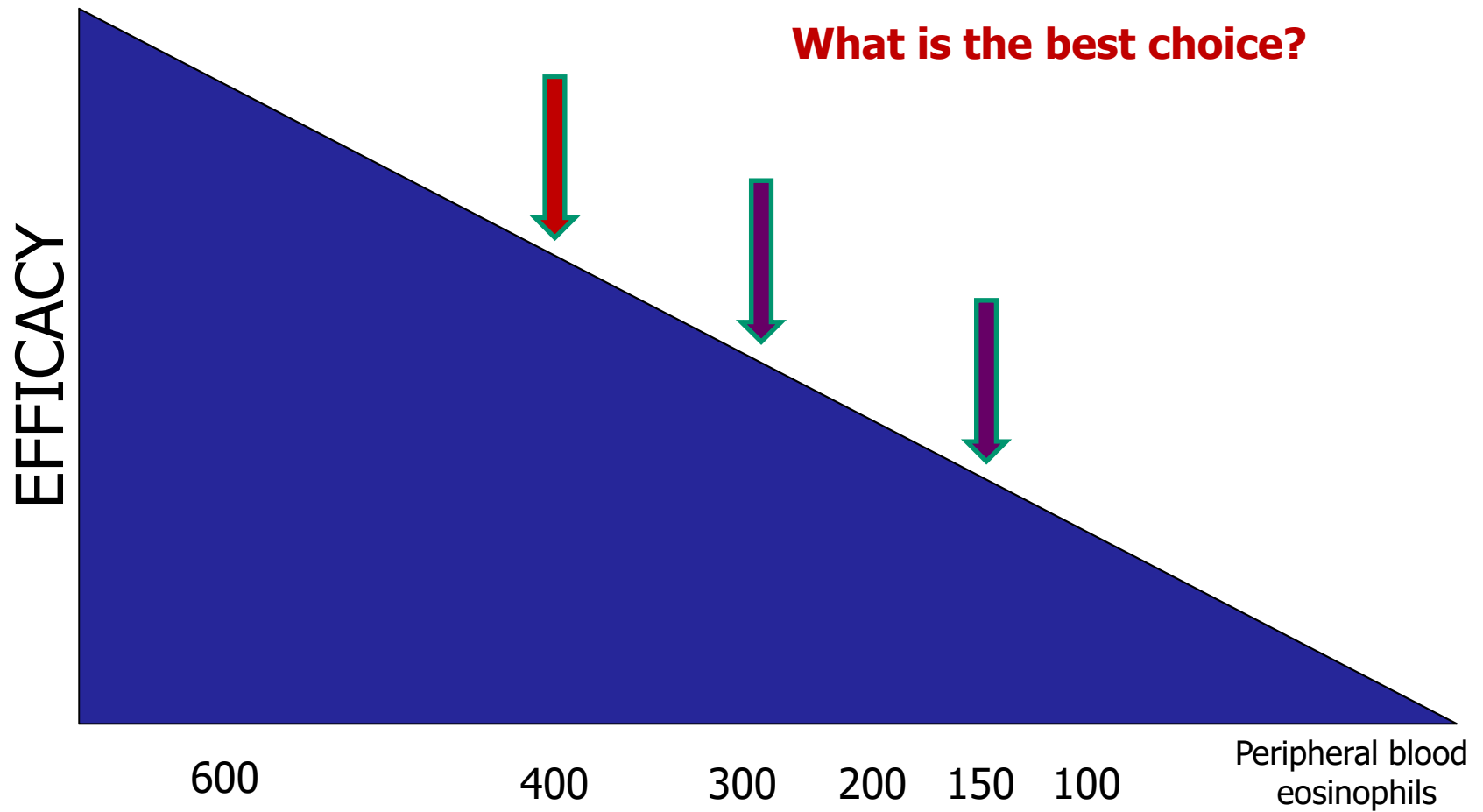
# Reslizumab for Inadequately Controlled Asthma With Elevated Blood Eosinophil Levels

*Leif Bjermer, et al.*

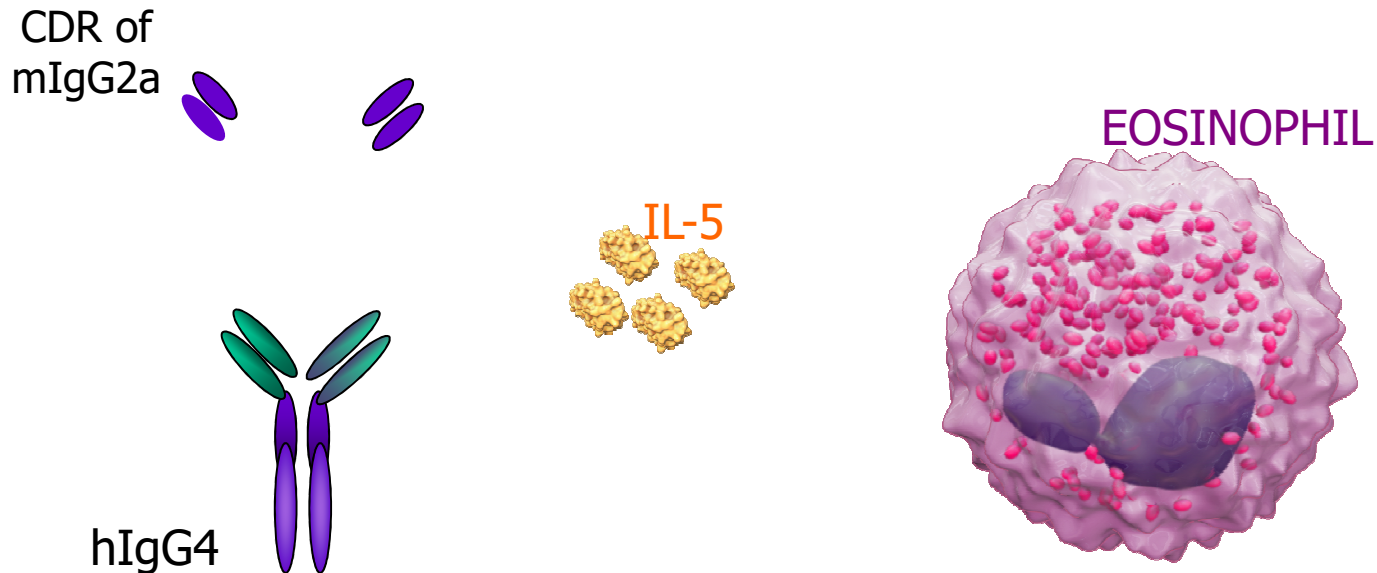




# Could clinical response to anti-IL-5 mAbs depend on eosinophil count in peripheral blood ?



# RESLIZUMAB STRUCTURE AND BIOLOGICAL/CLINICAL CONSEQUENCES



- Do not fix Complement
- Do not form ICC
- Do not induce ADCC

***In vitro*** data showed that Reslizumab:

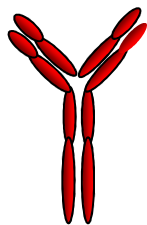
- Binds strongly to free IL-5 with a high affinity ( $K_d = 81 \text{ pM}$ )
- Inhibits IL-5 binding to cell-surface receptors ( $IC_{50} = 0.5 \text{ nM}$ )
- Strongly inhibits cell growth stimulated by IL-5 ( $IC_{50} = 45 \text{ pM}$ )

# Is there a rationale for choosing a biological agent for asthma treatment ?

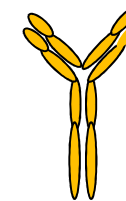
↑IgE  
Inflammation;  
symptoms

↑IgE and Eosinophils  
Inflammation;  
symptoms

↑ Eosinophils  
Inflammation;  
symptoms



Anti-IgE



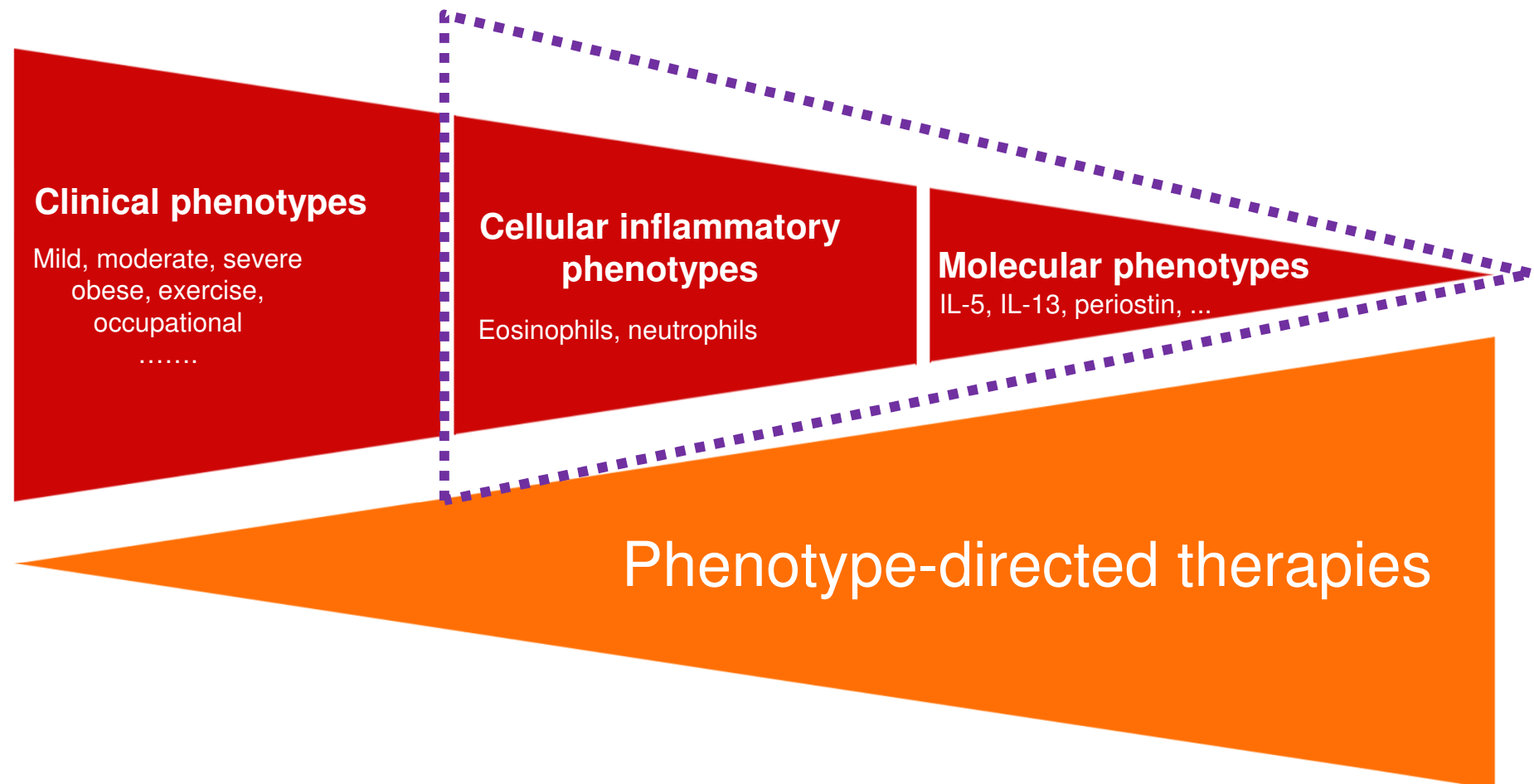
Anti-IL-5/R

# Asthma: developments in targeted therapy

EXPERT  
REVIEWS

Matucci, Vultaggio, Ridolo, Maggi, Canonica & Rossi

*Expert Rev. Clin. Immunol.* 8(1), 13–15 (2012)



# Acknowledgments



Dept. BIOMEDICINA  
Immunoallergology (F. Almerigogna)  
Immunology and Cellular Therapy (E. Maggi)

University of Florence, Italy  
Careggi Hospital

**Alessandra Vultaggio**  
Oliviero Rossi

Francesca Nencini  
Sara Pratesi



Carolina Orsi Battaglini  
Giulia Carli  
Anna Radice  
Laura Dies

