



# Mepolizumab in the management of severe eosinophilic asthma with real world data

**Shih-Lung Cheng MD, PhD**

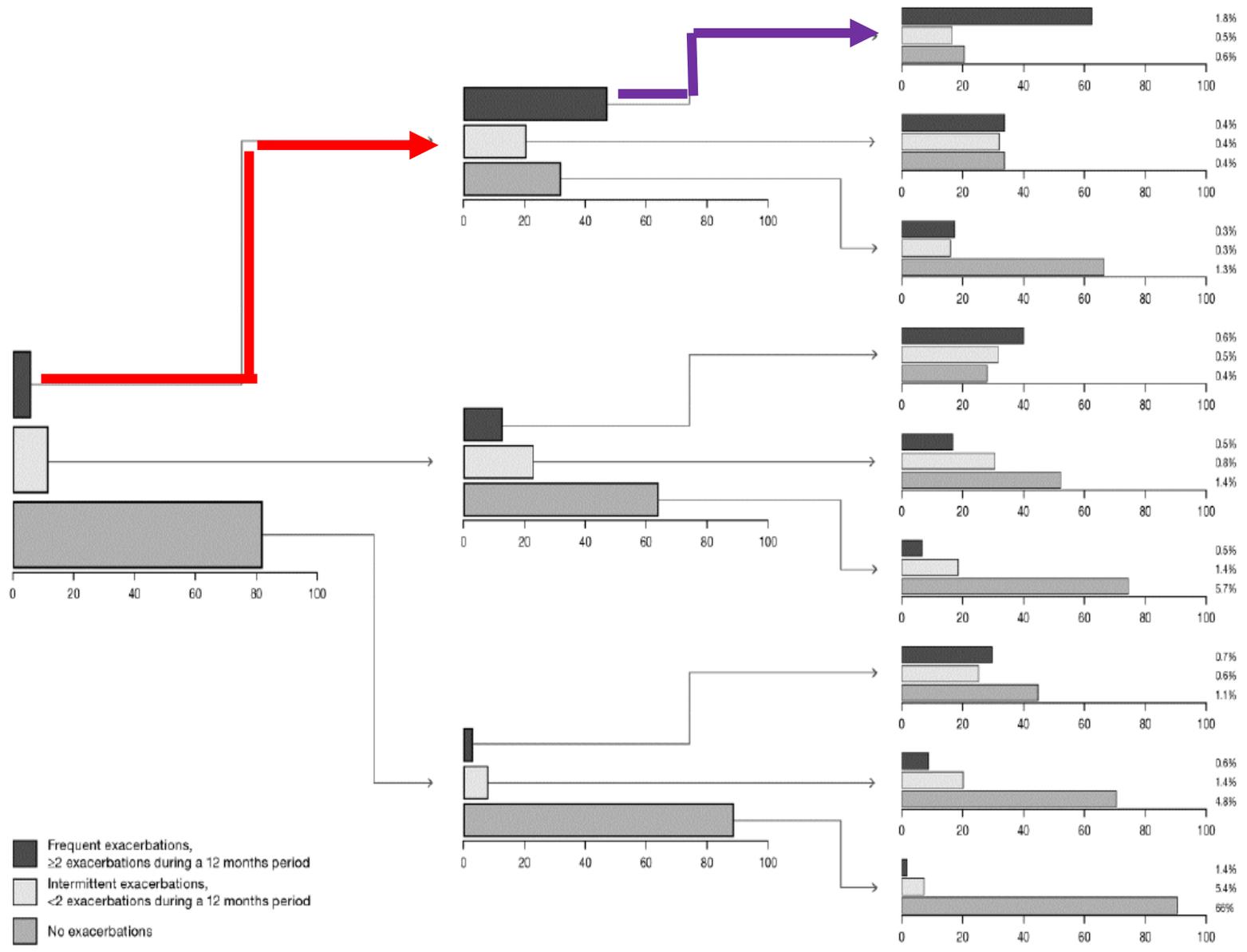
Division for Pulmonary Medicine ,

Department of Internal Medicine

Far Eastern Memorial Hospital



# Frequent A.E phenotype in asthma?

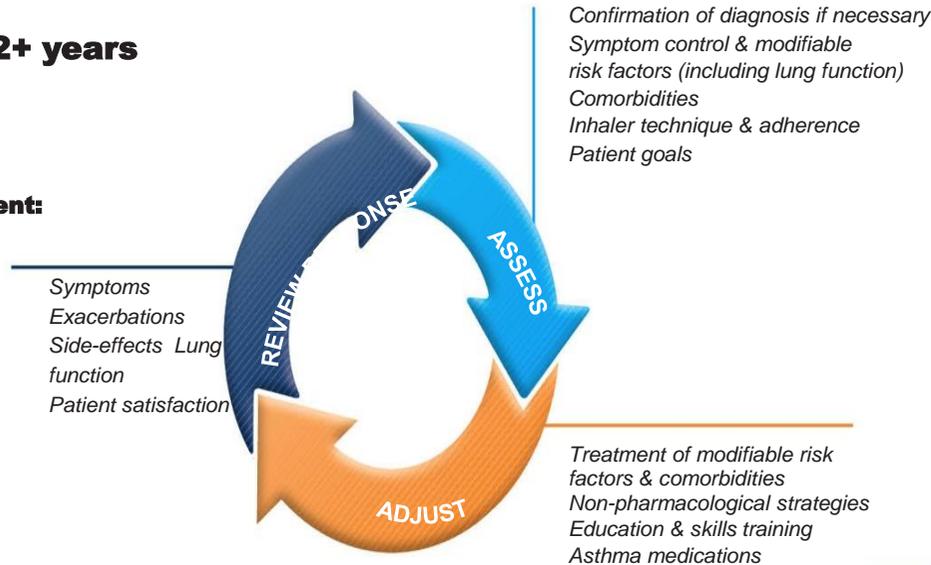


# Adults & adolescents 12+ years



## Personalized asthma management:

Assess, Adjust, Review response



## Asthma medication options:

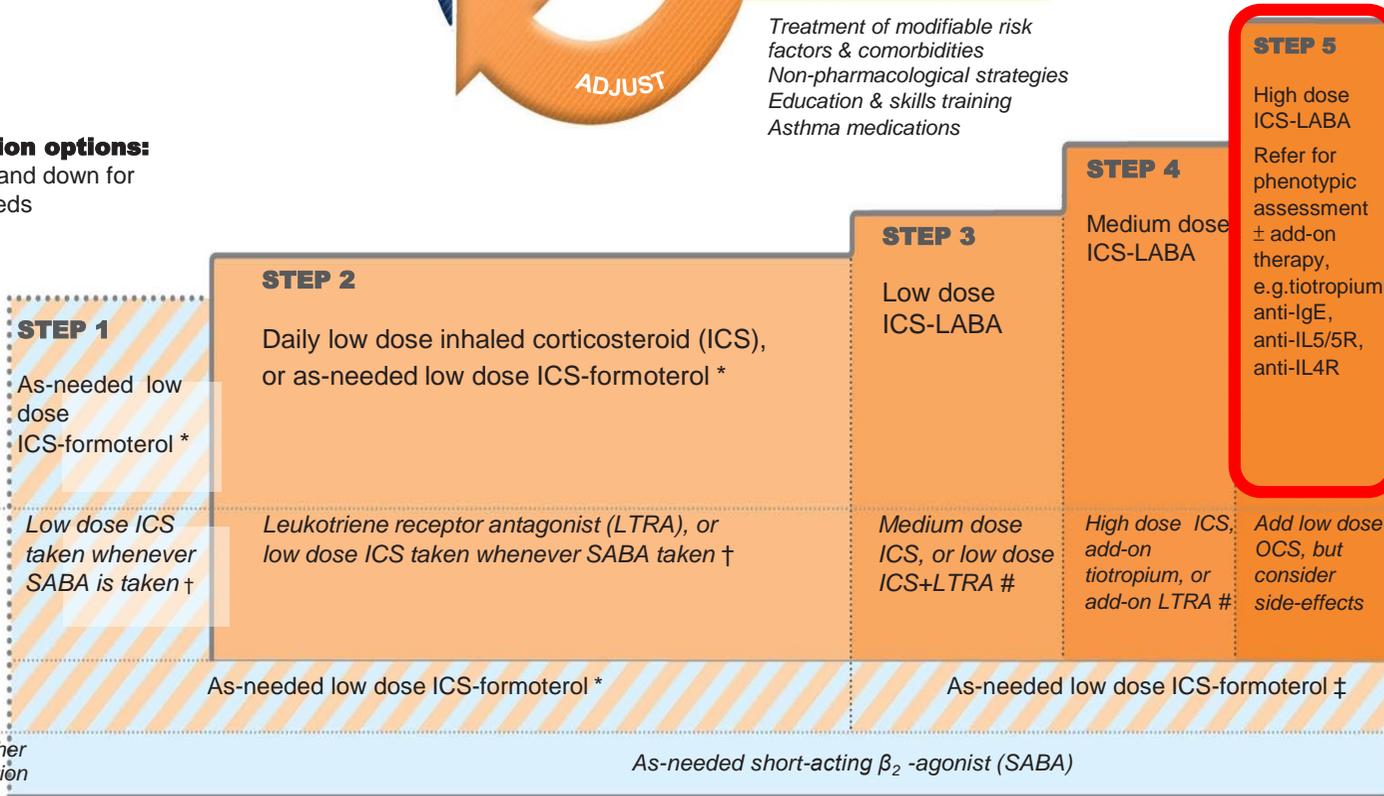
Adjust treatment up and down for individual patient needs

**PREFERRED CONTROLLER**  
to prevent exacerbations and control symptoms

Other controller options

**PREFERRED RELIEVER**

Other reliever option



\* Off-label; data only with budesonide-formoterol (bud-form)

† Off-label; separate or combination ICS and SABA inhalers

‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy

# Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV<sub>1</sub> >70% predicted



臨床上診斷的順序應為 Uncontrolled asthma → Difficult-to-treat asthma → Severe asthma.  
經討論建議採用新版 2018 GINA pocket guideline 定義。

**Uncontrolled asthma**：氣喘控制的評估應包含症狀的控制及未來風險。未控制氣喘定義含氣喘症狀控制不良（頻繁的症狀或緩解劑使用，因氣喘而活動受限或夜間醒來）或/及頻繁發作需使用口服類固醇（每年最少兩次），或需要住（每年最少一次）。

**Difficult-to-treat asthma**：困難治療氣喘 GINA 第四或五階治療，氣喘仍未受控制；或是需要這些治療以維持氣喘症狀控制及減少惡化風險。通常困難治療氣喘的病人都有  
一些可以修正的因素以改善氣喘控制，如吸入器使用技巧、服藥順從性、吸菸及共病症  
等。另外要考慮診斷是否正確。

**Severe asthma**：需使用 GINA 氣喘第四或五階治療以維持氣喘控制 (high dose ICS and LABA or leukotriene modifier/theophylline)，或是仍無法控制者。

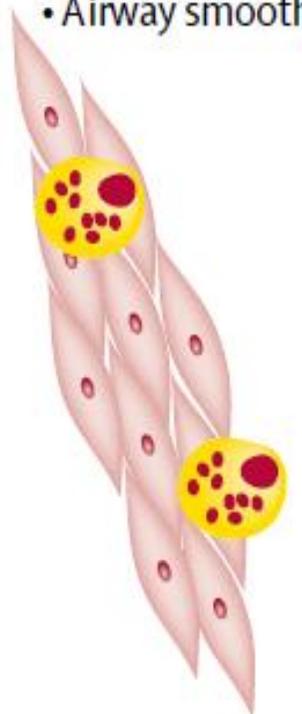
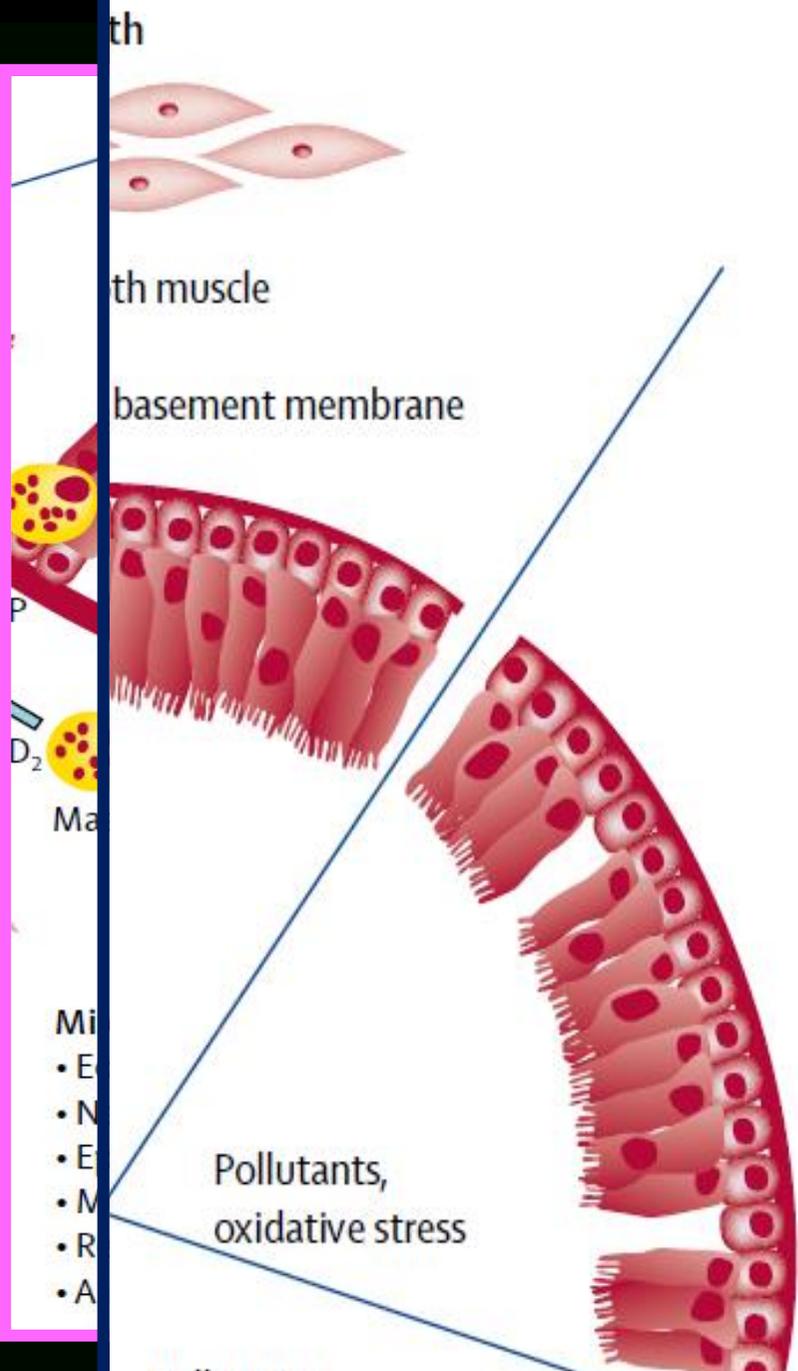
# 嚴重氣喘的診斷與評估

專家建議	臨床建議內容
GP	嚴重氣喘的診斷需要系統性地逐步評估，以確保相關步驟都能被注意及執行。首先應確定患者有氣喘，排除其他鑑別診斷。
GP	對於所有的嚴重氣喘患者，在確立診斷後，均應評估氣喘用藥之遵囑性，並檢查吸入藥物之使用技巧。

# Non-eosinophilic asthma

## Paucigranulocytic

- Eosinophil -
- Neutrophil -
- Epithelial damage +
- Mucus +/-
- Reticular basement membrane thickening +/-
- Airway smooth muscle mass +



ation

+

# Phenotypes in Severe Asthma

If not adherent, provide patient education, frequent follow-up visits, evaluate factors associated with non-adherence.

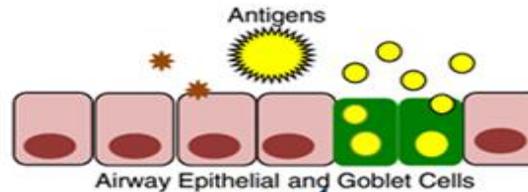
Confirm diagnosis of severe asthma.

Evaluate adherence to GINA steps 4-5 medications<sup>a</sup>.

## Phenotype Evaluation:

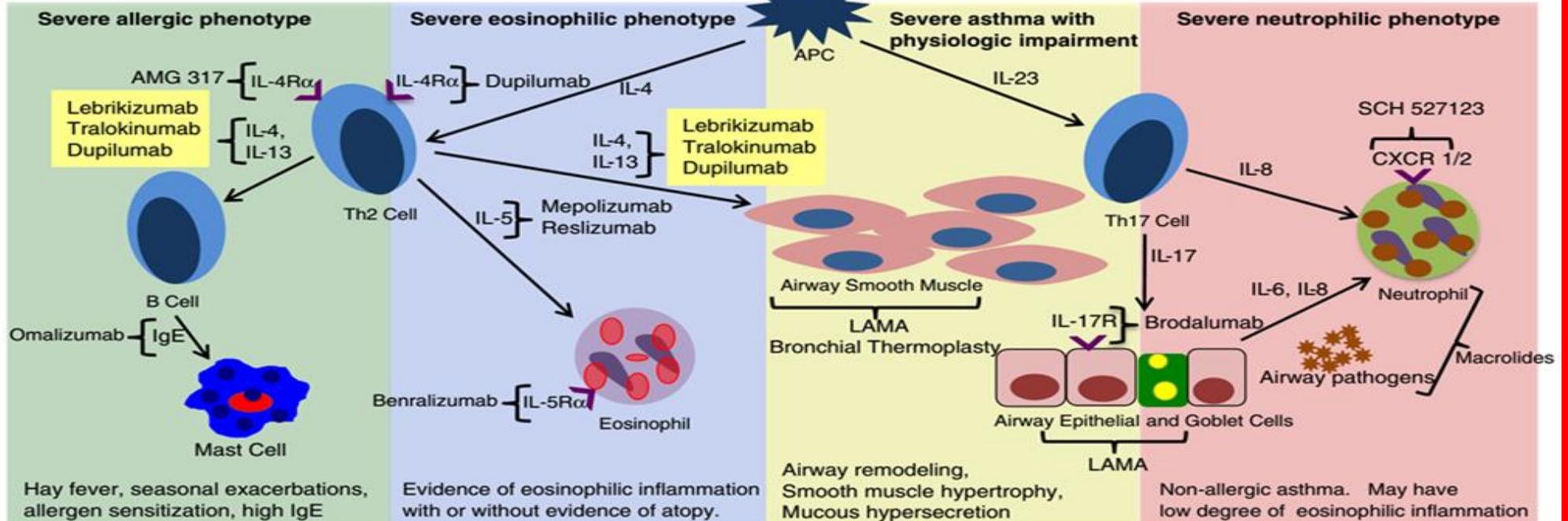
Spirometry<sup>b</sup>  
 Assess asthma control  
 Assess asthma symptoms  
 Assess for allergies  
 Assess asthma history e.g. age of asthma onset, family history of asthma  
 Assess exacerbations including steroid bursts and healthcare utilization  
 Assess comorbidities e.g., GERD, severe sinus disease, obesity, OSA, recurrent LRTI

## Phenotype and biomarker evaluation.



## Biomarker Evaluation:

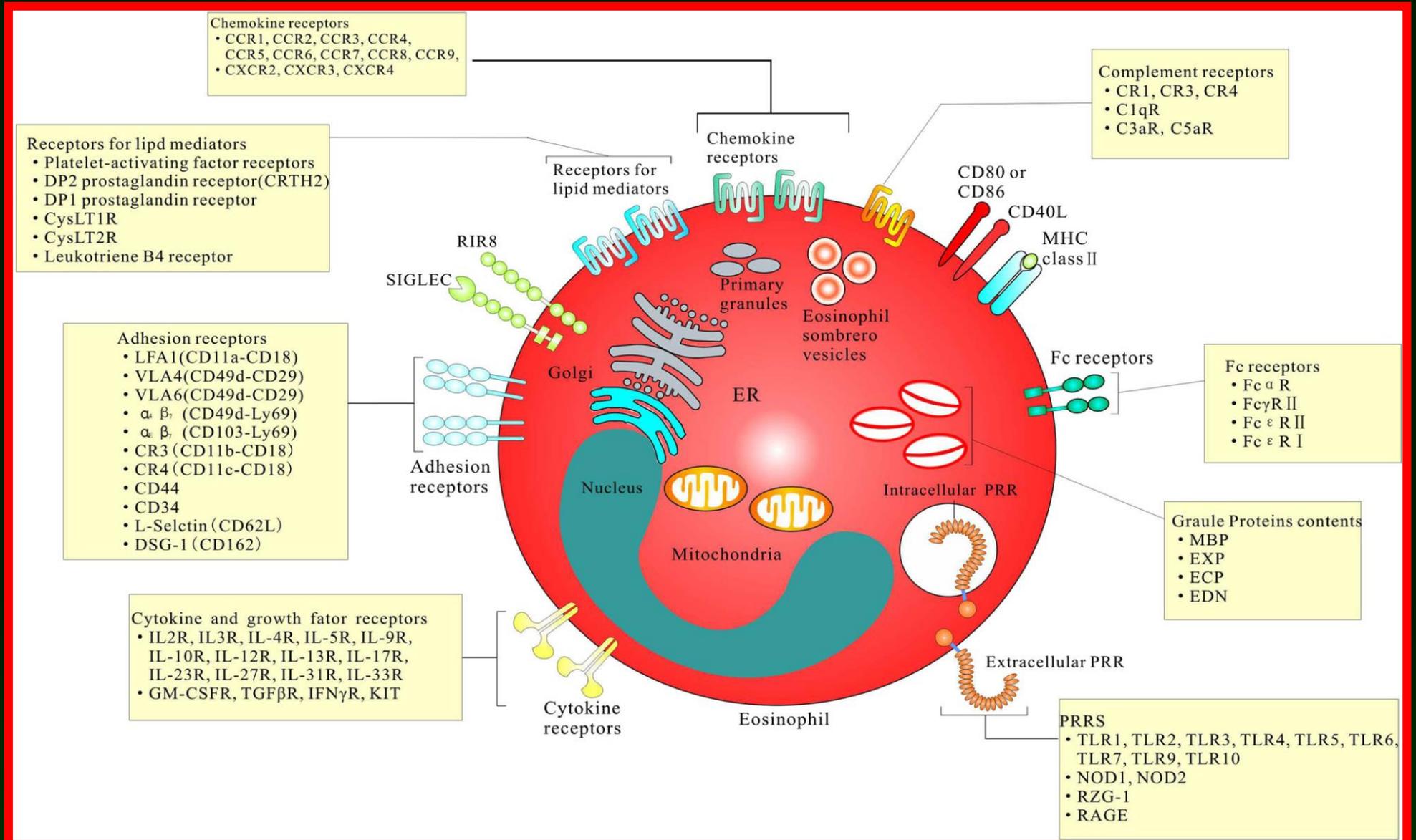
Allergy sensitization evaluation:  
 Skin prick Testing or Radioallergosorbent testing  
 Total IgE level  
 Complete blood count with differential  
 Fraction of exhaled nitric oxide



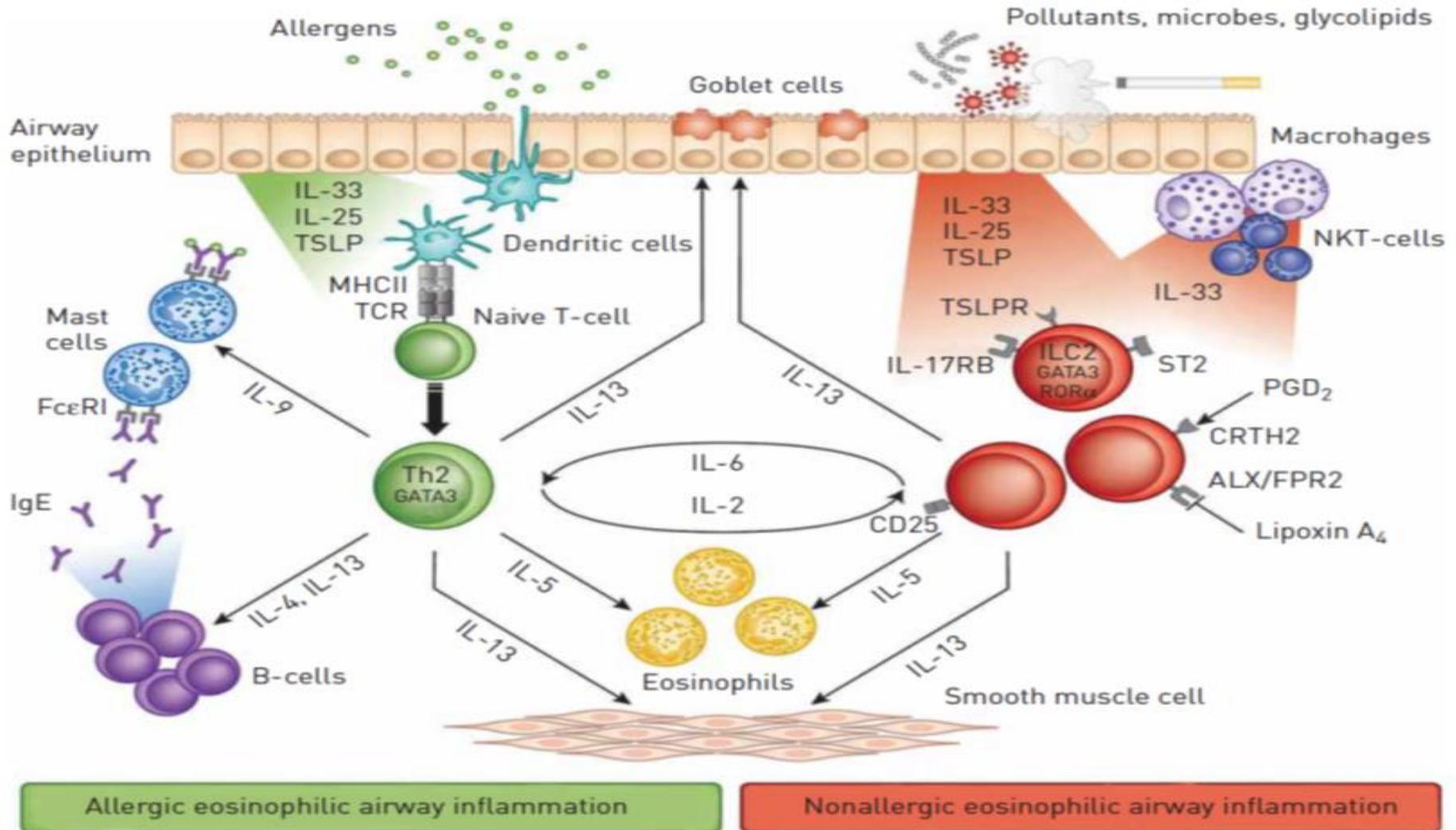
# Classifications for severe asthma (phenotypes)

- (一) 、 severe allergic asthma
- (二) 、 severe eosinophilic asthma
- (三) 、 severe neutrophilic asthma
- (四) 、 Severe pauci-granulocytic asthma

# Eosinophil

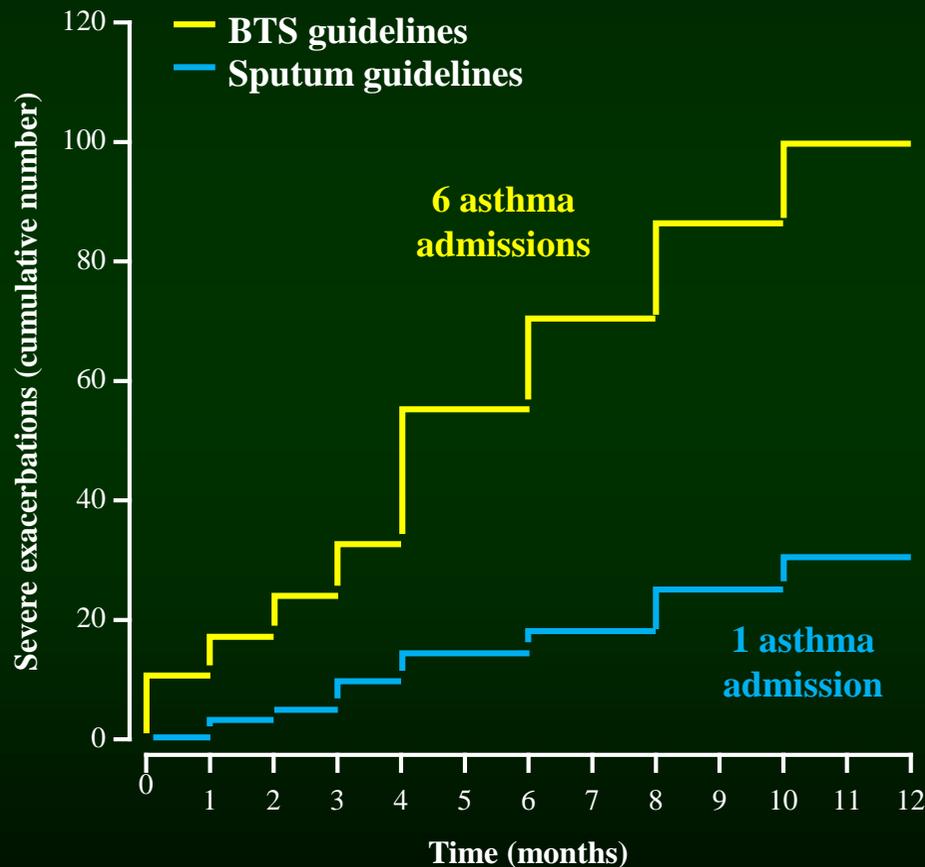


# Allergic and non-allergic in asthma

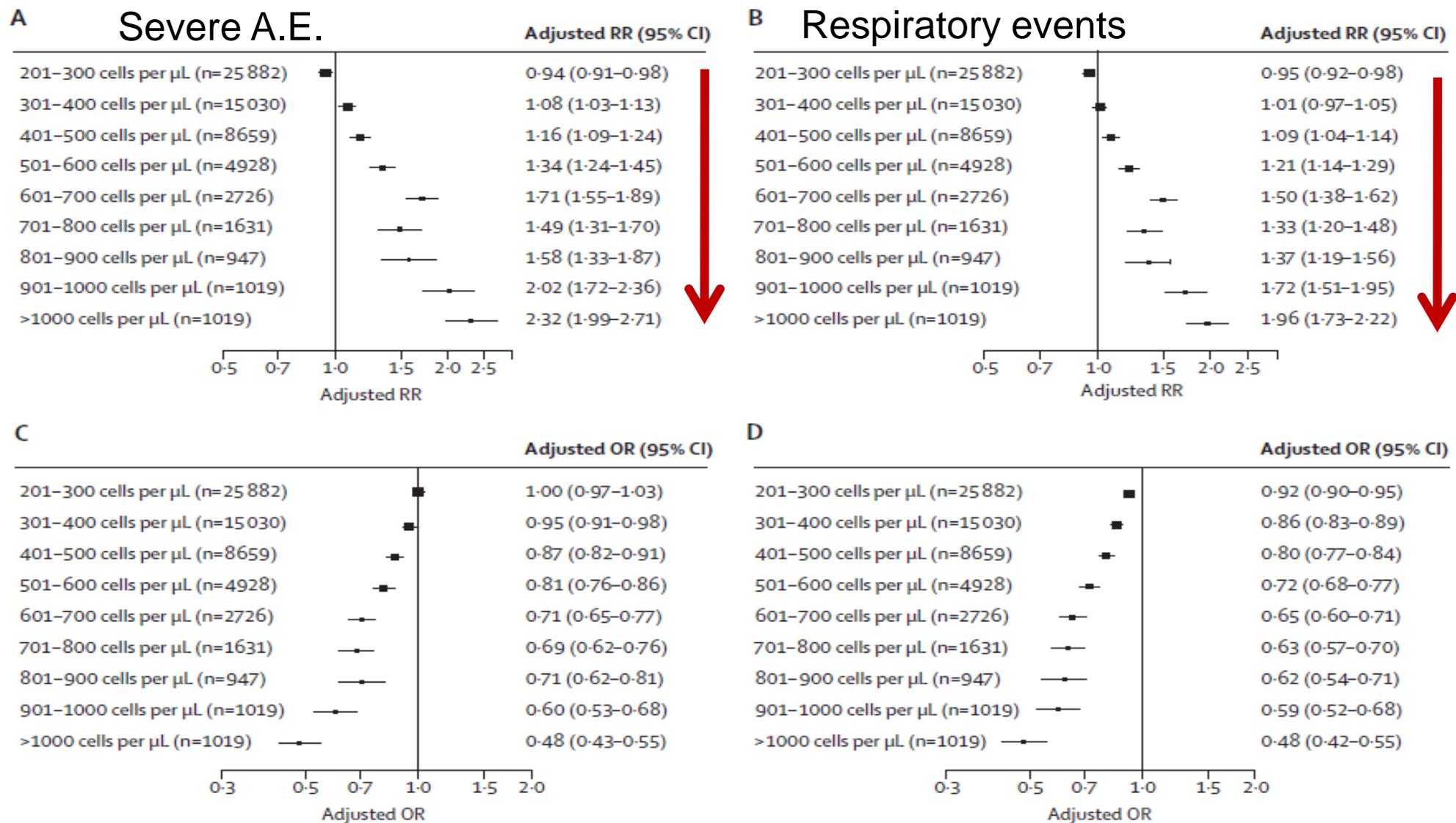


# Potential therapy options for eosinophilic asthma

Inflammatory phenotypes: managing eosinophil levels reduces exacerbations

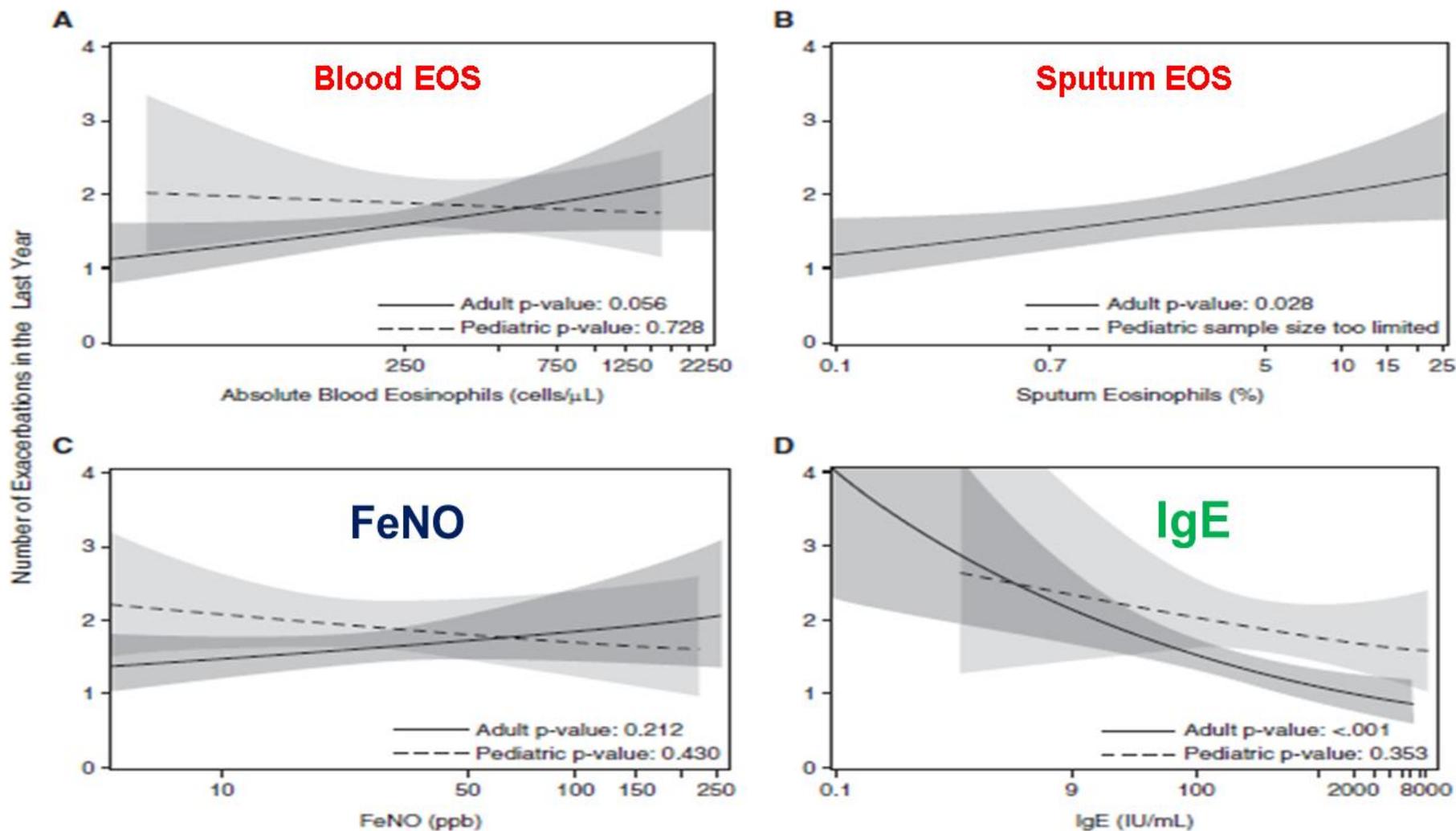


- Patients in the sputum management group had significantly fewer severe asthma exacerbations than patients in the BTS management group (35 vs 109;  $p=0.01$ )
- Significantly fewer patients in the sputum management group were admitted to hospital with asthma (1 vs 6 in the BTS management group;  $p=0.047$ )
- The average daily dose on ICS or OCS did not differ between the two groups



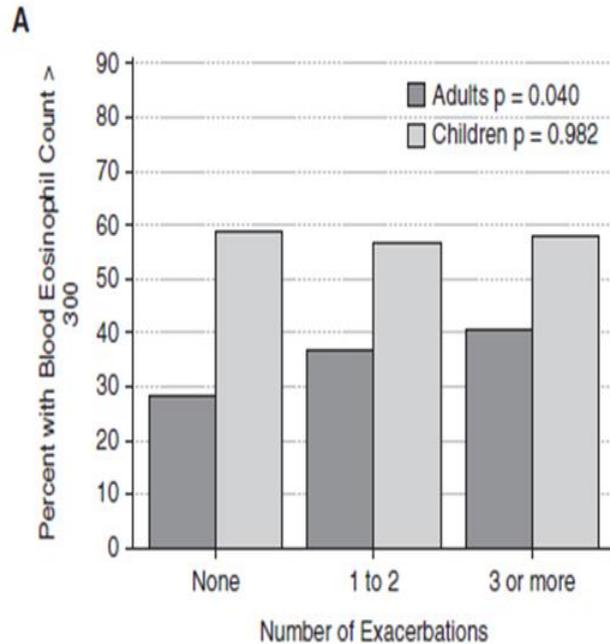
**Figure 3: Adjusted rate ratios (RRs) for severe exacerbations (A) and acute respiratory events (B), and adjusted odds ratios (ORs) for risk-domain asthma control (C) and overall asthma control (D), for patients assigned to nine ascending eosinophil count categories as compared with a reference category of peripheral blood eosinophil count of 200 cells per  $\mu\text{L}$  or less ( $n=68\,407$ ) during 1 outcome year**  
 Adjusted for age, sex, body-mass index, smoking status, and Charlson comorbidity index score.

# Severe asthma with frequent exacerbations

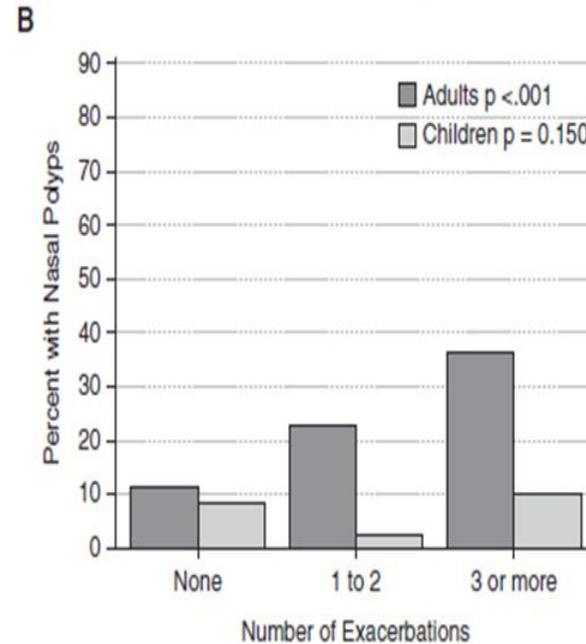


# Severe asthma with frequent exacerbations

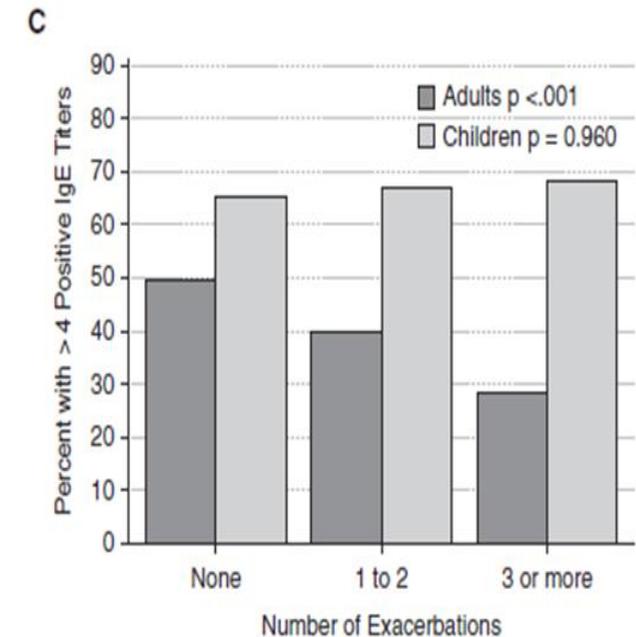
## % Blood EOS>300



## % Nasal polyps



## % >4 positive IgE titers



Suggest that the adult exacerbation-prone phenotype is not driven by allergic sensitization

## Biomarkers of eosinophilic inflammation in RCTs with monoclonal antibodies to preselect patients in adult asthma

Biomarker	Association with treatment response	Invasiveness	Comments
<b>FeNO</b>	Corticosteroids, anti-IL13, anti-IL4/13, anti-IgE	Non-invasive	Easy, quick, not specific, cheap
Serum <b>periostin</b>	Anti-IL13*	Minimal	Effect shown with anti-IL-13, high costs
Blood <b>eosinophil</b> count	Anti-IL5*, anti-IL4/13	Minimal	Generally available, high clinical impact
Sputum <b>eosinophil</b> count	Corticosteroids, anti-IL5	Non-invasive	Specialist centers, tissue specific, time consuming
<b>Serum IgE</b>	<b>Not associated</b>	Minimal	<u>No clear association between IgE as a biomarker and treatment responses or clinical outcome</u>

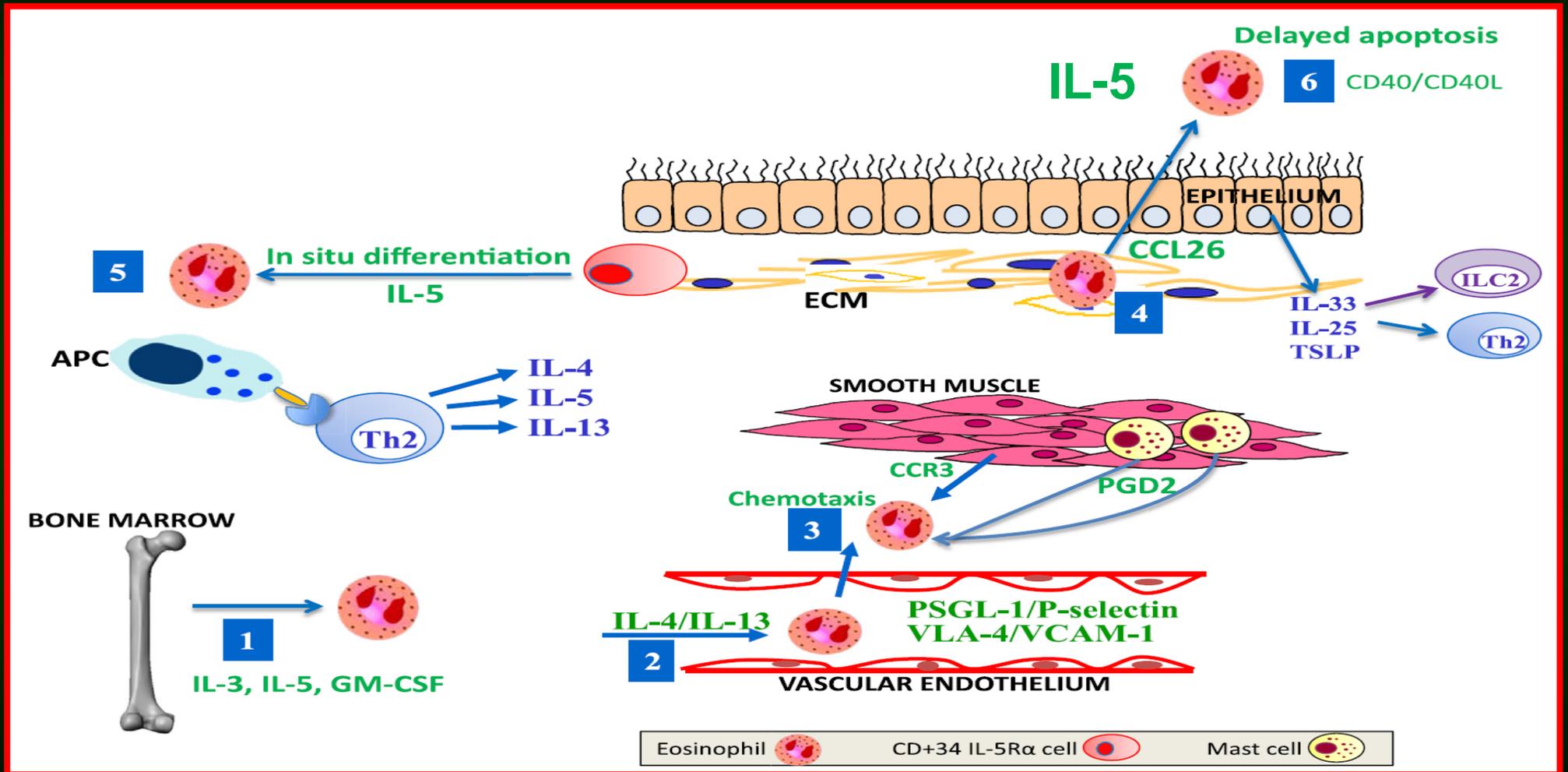
# Different clinical features and biomarkers between allergic and eosinophilic asthma

TABLE 2 Clinical features and biomarkers that can be used to differentiate between allergic and eosinophilic T2-high severe asthma

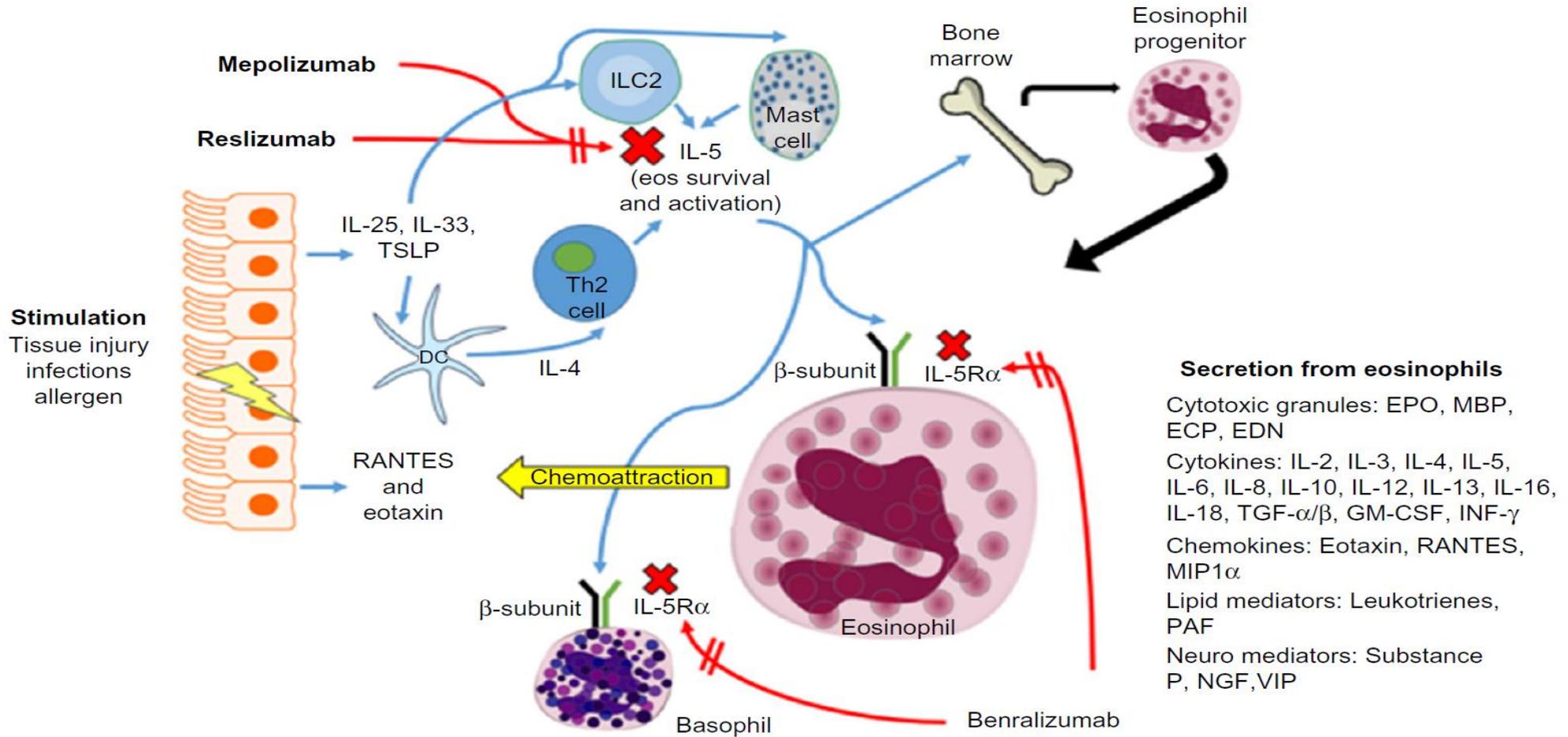
	<b>A: allergic-predominant asthma</b>	<b>B: eosinophilic-predominant asthma</b>
<b>1</b>	Early onset	Late onset
<b>2</b>	SPT/RAST+ with clinically significant allergies <sup>#</sup>	SPT/RAST- or + with no clinically significant allergies
<b>3</b>	IgE >100 IU·mL <sup>-1</sup>	IgE <100 IU·mL <sup>-1</sup>
<b>4</b>	Allergic rhinitis	Nasal polyps
<b>5</b>	High <i>F</i> <sub>ENO</sub> (30–50 ppb)	Very high <i>F</i> <sub>ENO</sub> (>50 ppb)
<b>6</b>	Blood eosinophils <300 cells·μL <sup>-1</sup>	Blood eosinophils >300 cells·μL <sup>-1</sup> <sup>#</sup>

SPT: skin prick test; RAST: radioallergosorbent test; *F*<sub>ENO</sub>: exhaled nitric oxide fraction. Check the number of relevant patient characteristics per column. If a patient has more features from column A or B it is more likely that he/she has allergic- or eosinophilic-predominant asthma, respectively. If the patient shares features from both columns, it is more likely that he/she suffers from eosinophilic/allergic overlap asthma. <sup>#</sup>: obligatory characteristics for allergic and/or eosinophilic asthma.

# Eosinophils in asthma (IL-5)

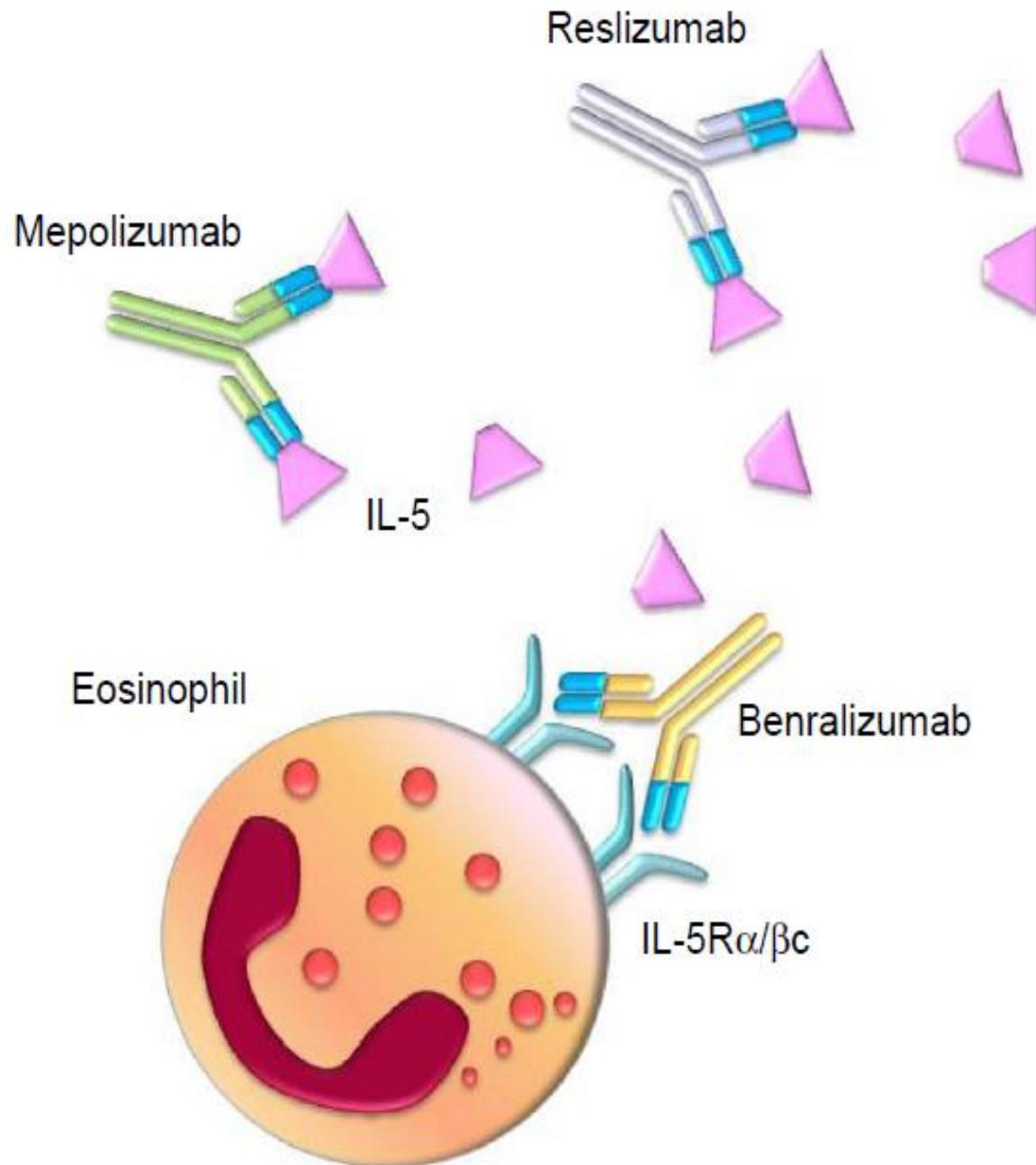


# Target on IL-5 and eosinophils in asthma



Molecu

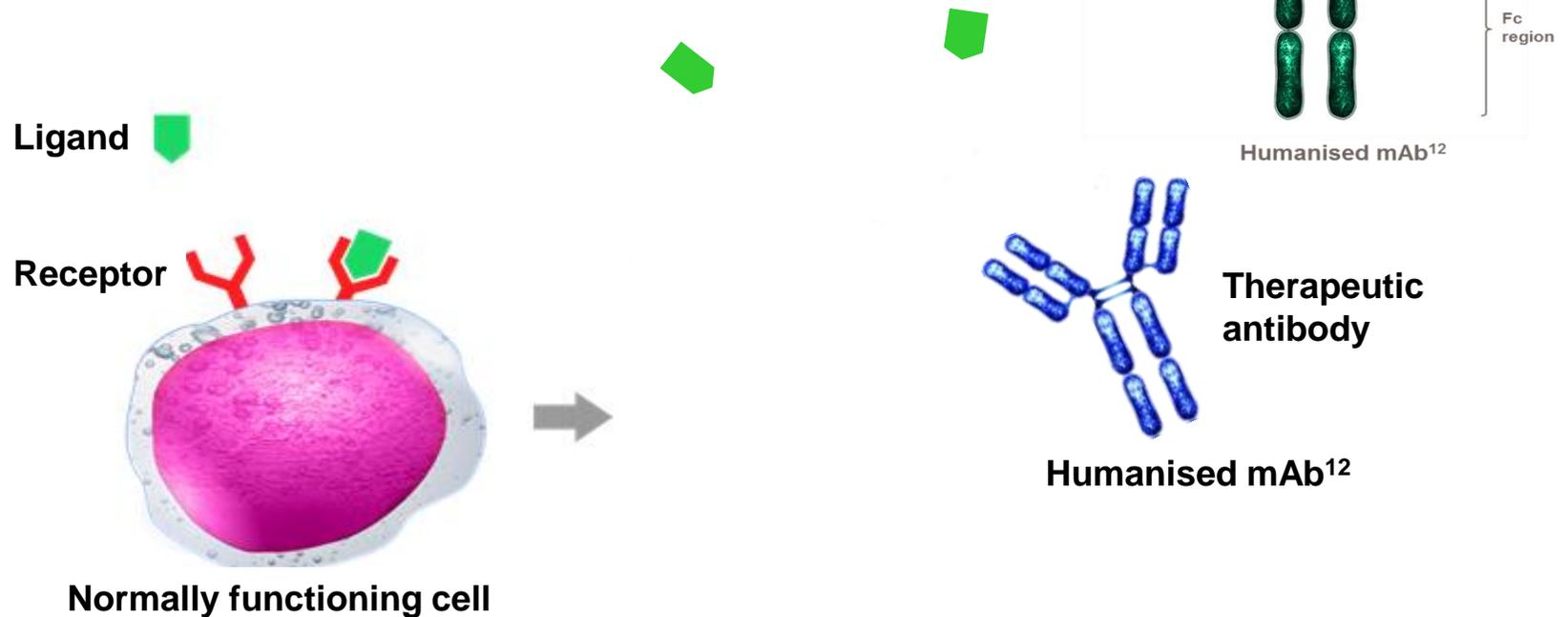
ways



# Mepolizumab

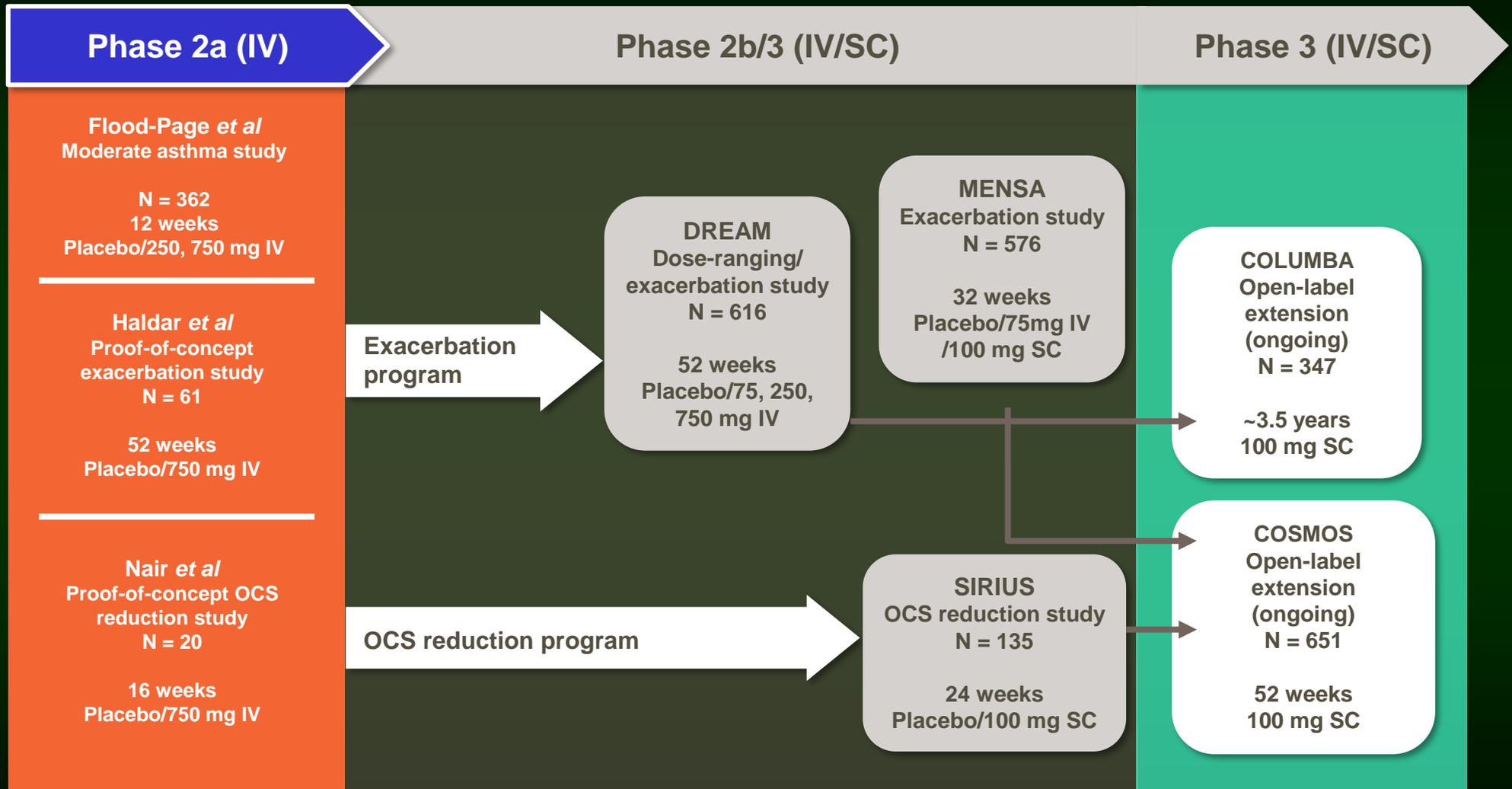
Mepolizumab is a humanised, Chinese-hamster ovary–derived mAb targeted against human interleukin-5 (IL-5).

It was created by fusing IL5–specific complementarity-determining regions (CDRs) to human immunoglobulin G1κ (IgG1κ) heavy and light chains.



# Mepolizumab: A treatment for patients with severe eosinophilic asthma

## Key Clinical Efficacy and Safety Studies

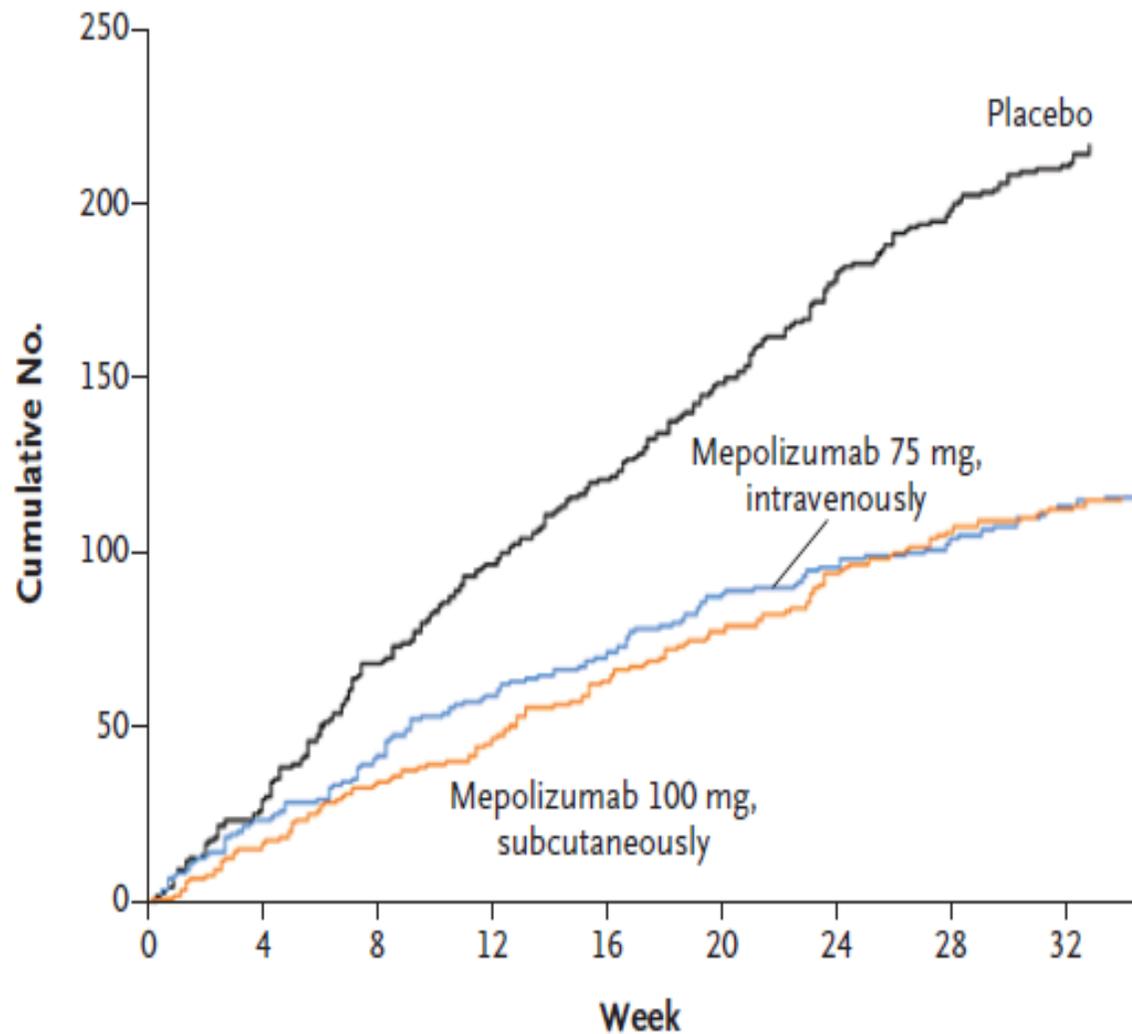


IV = intravenous; SC = subcutaneous; OCS = oral corticosteroid.

1. GlaxoSmithKline. Data on file. Module 2.5: Clinical Overview. 2. Flood-Page P, et al. *Am J Respir Crit Care Med.* 2007;176:1062-1071. 3. Haldar P, et al. *N Engl J Med.* 2009;360:973-984. 4. Nair P, et al. *N Engl J Med.* 2009;360:985-993. 5. Pavord ID, et al. *Lancet.* 2012;380:651-659.

# Mepolizumab (anti-IL-5) for severe

A Asthma Exacerbations



n=449

75 mg  
100 mg

# Case Presentation

- 李孟O, 66y/o female.
- Admission 12 times from 2003 to 2008  
4 times respiratory failure  
Medications with: Seretide evohaler (250/25),  
Combivent MDI, oral LABA, Allegra, (xanthium  
induced GI upset), and PRN oral steroid used.
- 2008 李秀O,

# Case Presentation

- Review of the history:  
Aspirin-related Asthma,  
Allergy: NSAID, Solu-medrol → 眼睛紅腫
- Add Singulair (10mg) 1# hs used.  
Shifted to Symbicort used with SMART therapy  
Flixonase nasal auqa spray

# Case Presentation

- 2012: frequent attack....
- Poor control by ICS (higher dose or SMART), LABA, Singulair, xanthium used. Frequent use of steroid and rescue medications
- Lung function: FEV1: 1.02L (43% of predicted) to 1.32L (61% of predicted), FVC: 2.15L, BD(+)
- BMI: 31.5
- Sputum : eosinophil count < 3%
- Serum IgE: 701

- 常常吸到燒金紙的味道, 故常會有Cough, 胸悶, 喘, wheezing, 呼吸不順, sputum 量多, 難咳
- ACT: 13, PEF: 130-160
- 健保申請Xolair (Anti-IgE) therapy
- 被退件
- 原因: IgE太高

1. In the past **4 weeks**, how much of the time did your **asthma** keep you from getting as much done at work, school or at home?

All of the time	1	Most of the time	2	Some of the time	3	A little of the time	4	None of the time	5	SCORE	2
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2. During the past **4 weeks**, how often have you had shortness of breath?

More than once a day	1	Once a day	2	3 to 6 times a week	3	Once or twice a week	4	Not at all	5	SCORE	2
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3. During the past **4 weeks**, how often did your **asthma** symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

4 or more nights a week	1	2 or 3 nights a week	2	Once a week	3	Once or twice	4	Not at all	5	SCORE	4
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4. During the past **4 weeks**, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

3 or more times per day	1	1 or 2 times per day	2	2 or 3 times per week	3	Once a week or less	4	Not at all	5	SCORE	3
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5. How would you rate your **asthma** control during the **past 4 weeks**?

Not controlled at all	1	Poorly controlled	2	Somewhat controlled	3	Well controlled	4	Completely controlled	5	SCORE	2
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# Add inhaled LAMA

- Add inhaled Tiotropium, general condition improved status.
- No asthma attack for several years.
- Poor asthma controlled and frequent attack since 2018,

# Serum Eosinophil counts

2016-07-26 11:23	2016-07-29 12:39	2016-08-02 13:04	2016-08-12 10:22	2016-10-11 15:41	2017-03-10 09:31	2017-05-12 09:10	2017-11-12 19:22	2018-04-25 09:40
<b>12.81</b>	<b>5.77</b>	<b>6.57</b>	<b>6.57</b>	<b>9.93</b>	6.99	<b>7.17</b>	<b>11.60</b>	<b>7.21</b>
<b>5.7</b>	<b>13.0</b>	<b>13.2</b>	<b>9.1</b>	<b>4.3</b>	2.3	<b>9.1</b>	<b>9.9</b>	<b>22.</b>

2018-04: serum eosinophil count =1586 cells/uL

2018-04: IgE: 946 IU/ML

# Add on Mepolizumab

- Add on anti-IL 5 agent (Nucala) 1amp/ month since 2018-09
- Improved status after 2-3 days' injection
- ACT: 19-22, no more attack
- Serum eosinophil counts:

2018-10-11 15:41	2018-10-15 09:31	2018-10-30 09:10	2017-11-30 19:22	2018-12-22 09:40
0.4	0.0	0.0	0.0	0.1

# Nucala experiences-clinical data

	Sex	Age	FEV1(%)	CRSwNP	Eos.	IgE	Xolair	OCS
李OO	F	78	61	+	1586	946	+	5mg/day
黃石OO	F	72	57.4	-	505	471	+	5mg/day
張OO	F	68	52.8	+	1304	2730	+	10mg/day
詹OO	M	66	67.2	+	885	28.4	-	10mg
林OO	M	54	64.6	+	884	443	+	10mg

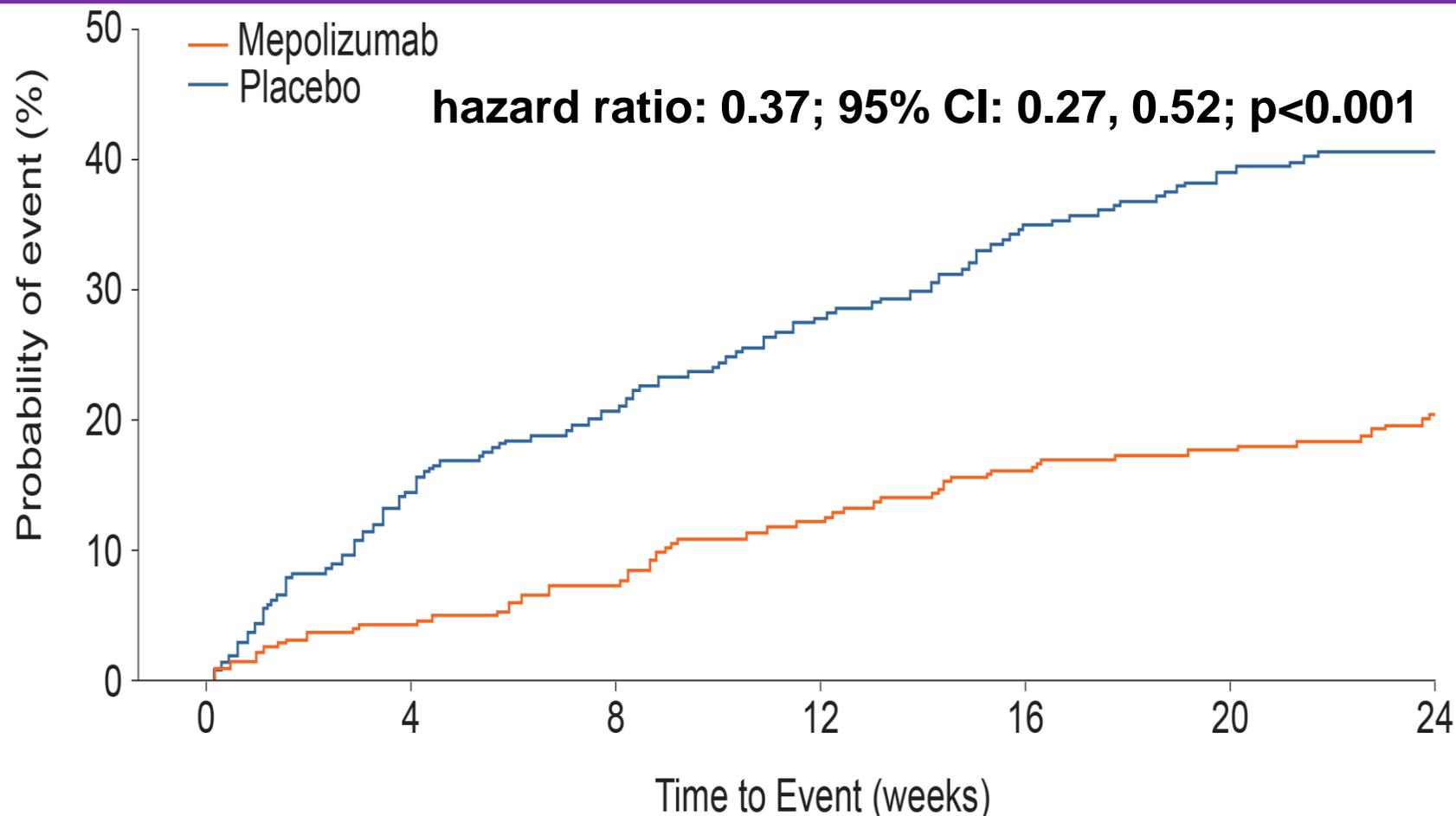
# Nucala experiences- 4 months

	FEV1(%)	FEV1 (%) After Nu.	Eos.	Eos. After Nu.	A.E	OCS
李OO	61	66.4	1586 (22%)	26 (0.2%)	-	-
黃石OO	57.4	61.7	505 (5.8%)	16 (0.1%)	-	-
張OO	52.8	59.3	1304 (15%)	34 (0.3%)	-	-
詹OO	67.2	73.9	885 (8.5%)	69 (1.5%)	-	-
林OO	64.6	69.5	884 (17%)	27 (1.2%)	-	-

# Mepolizumab Improves Lung Function and Exacerbation Rates in Severe Eosinophilic Asthma:

2019 ATS

Adjusted mean change from baseline (mL)

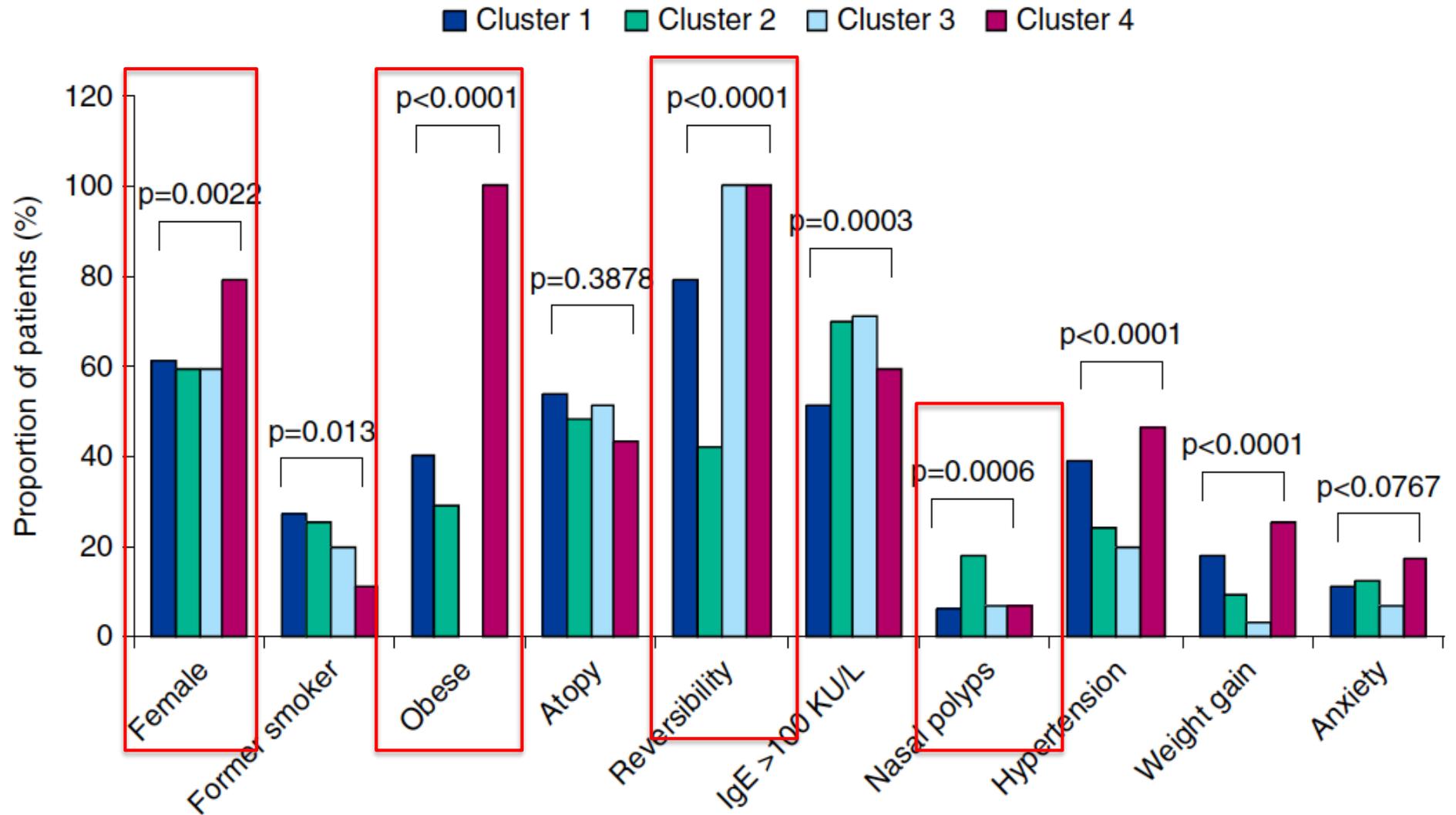


Number at risk

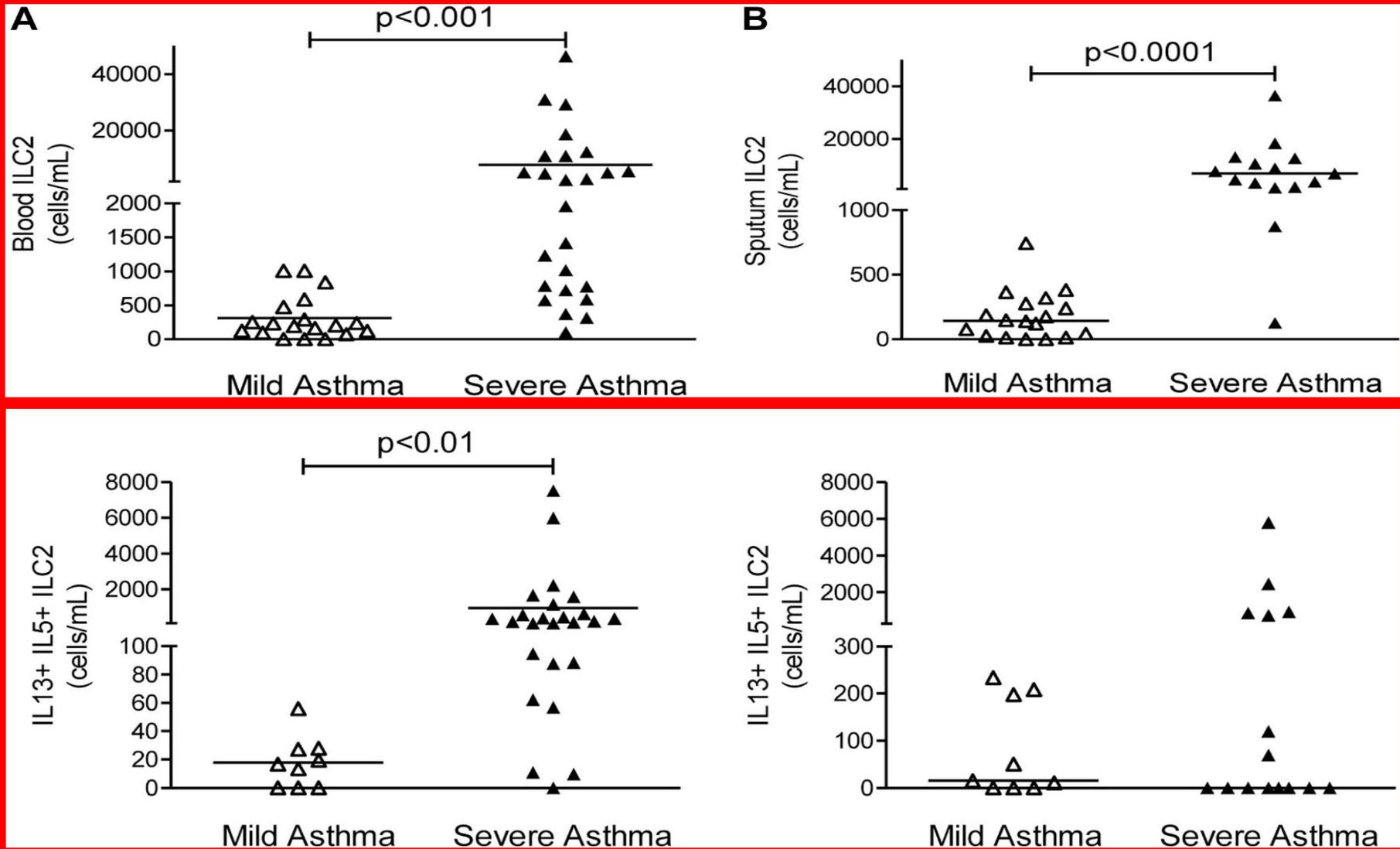
Placebo	277	225	213	192	172	160	116
Mepolizumab	274	262	251	236	225	221	179

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\*\*  
24

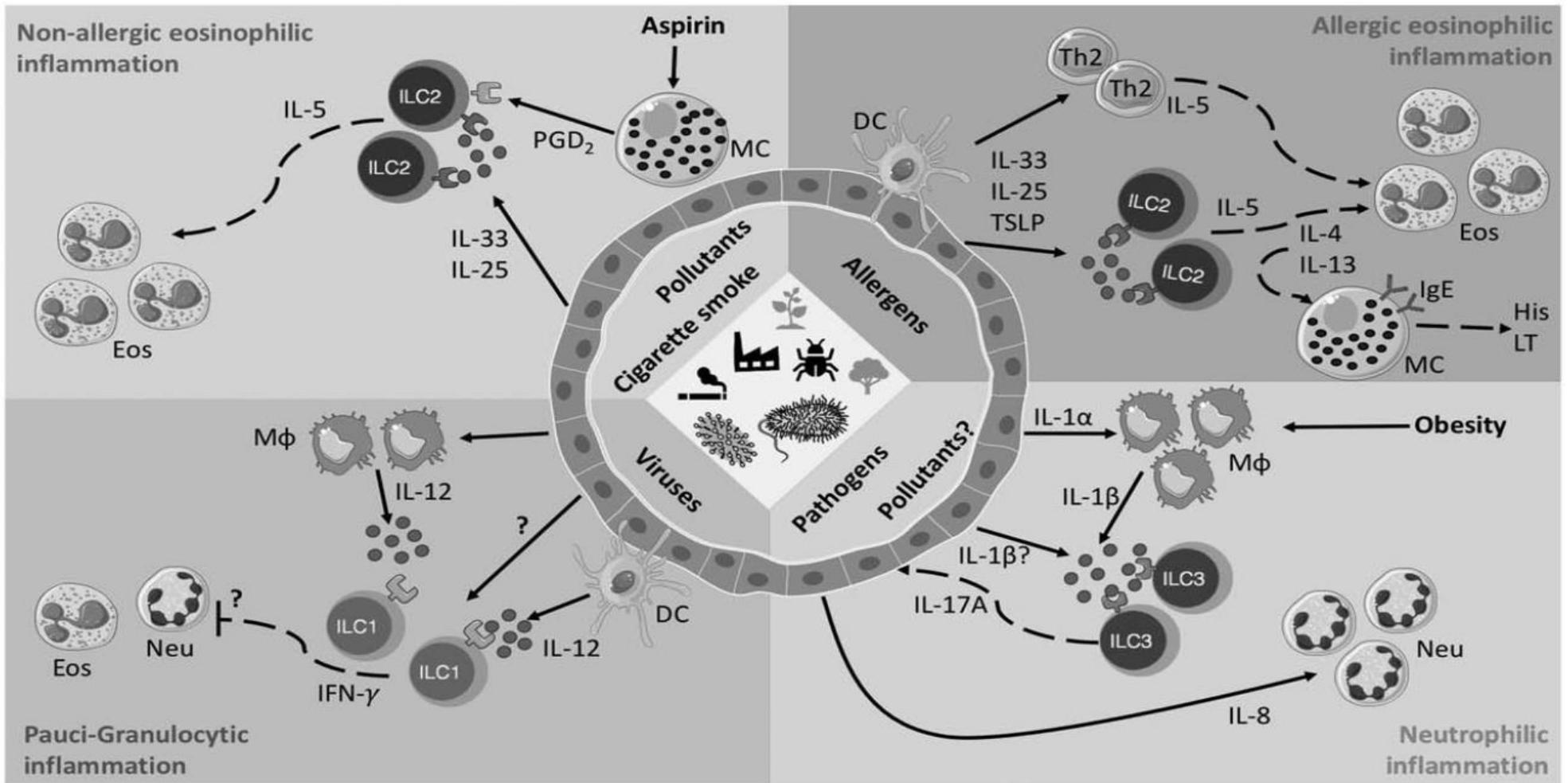
# Responder to Mepolizumab



# ILC2 and severe asthma



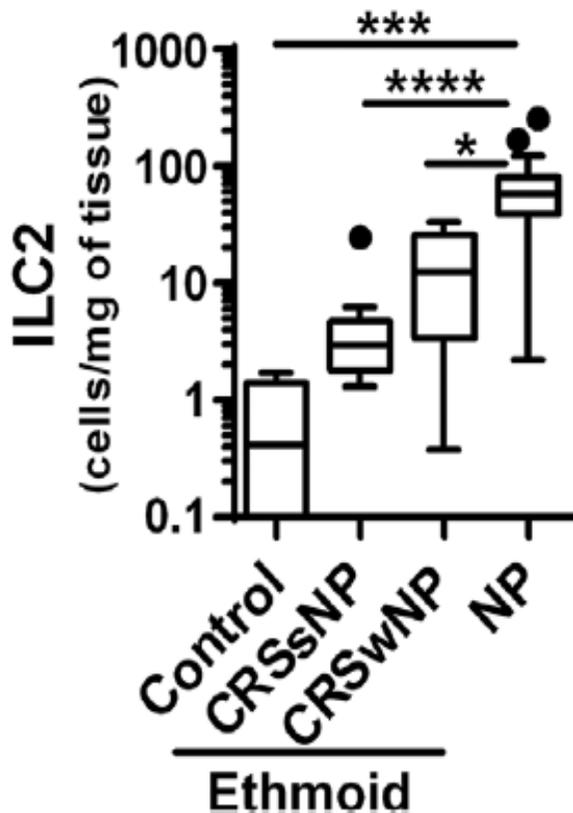
# innate lymphoid cell subtypes in different asthma inflammatory phenotypes



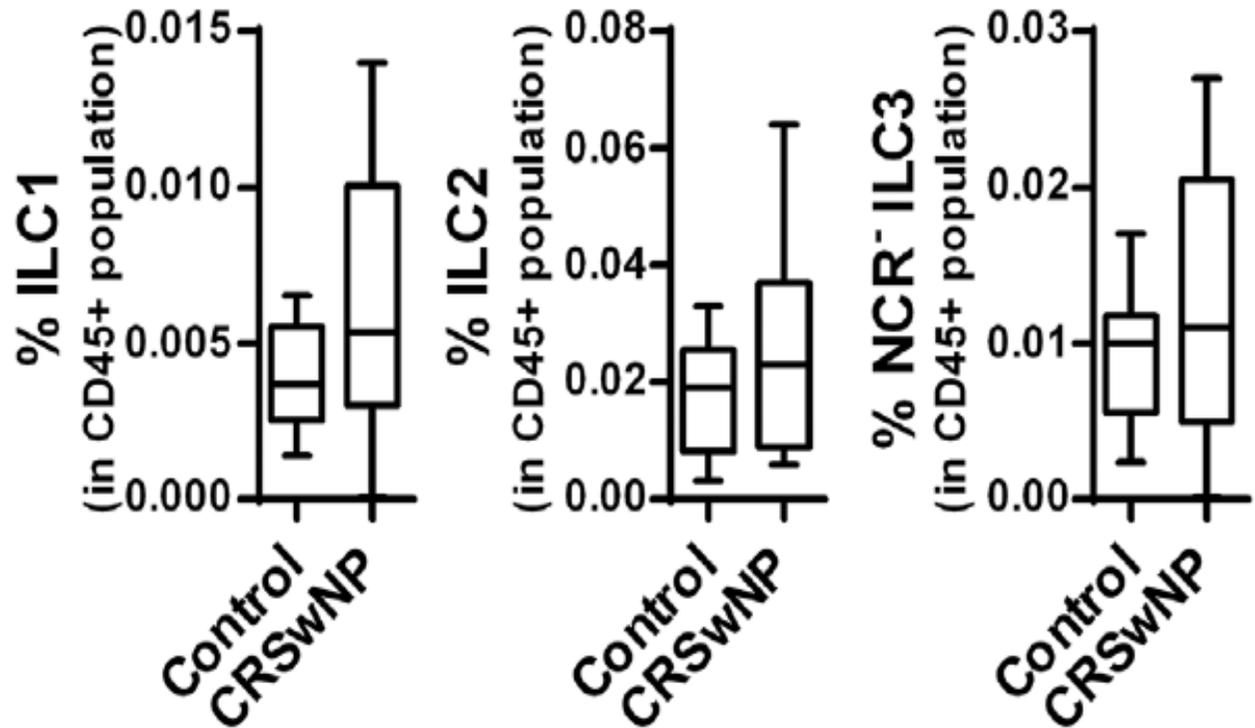


# ILC-2 and chronic rhinosinusitis with nasal polyps (CRSwNP)

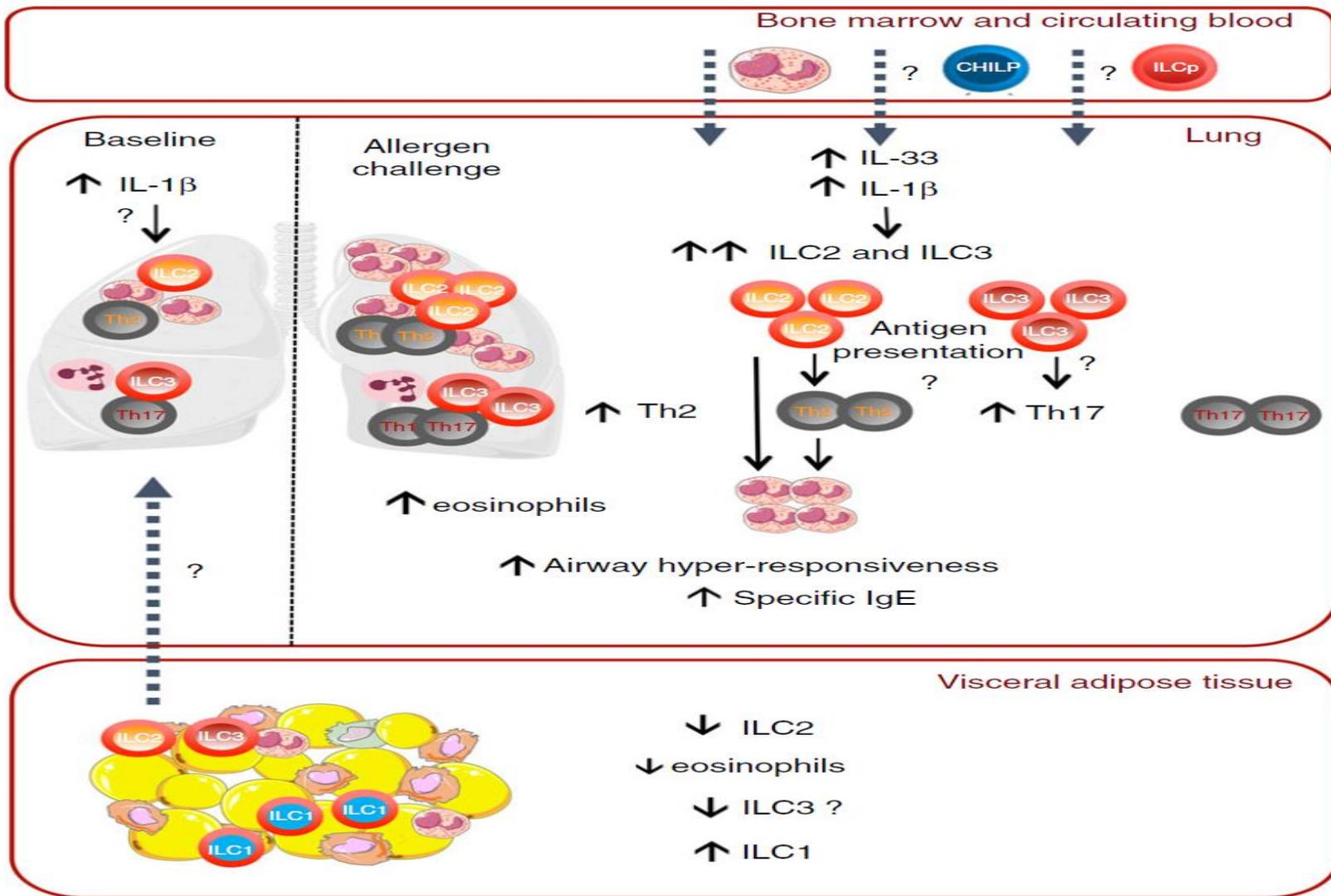
**C. Sinus tissue**



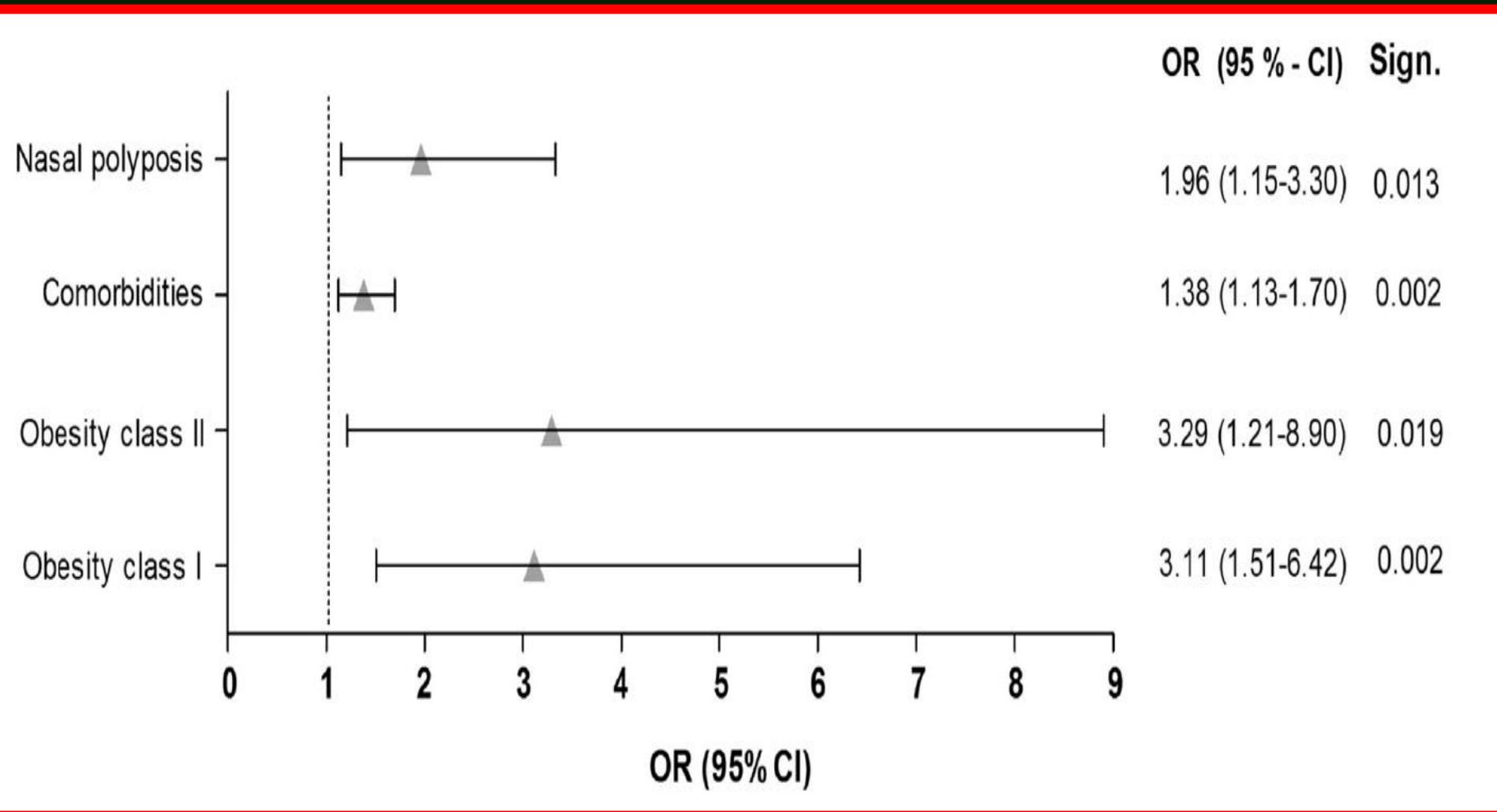
**D. PBMC**



# ILC-2 with asthma and obesity



# Factors reducing omalizumab response in severe asthma



# The clinical benefit of mepolizumab replacing omalizumab in uncontrolled severe eosinophilic asthma.

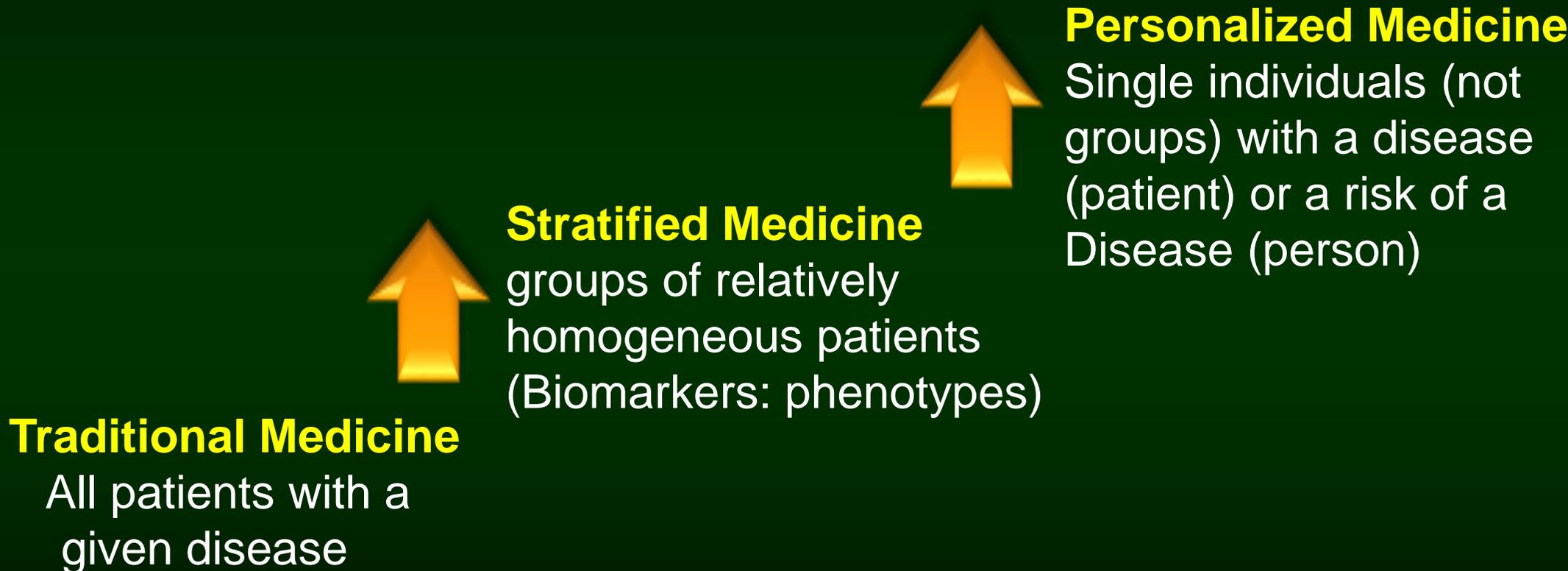
- At baseline, patients with blood eosinophil counts  $\geq 150$  cells/ $\mu\text{L}$  (or  $\geq 300$  cells/ $\mu\text{L}$  in the prior year) and an Asthma Control Questionnaire (ACQ)-5 score  $\geq 1.5$  discontinued omalizumab and immediately commenced mepolizumab 100 mg subcutaneously every 4 weeks.
- with **77% and 79% of patients achieving the minimum clinically important differences (ACQ-5:  $\geq 0.5$  points; SGRQ:  $\geq 4$  points)**, respectively. The annualized rate of clinically significant exacerbations **was 1.18 events/year, a 64% reduction** from 3.26 events/year during the previous year. Safety and immunogenicity profiles were consistent with previous trials.

# Key Updates in GINA Pocket Guide April 2019 Version

	Anti-IgE	Anti-IL5	Anti-IL-4R
Eligibility Criteria	Severe allergic asthma <ul style="list-style-type: none"> <li>• Sensitization on skin prick testing or specific IgE</li> <li>• Total serum IgE and weight within dosage range</li> <li>• Exacerbations in last year</li> </ul>	Severe eosinophilic asthma <ul style="list-style-type: none"> <li>• Exacerbations in last year</li> <li>• Blood eosinophils <math>\geq 300</math></li> </ul>	Severe eosinophilic asthma/Type 2 asthma <ul style="list-style-type: none"> <li>• Exacerbations in last year</li> <li>• Blood eosinophils <math>\geq 150</math> or FeNO <math>\geq 25</math></li> </ul> Or need for maintenance OCS
Predictive Factors for good asthma response	<ul style="list-style-type: none"> <li>• Blood eosinophils <math>\geq 260</math>++</li> <li>• FeNO <math>\geq 20</math>+</li> <li>• Allergen-driven symptoms+</li> <li>• Childhood-onset asthma+</li> </ul>	<ul style="list-style-type: none"> <li>• Higher blood eosinophils+++</li> <li>• More exacerbations in previous year+++</li> <li>• Adult-onset asthma++</li> <li>• Nasal polyposis++</li> </ul>	<ul style="list-style-type: none"> <li>• Higher blood eosinophils+++</li> <li>• Higher FeNO+++</li> </ul> Anti-IL4R may also be used to treat <ul style="list-style-type: none"> <li>• Moderate/severe atopic dermatitis</li> <li>• Nasal polyposis</li> </ul>
<b>+++ , ++ , +: Plus signs indicate the strength of an association</b>			

# Treatable traits:

toward precision medicine of chronic airway diseases



Agusti *et al.* *Am J Respir Crit Care Med.* 2015; 191: 391-401.

Agusti *et al.* *Eur Respir J.* 2016; 47: 410-419.

# Take Home Message

- Systemic approach including inhaler techniques, adherence and comorbidities
- Higher serum eosinophil counts and CRSwNP with higher exacerbation rates and poor asthma control
- Allergic and non-allergic related severe eosinophilic asthma inflammation
- ILC2 play important roles
- Anti-IL 5 agents (mepolizumab) improved asthma controlled, decreased A.E and lung function improved esp. in patients with Late onset, higher EOS, CRSwNP, Obese phenotypes.

*Thanks for Your Attention*

