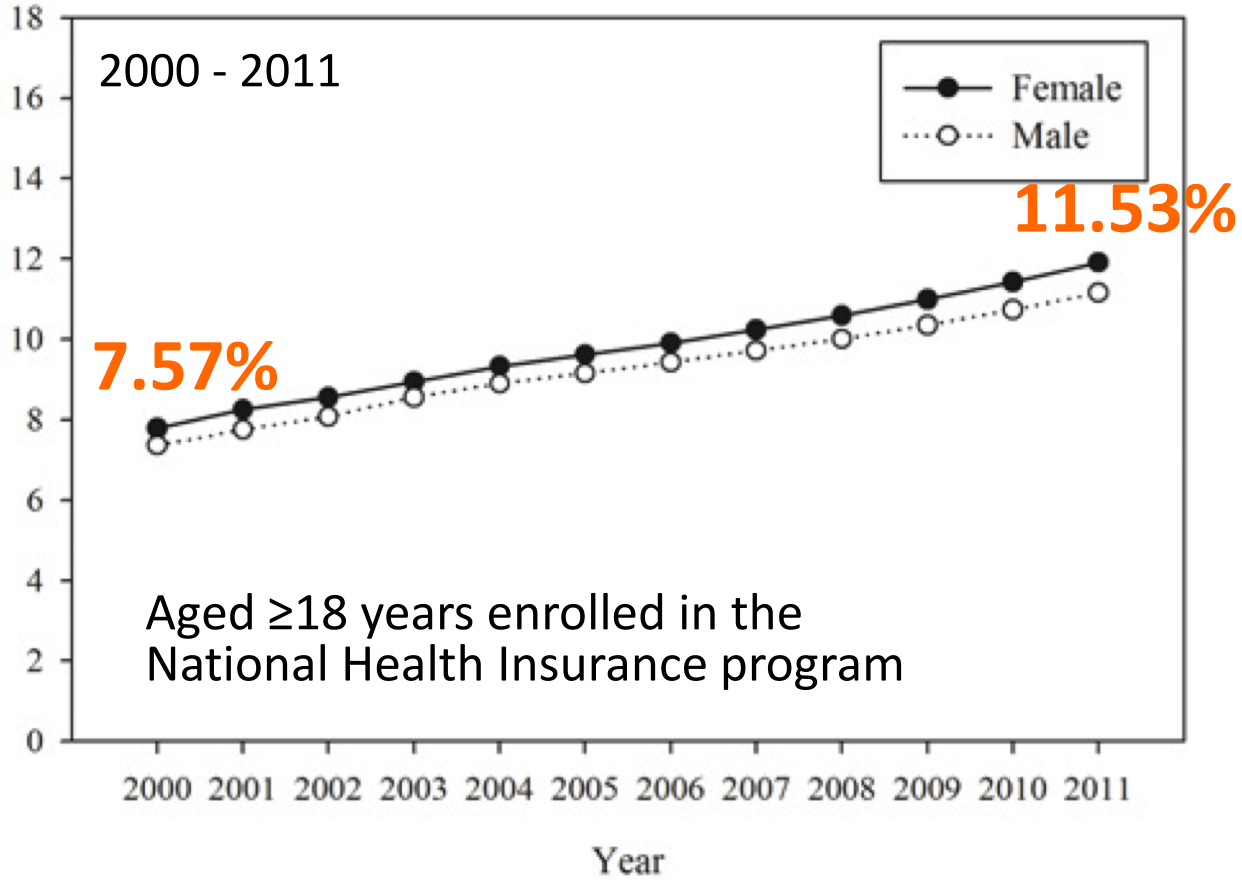
# The severe asthma treatment, biologics as an accessible options-Taiwanese experience

Kang-Yun Lee, MD PhD

Shuang Ho Hospital
Taipei Medical University

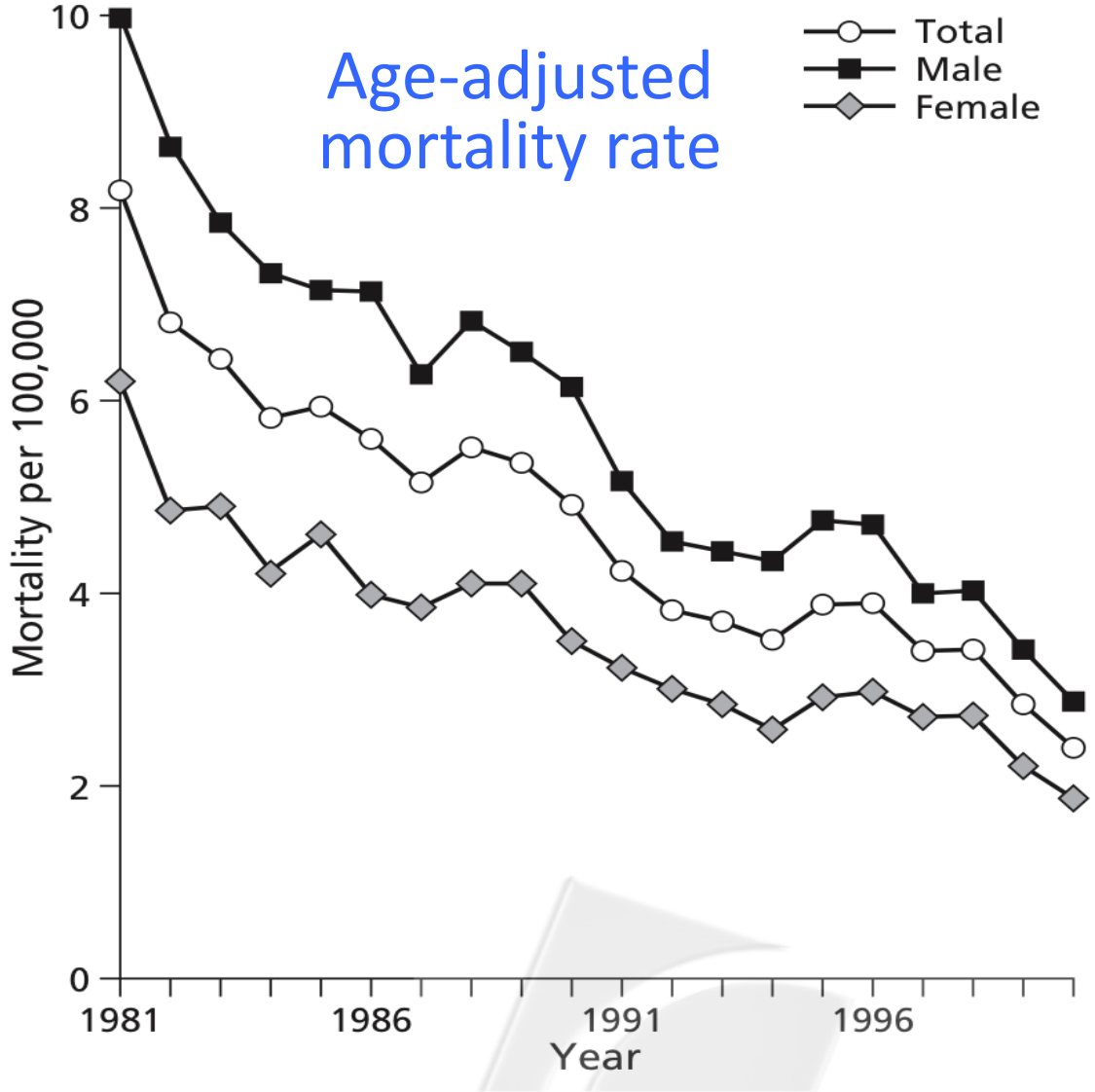
# Burden of Asthma in Taiwan

## The crude annual prevalence of adult diagnosed asthma in Taiwan




Ma YC, PLoS One. 2015 Oct 20;10(10):e0140318.

## Age-adjusted mortality rate




J Formos Med Assoc 2003;102(8):534-8.

# Health care utilization and costs of adult asthma in Taiwan

95,110 patients, 18 –55 years old,
he National Health Insurance Research Database
January 1 to December 31, 2002.

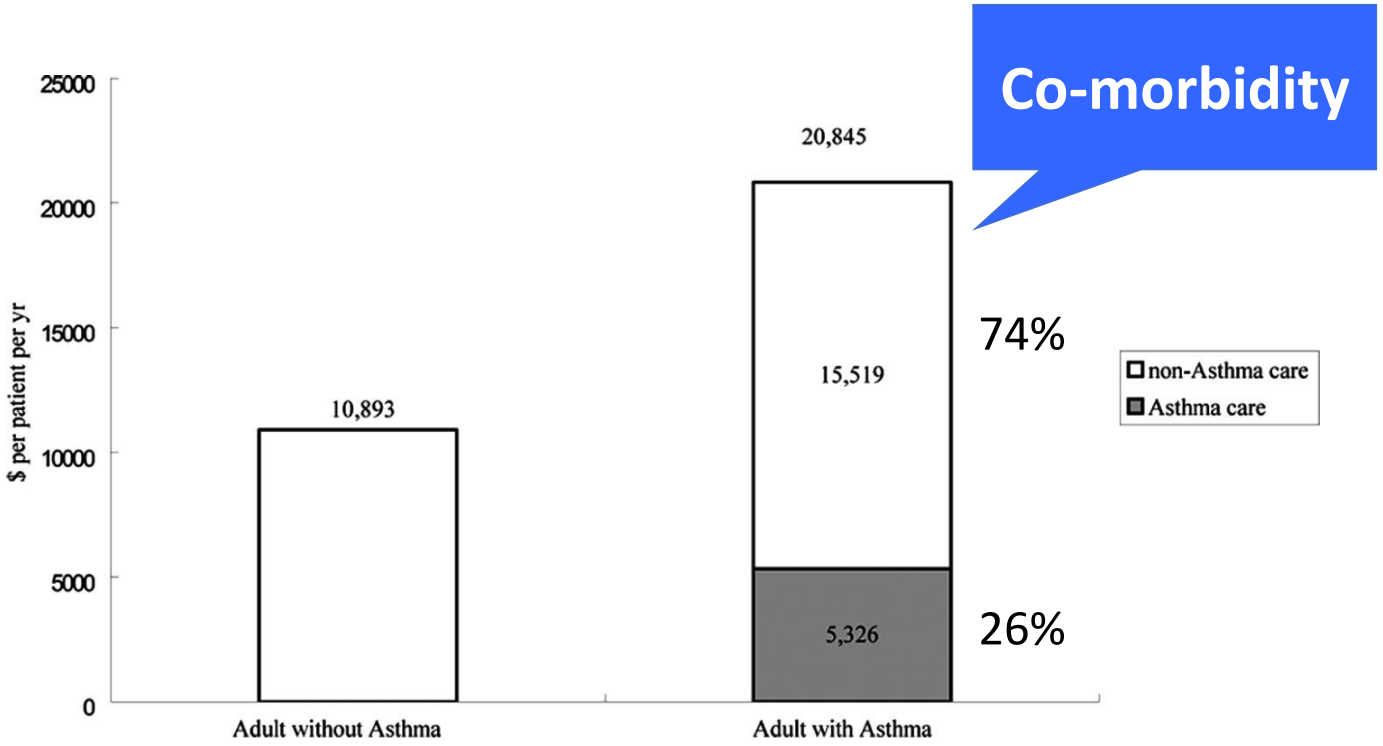
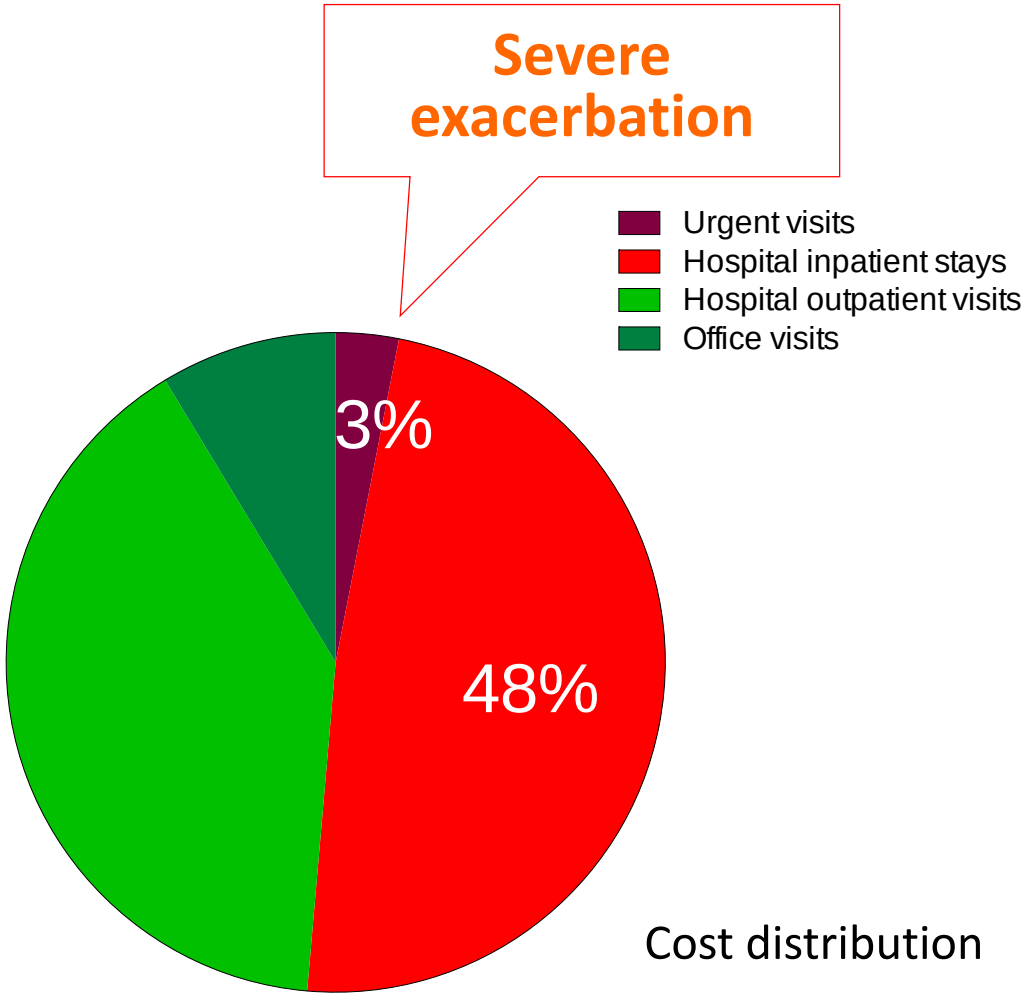



*Figure 1. Distribution of costs in patients with and patients without asthma.*




Cost distribution

Sun HL, Allergy and asthma proceedings 2008;29(2):177-81.

# Committee for Severe Asthma Consensus (2019)

台灣成人氣喘
# Taiwan Guideline for Adult Asthma
診療指引

**TSPCCM** Taiwan Society of Pulmonary and Critical Care Medicine collaborated with **Cochrane Taiwan**, following The **GRADE** approach (Grading of Recommendations Assessment, Development and Evaluation)

Published in July **2018**

台灣胸腔暨重症加護醫學會
Taiwan Society of Pulmonary and Critical Care Medicine

# Approach for Uncontrolled Asthma

**Compliance** — 吸入劑使用、藥物順從性

**Diagnosis** — 重新確認氣喘診斷

**Co-morbidity** — 危險因子/ 共病症

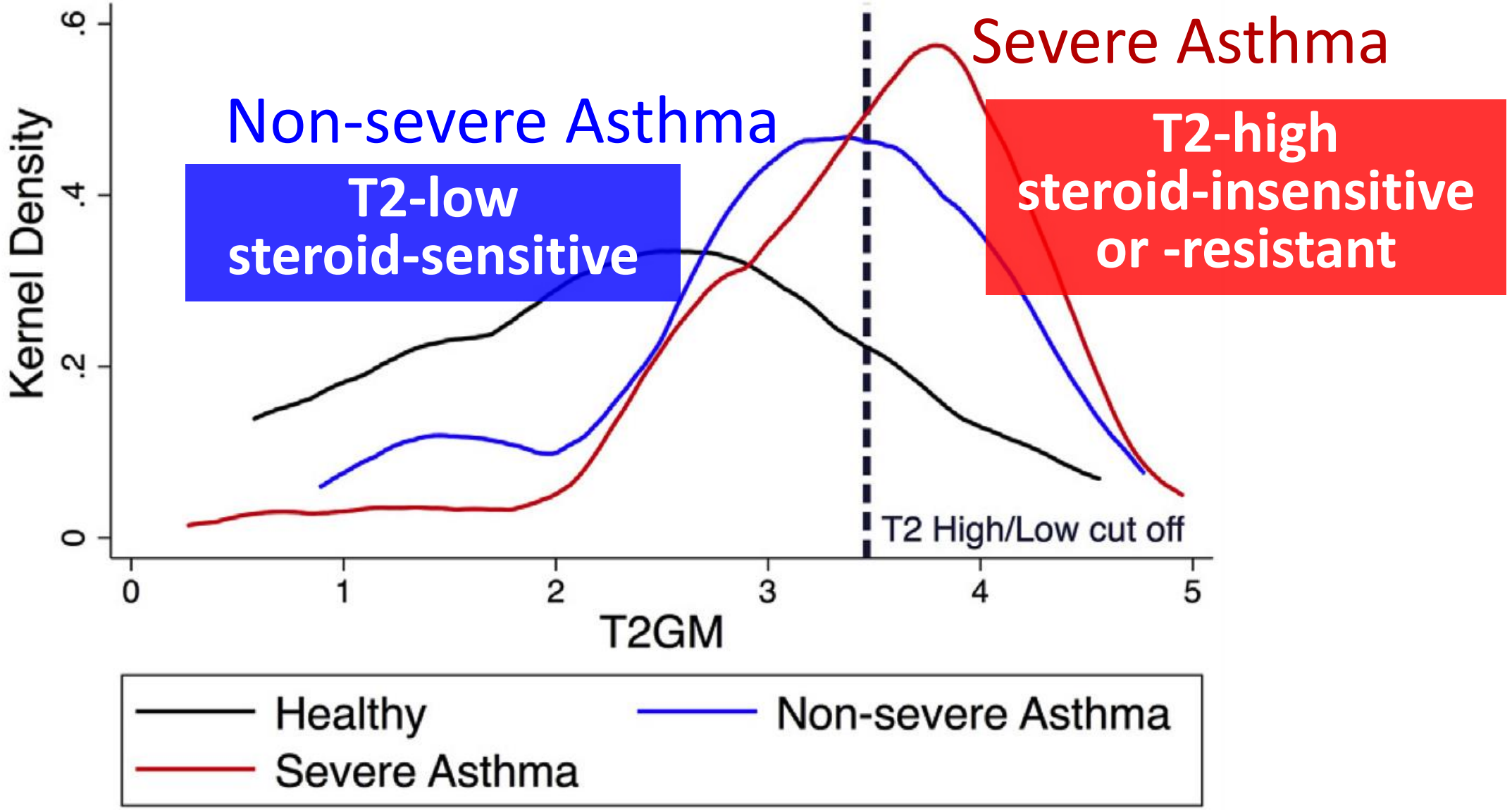
**Step-up** — 考慮升階治療

**Referral** — 轉診至專科醫師進行評估


上方流程圖呈現常見的臨床議題，但處理順序可依醫療資源和臨床狀況進行調整

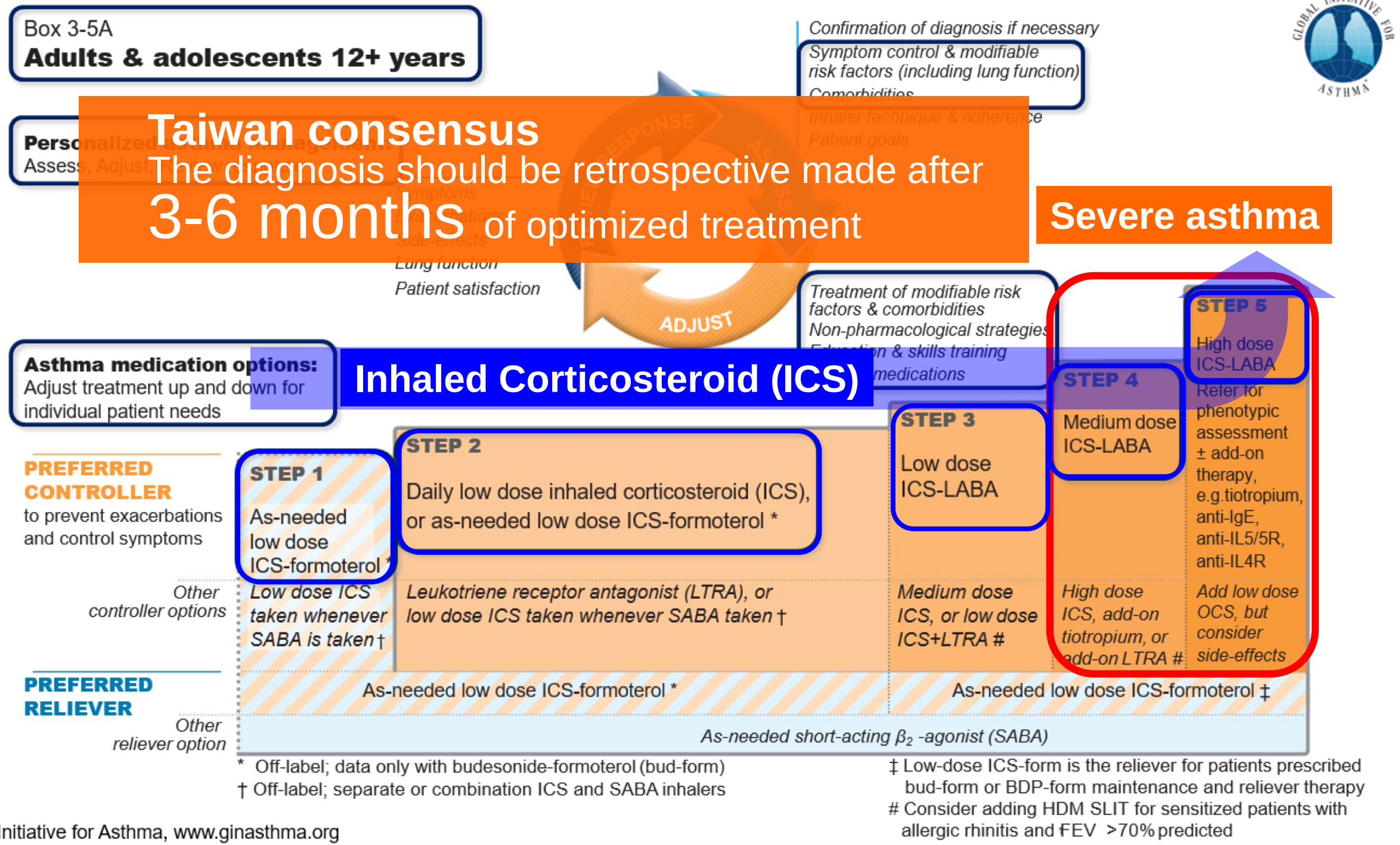
Global Initiative for Asthma. 2017 GINA Report, Global Strategy for Asthma Management and Prevention.

# Sputum Type 2 Gene Expression in Patients with Asthma Receiving ICSs

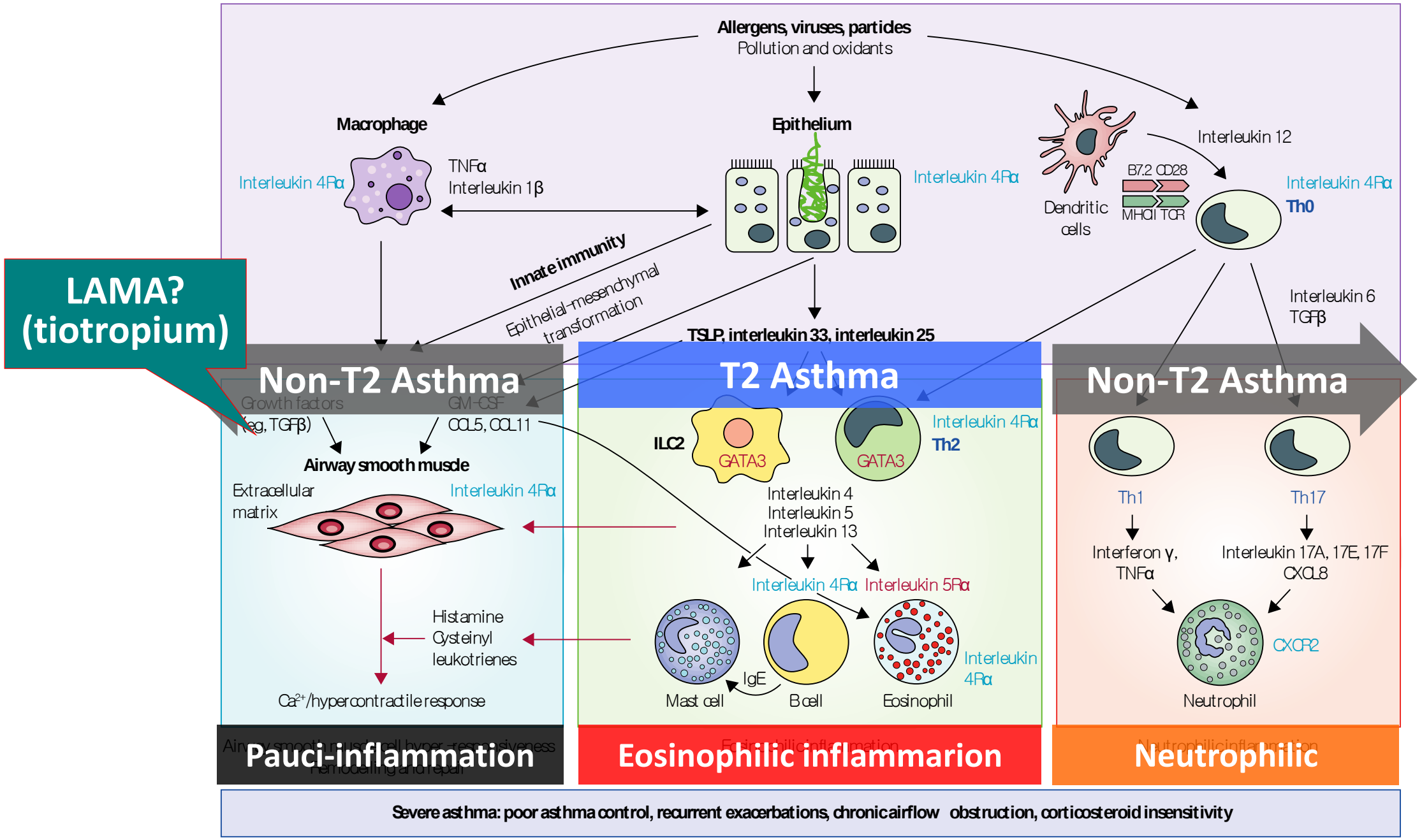



NHLBI Severe Asthma Research Program 3

Peters MC, J Allergy Clin Immunol. 2018 Mar 7. [Epub ahead of print]



# Pathophysiological Mechanisms Underlying Severe Asthma



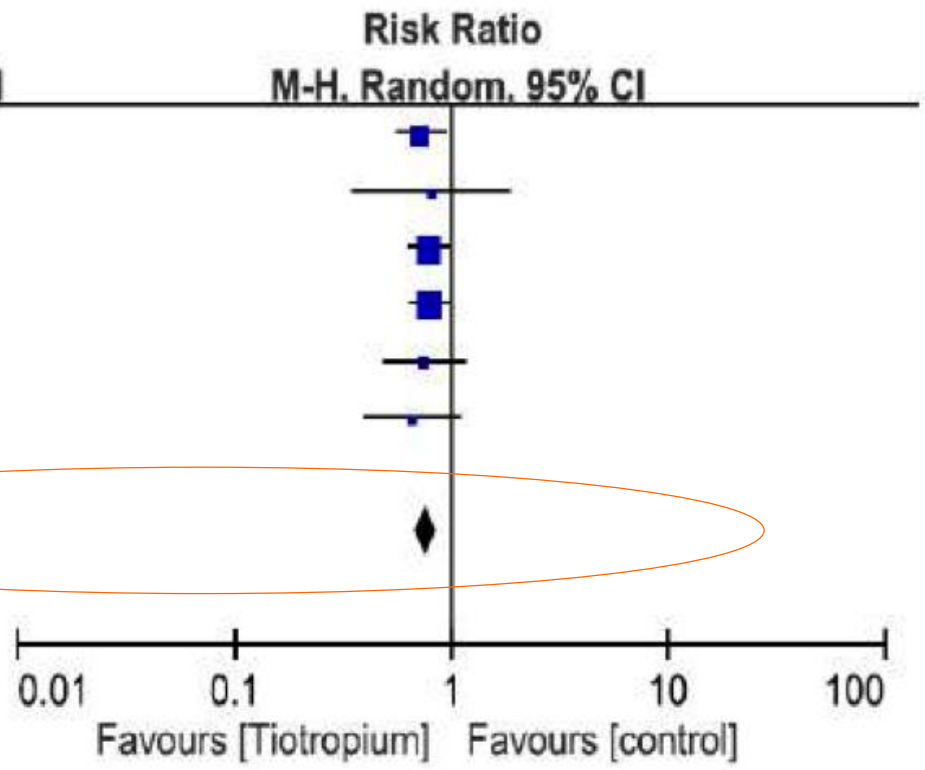

Chung KF, Lancet 2015; 386: 1086–96

# The Role of Tiotropium in Acute Exacerbation for Severe Asthma

**LAMA (Tiotropium)**
should be considered before using biologics
**GRADE 1A**

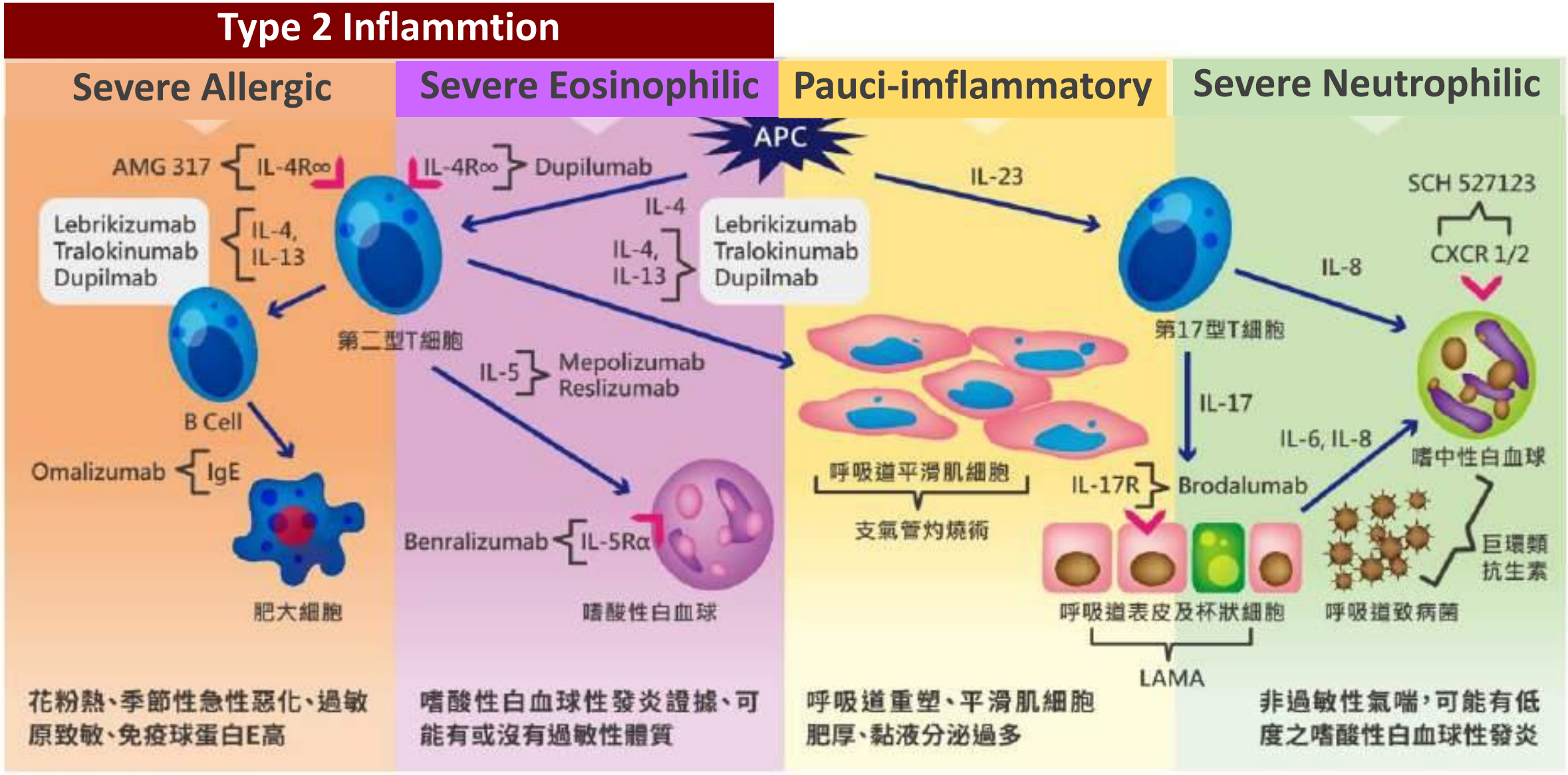
| Study or Subgroup | Tiotropium Events | Tiotropium Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Casale 2015 | 82 | 519 | 115 | 523 | 20.7% | 0.72 [0.56, 0.93] |
| Disse 2011 | 9 | 104 | 11 | 103 | 1.9% | 0.81 [0.35, 1.87] |
| Kerstjens Trial 1 2012 | 91 | 237 | 109 | 222 | 30.8% | 0.78 [0.63, 0.96] |
| Kerstjens Trial 2 2012 | 91 | 219 | 123 | 234 | 34.3% | 0.79 [0.65, 0.96] |
| Ohta 2015 | 33 | 114 | 22 | 57 | 7.1% | 0.75 [0.49, 1.16] |
| Szefler 2017 | 20 | 136 | 30 | 134 | 5.1% | 0.66 [0.39, 1.10] |
| **Total (95% CI)** | | **1329** | | **1273** | **100.0%** | **0.76 [0.68, 0.86]** |
| Total events | 326 | | 410 | | | |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.76$, $df = 5$ ($P = 0.98$); $I^2 = 0\%$
Test for overall effect: $Z = 4.56$ ($P < 0.00001$)



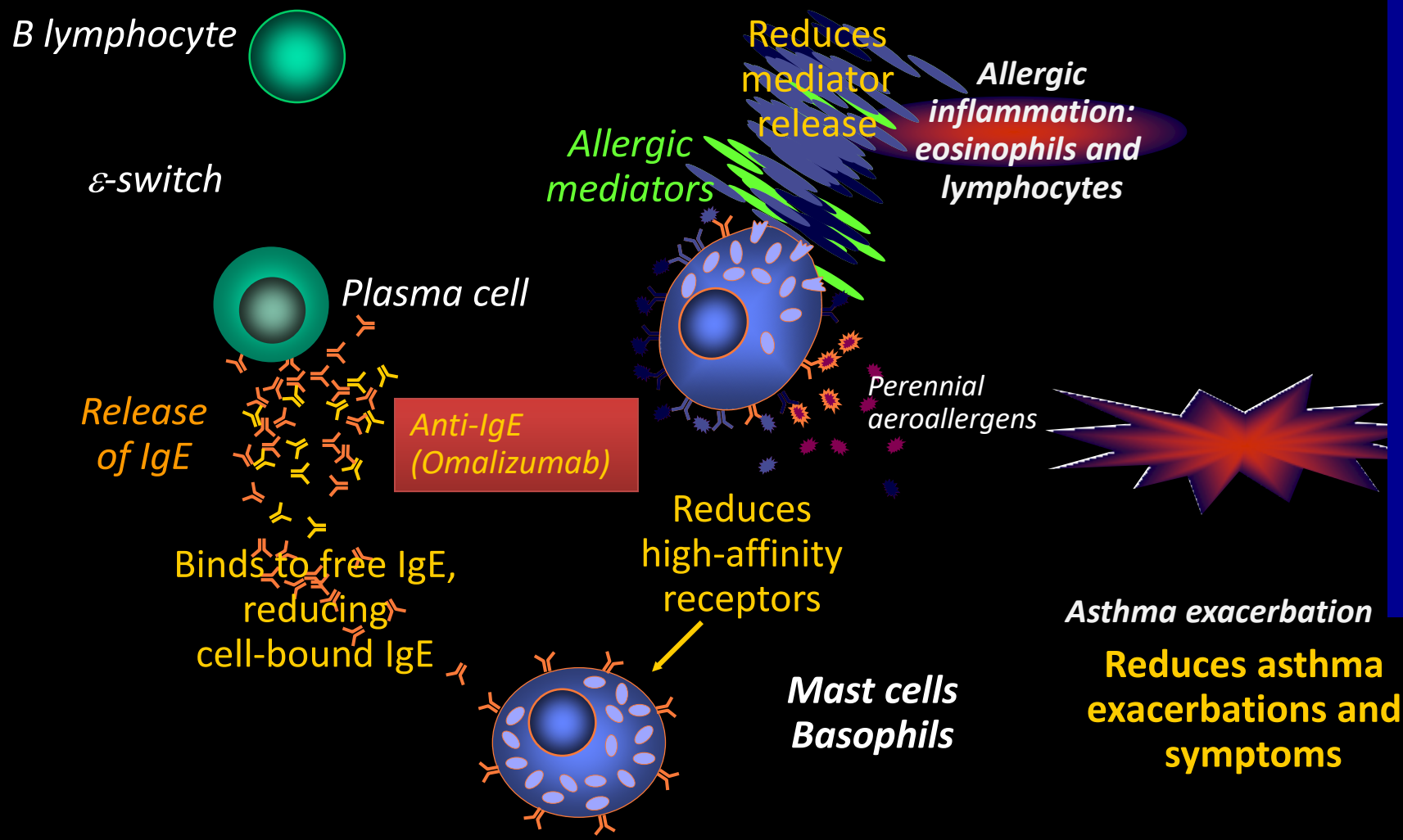

Taiwan Asthma Guideline, TSPCCM, 2018

# Phenotype-guided therapy for Severe Asthma




Taiwan Asthma Guideline, TSPCCM, 2018

# Anti-IgE therapy in Severe Allergic Asthma




## Omalizumab

**Taiwan NHI Payment Guidelines**

1. Severe persistent asthma
2. Non-smoker
3. Asthma history or PFT-documented asthma
4. High dose ICS + 2nd controller
5. **uncontrolled in 4 weeks**
6. **Total IgE : 30~1300IU/mL**

# Efficacy of omalizumab in patients with moderate to severe predominately chronic oral steroid dependent asthma in Taiwan

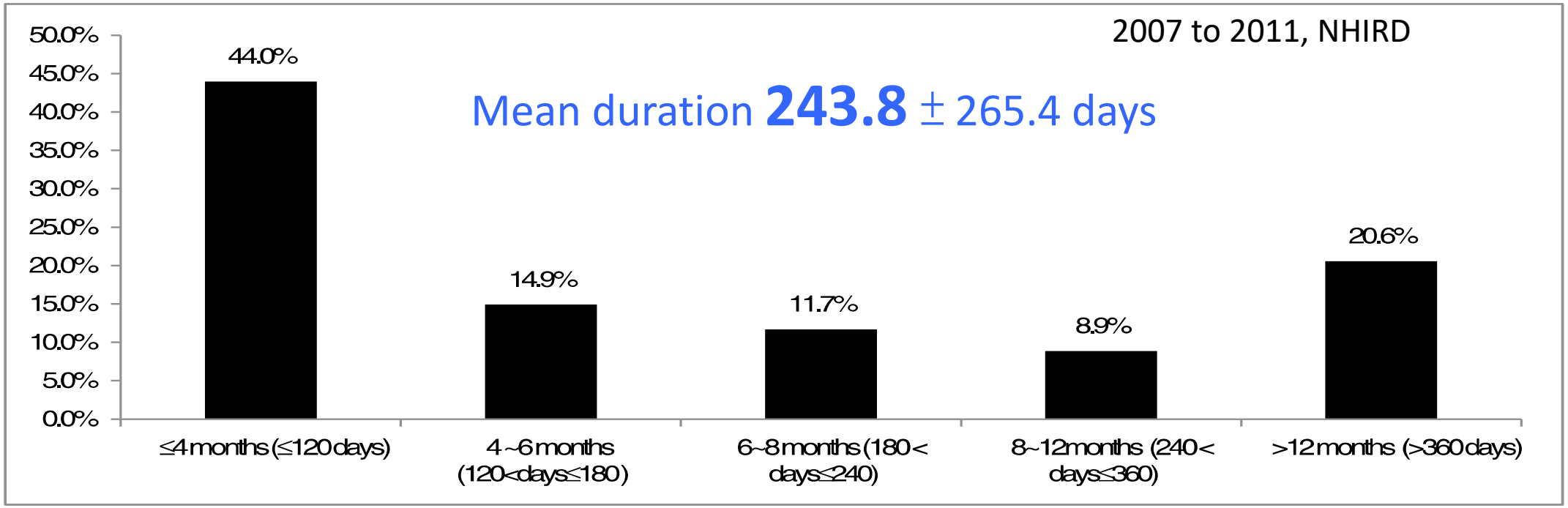



**Table 3** Changes in LABA/ICS dosages, OCS, SAMA, and LAMA post omalizumab therapy

| Duration >120 days | Baseline[a] | Follow-up[b] | Change from baseline | *p*-value[c] |
|---|---|---|---|---|
| *N* = 158 | Mean ± SD | Mean ± SD | Mean ± SD | |
| ICS plus LABA | | | | |
| Dose of salmeterol and fluticasone (mcg/day) | 302.73 ± 236.28 | 215.82 ± 243.06 | −86.91 ± 198.03 | <0.001* |
| Dose of formoterol and budesonide (mcg/day) | 162.72 ± 157.55 | 102.95 ± 149.38 | −59.76 ± 138.84 | <0.001* |
| OCS(tab/day) | 0.81 ± 1.61 | 0.00 ± 0.00 | −0.81 ± 1.61 | <0.001* |
| SAMA(bottle/month) | 0.44 ± 0.88 | 0.03 ± 0.21 | −0.41 ± 0.86 | <0.001* |
| LAMA(bottle/month) | 0.15 ± 0.36 | 0.13 ± 0.47 | −0.01 ± 0.47 | 0.6935 |

**34.8 % OCS free due to omalizumab**

[a]Baseline: 1 year before the index date
[b]Follow-up: 2 months before discontinuation (discontinuation of therapy was defined as a gap in therapy of 56 days)
[c]Fisher's exact test, *$P < 0.05$

Chen et al. BMC Pulmonary Medicine (2016) 16:3

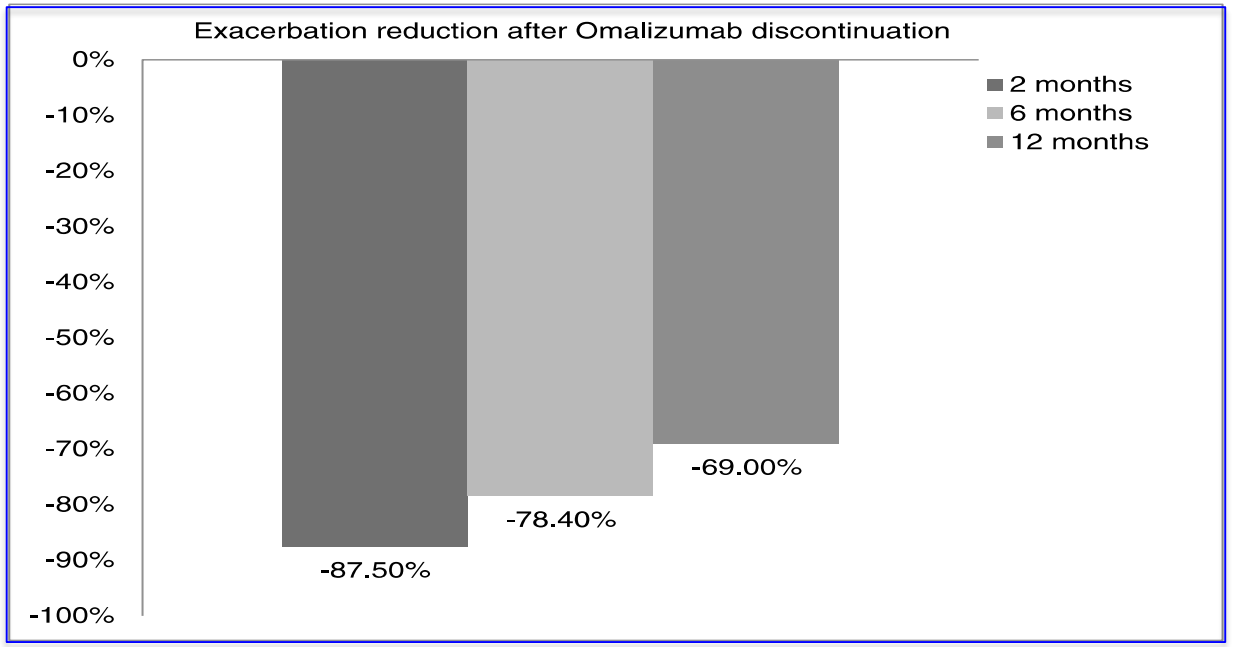
# Efficacy of omalizumab in patients with moderate to severe predominately chronic oral steroid dependent asthma in Taiwan

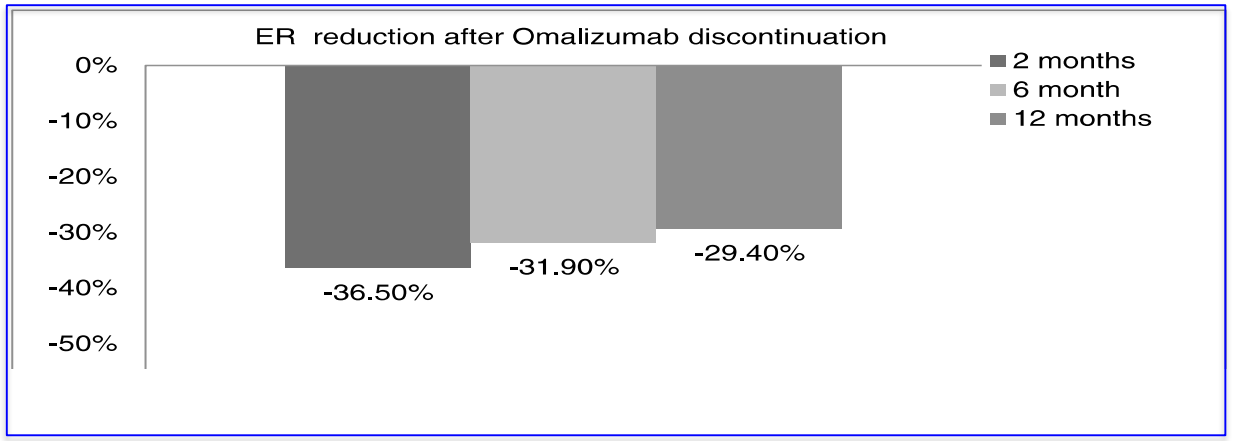
## Omalizumab Reduced ER Visits & Hospitalization

**Table 4** ER visits and hospitalizations post omalizumab therapy

| Duration >120 days | Baseline [a] | Follow-up [b] | *p*-value[c] |
|---|---|---|---|
| *N* = 158 | *N* (%) | *N* (%) | |
| ER visit | | | <0.001* |
| Yes | 69 (43.7 %) | 27 (17.1 %) | |
| No | 89 (56.3 %) | 131 (82.9 %) | |
| Inpatient visit | | | <0.001* |
| Yes | 55 (34.8 %) | 28 (17.7 %) | |
| No | 103 (65.2 %) | 130 (82.3 %) | |

[a]Baseline: 1 year before the index date
[b]Follow-up: 2 months before discontinuation (discontinuation of therapy was defined as a gap in therapy of 56 days)
[c]Fisher's exact test, *$P < 0.05$



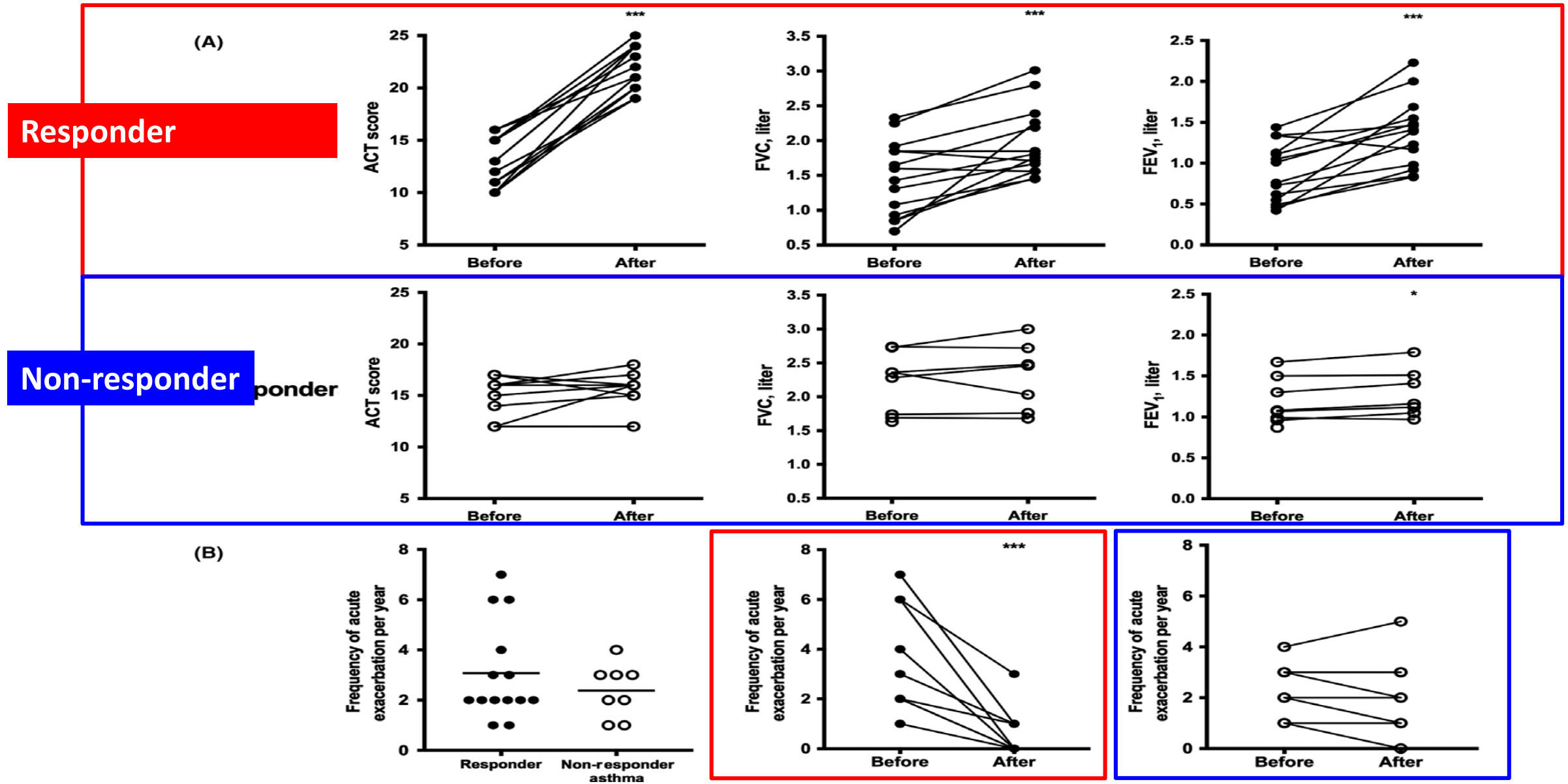




Chen et al. BMC Pulmonary Medicine (2016) 16:3

# Endotypes of severe allergic asthma patients who clinically benefit from anti-IgE therapy

**Responder**

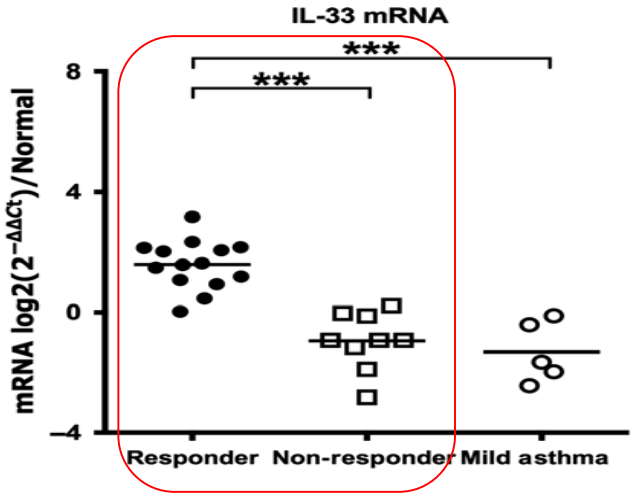
**Non-responder**

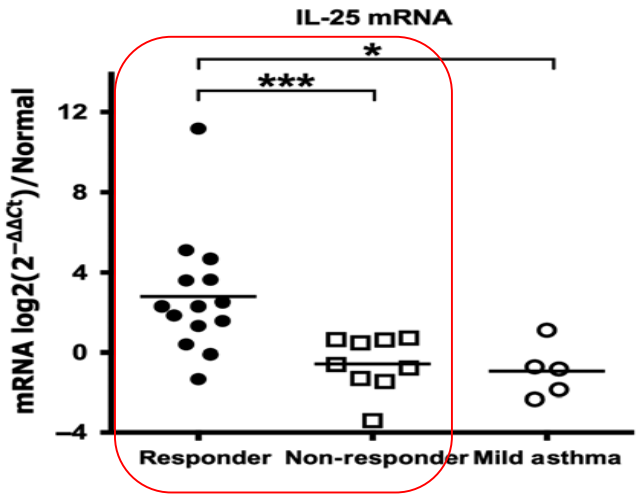


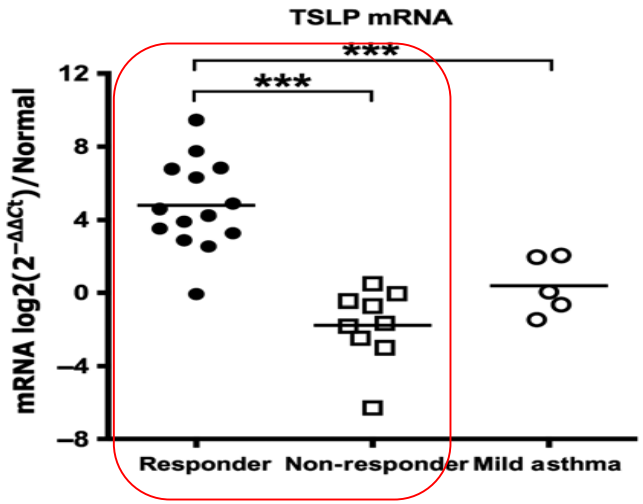

Huang YC, Clin Exp Allergy. 2018;1–10.

# Endotypes of severe allergic asthma patients who clinically benefit from anti-IgE therapy

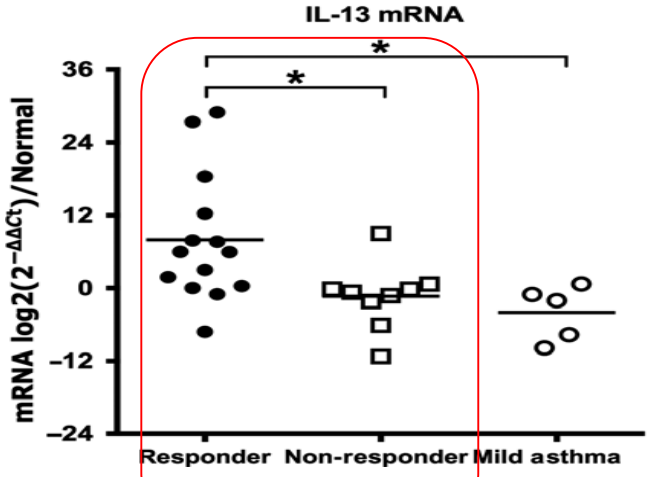
## Epithelium-derived Cytokines

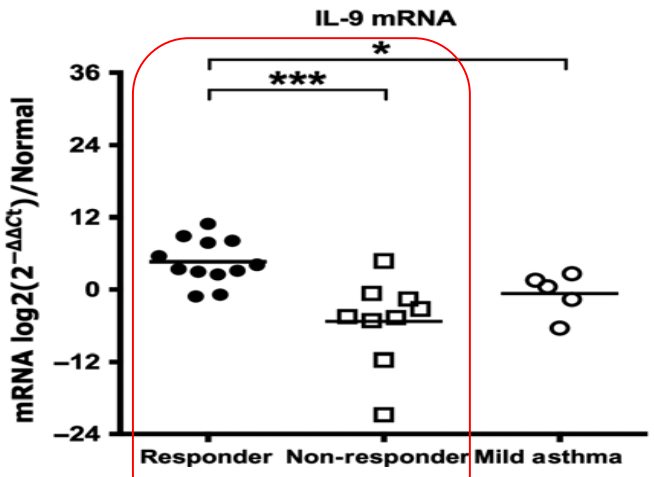


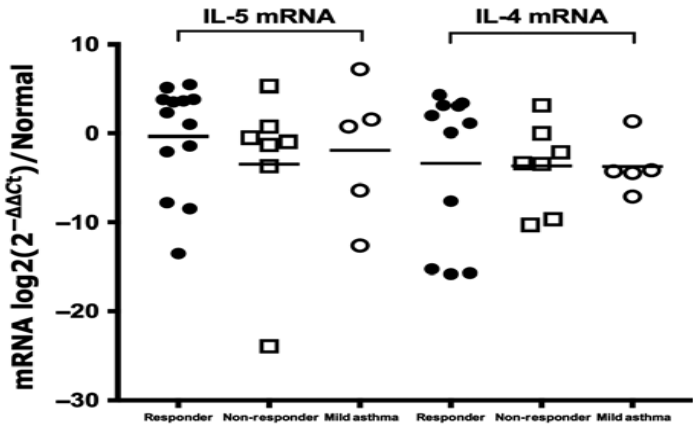




## Type 2 Cytokines



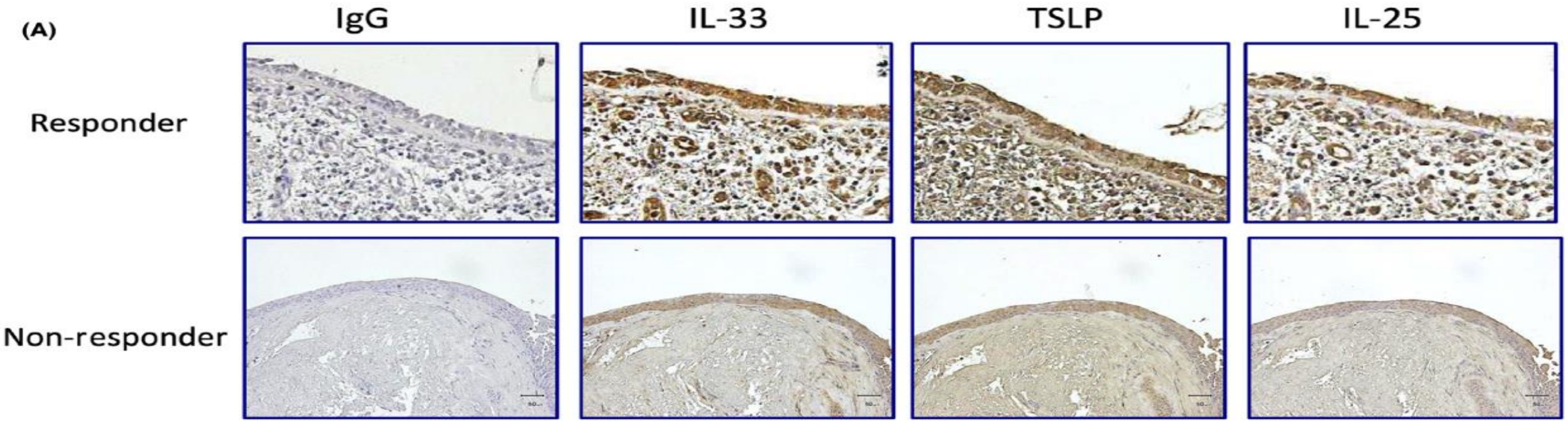




Bronchial biopsy

Huang YC, Clin Exp Allergy. 2018;1–10.

# Endotypes of severe allergic asthma patients who clinically benefit from anti-IgE therapy

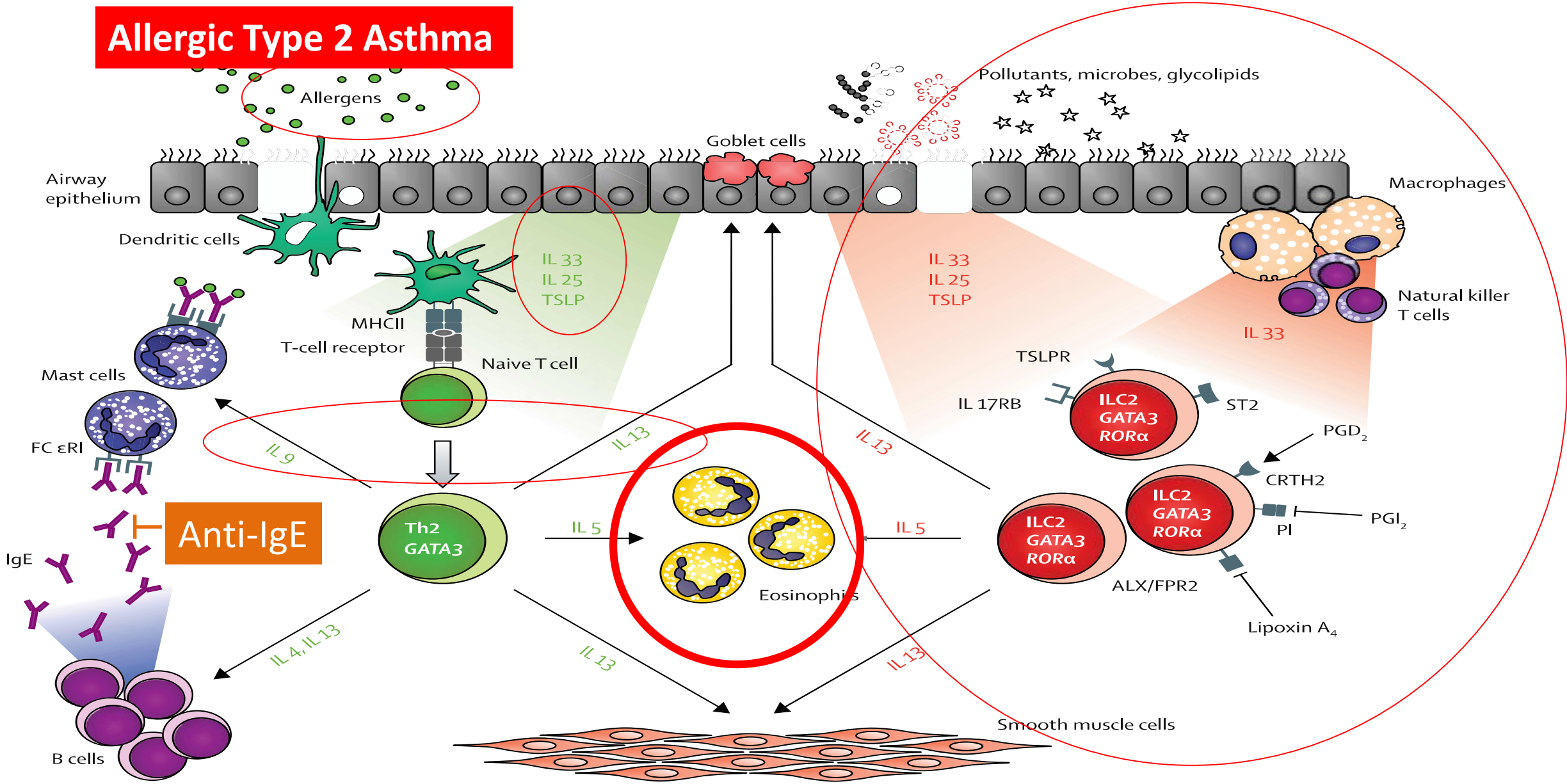
## Epithelium-derived Cytokines




**Omalizumab-responders are epithelium-triggered type 2 endotype asthma**

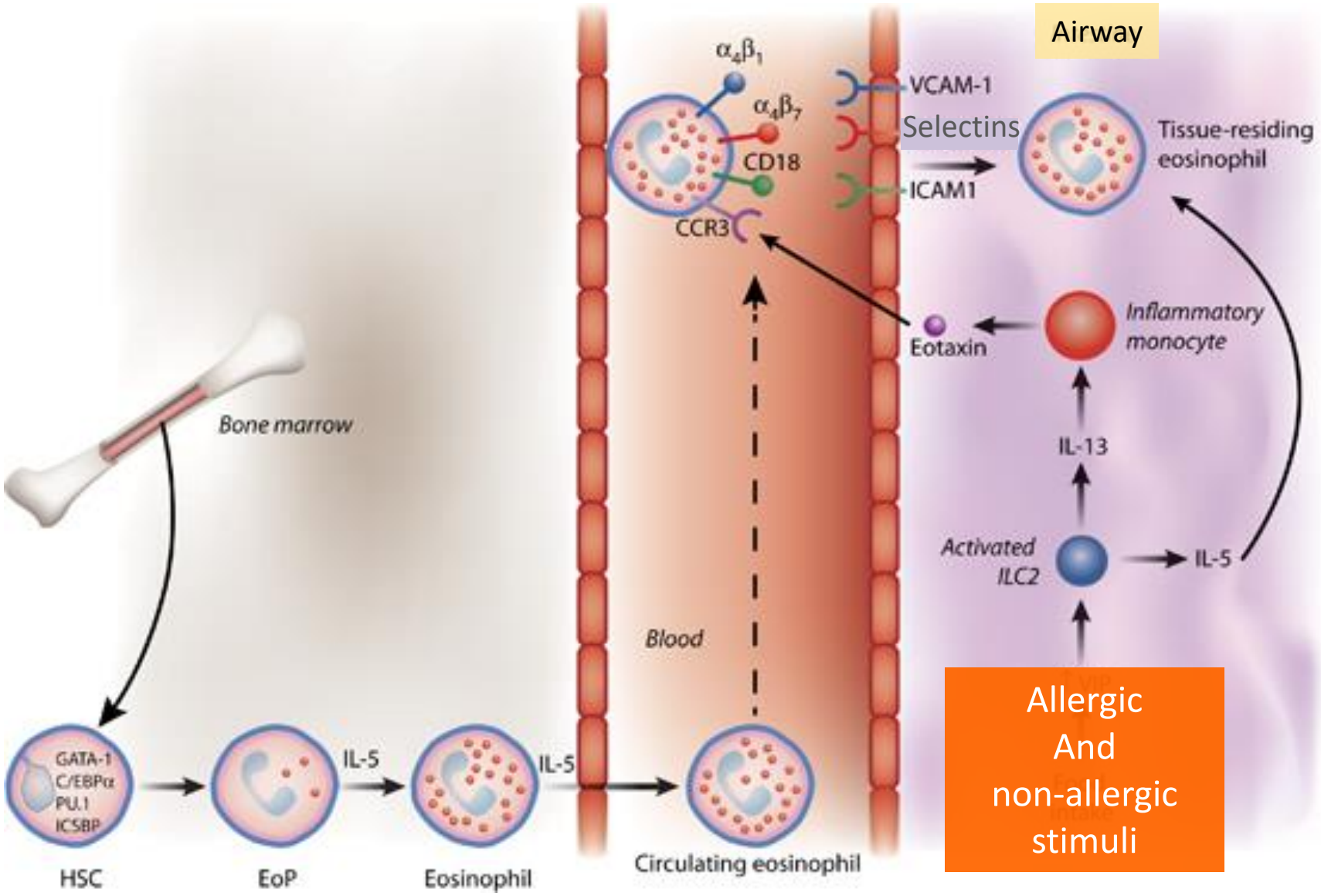
Huang YC, Clin Exp Allergy. 2018;1–10.

# Two pathways leading to abnormal Type 2 Asthma




Brusselle GG, Nat Med. 2013 Aug;19(8):977-9.

# Systemic relevance of IL-5 signalling in asthma

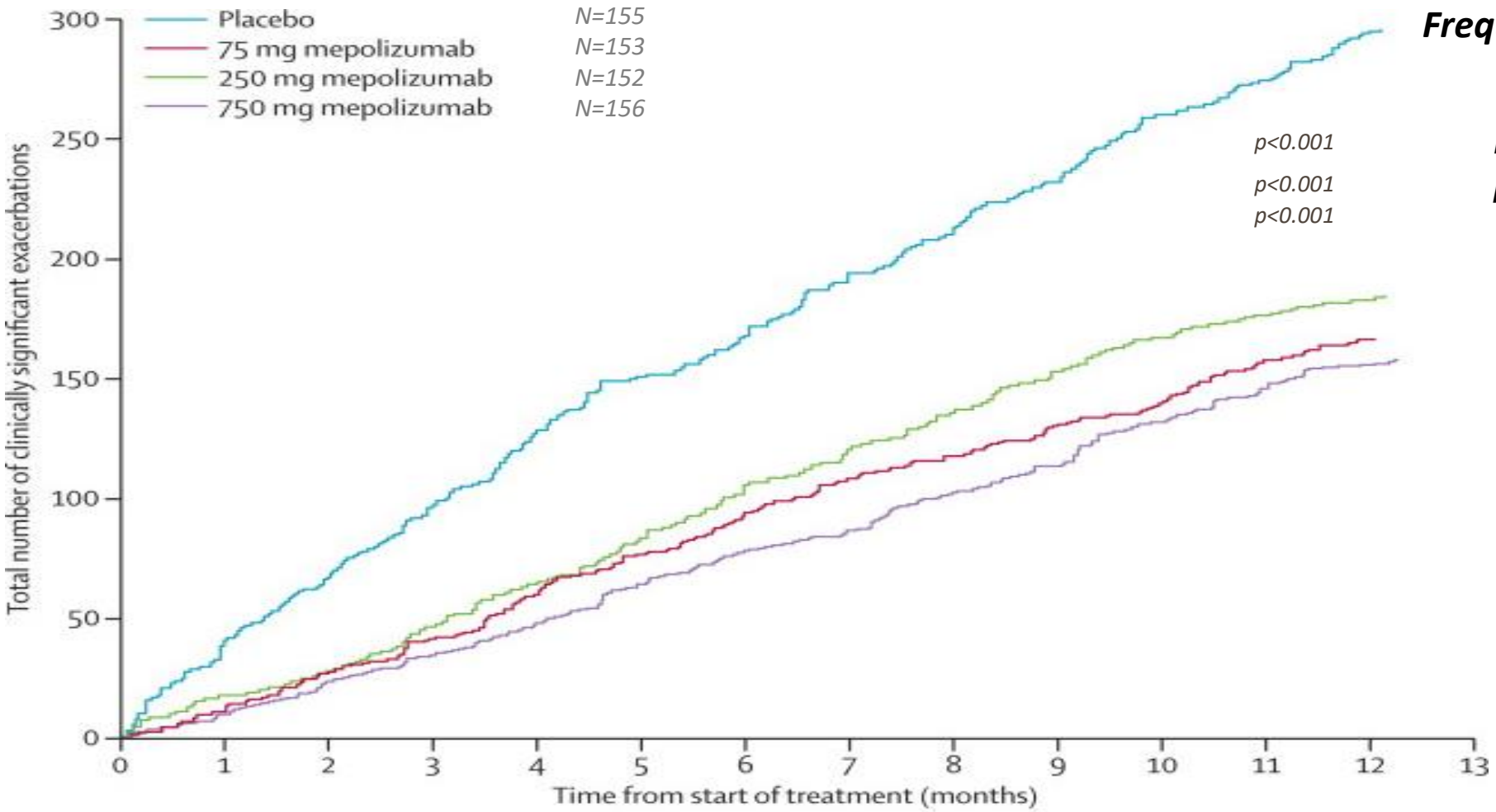



Adapted from Travers and Rothenberg Mucosal Immunology 2015; 8: 464-475

# Targeting IL-5

## The DREAM study **Mepolizumab** for Severe Asthma

*Significantly lower frequency of **clinically significant exacerbations***




***Frequency of clinically significant exacerbations***

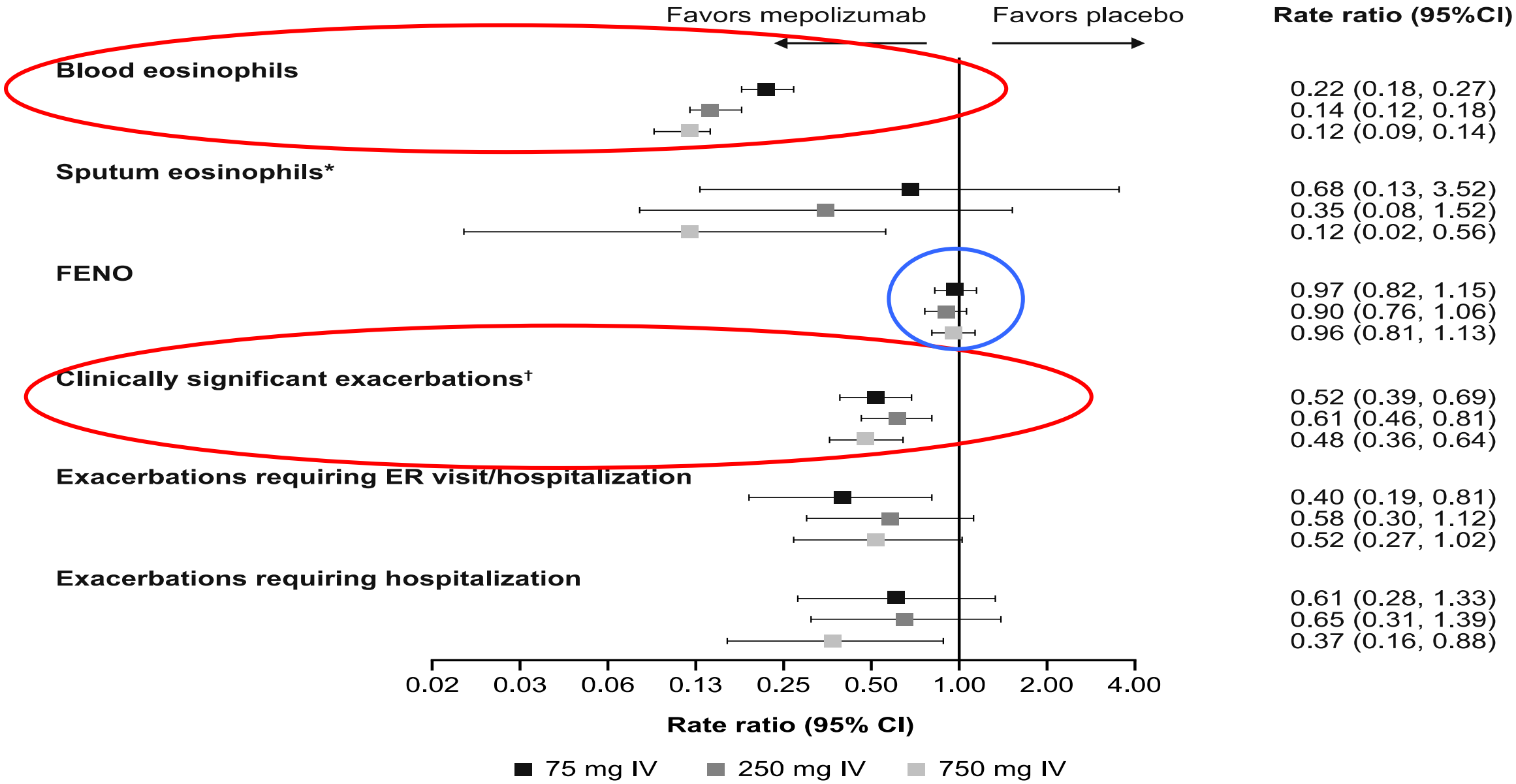
| ***Ratio to placebo*** | ***% reduction*** |
|---|---|
| ***0.61*** | ***39%*** |
| ***0.52*** | ***48%*** |
| ***0.48*** | ***52%*** |

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

**Mepolizumab 75mg, 250mg and 750mg IV are not licensed doses/routes of administration**

# Targeting IL-5

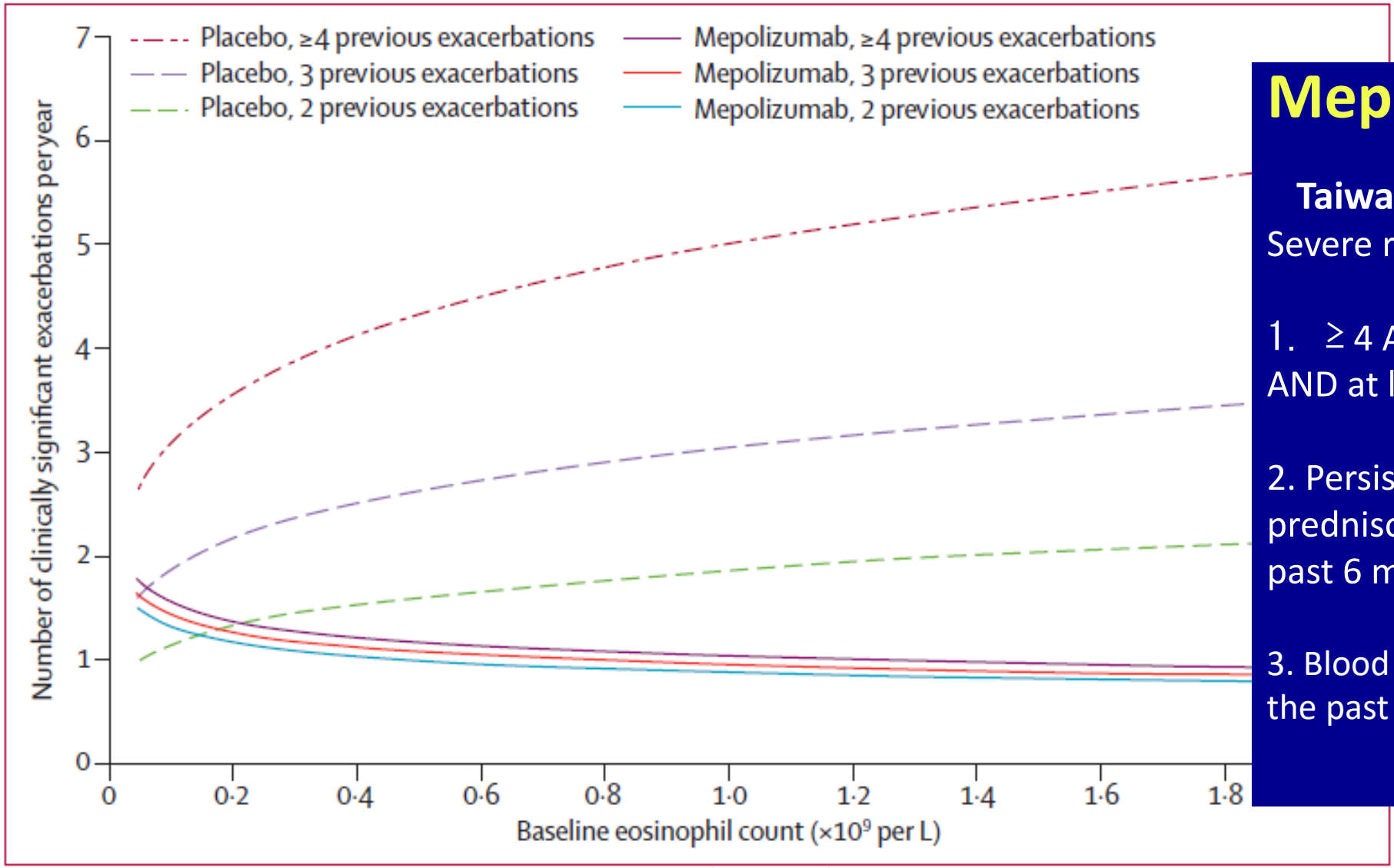
## The DREAM study Blood Eosinophil for Mepolizumab




Yancey SW, JACI,2017;140:1509-18.

DREAM

# Dose–response effect on blood eosinophil counts incorporated with exacerbation




**Predictive modelling of rate of exacerbations**

## Mepolizumab (Nucala)

**Taiwan NHI Payment Guidelines**

Severe refractory eosinophilic asthma

1. ≥ 4 AE in the past 12 months, AND at least including one ER or H

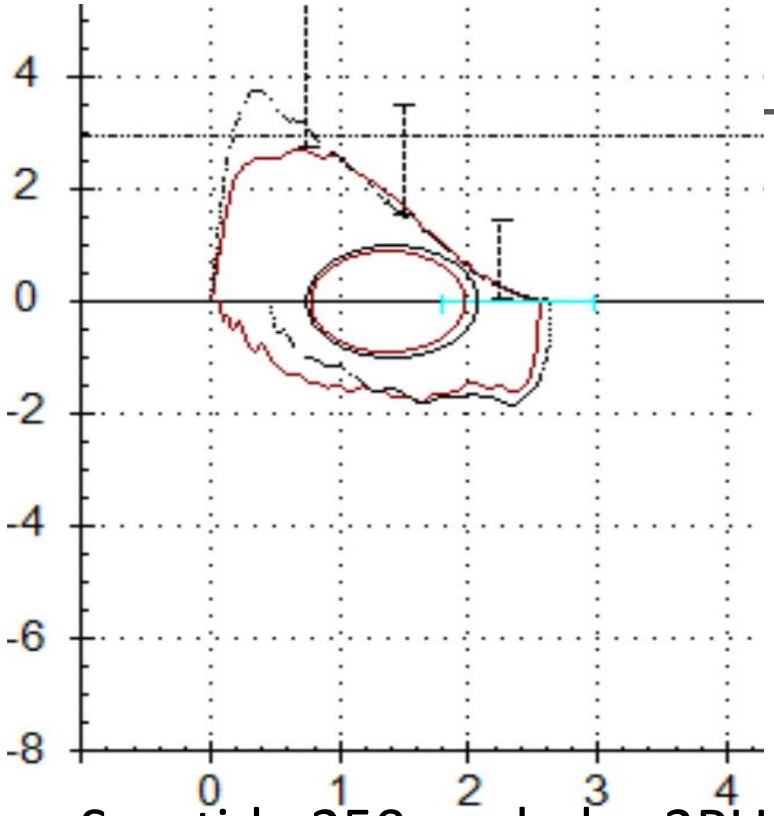
2. Persistently on OCS ≥ 5 mg prednisolone or equivalent in the past 6 months

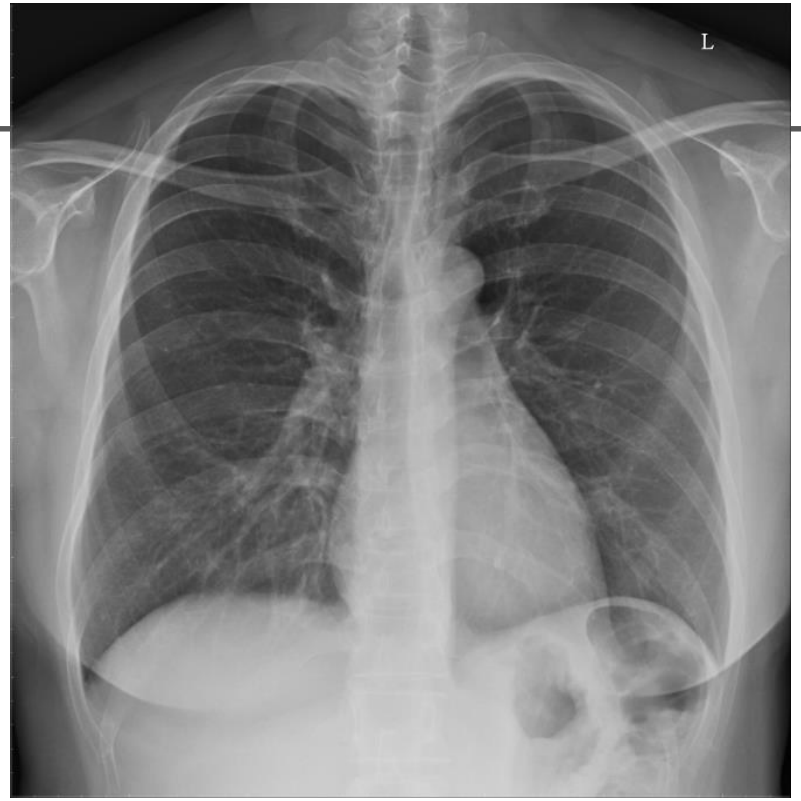
3. Blood eosinophil ≧300 cells/mcL in the past 12 months

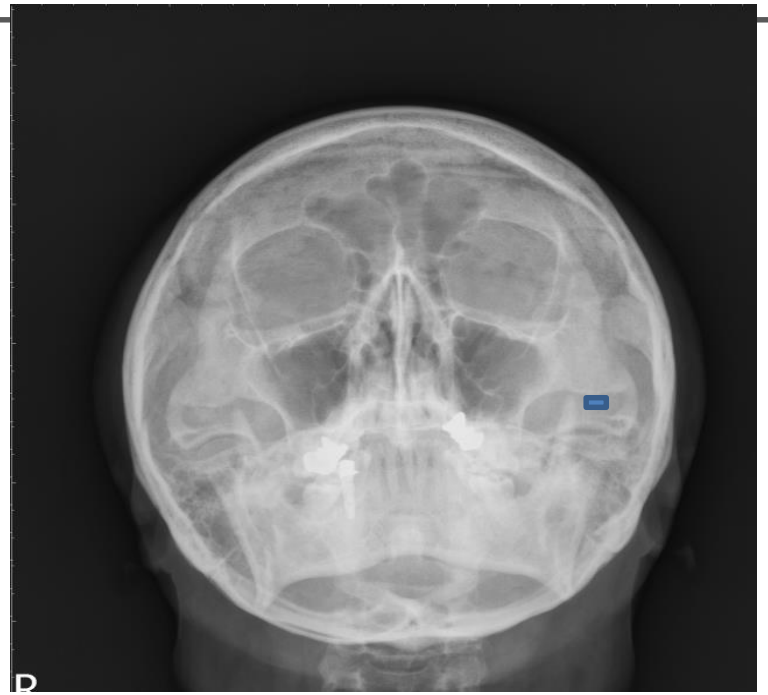
Pavord et al. Lancet 2012; 380(9842):651-659.

# 47 Year-old Female

**Very frequent AE**
**Intermittent cough**
**Dyspnea with wheeze**



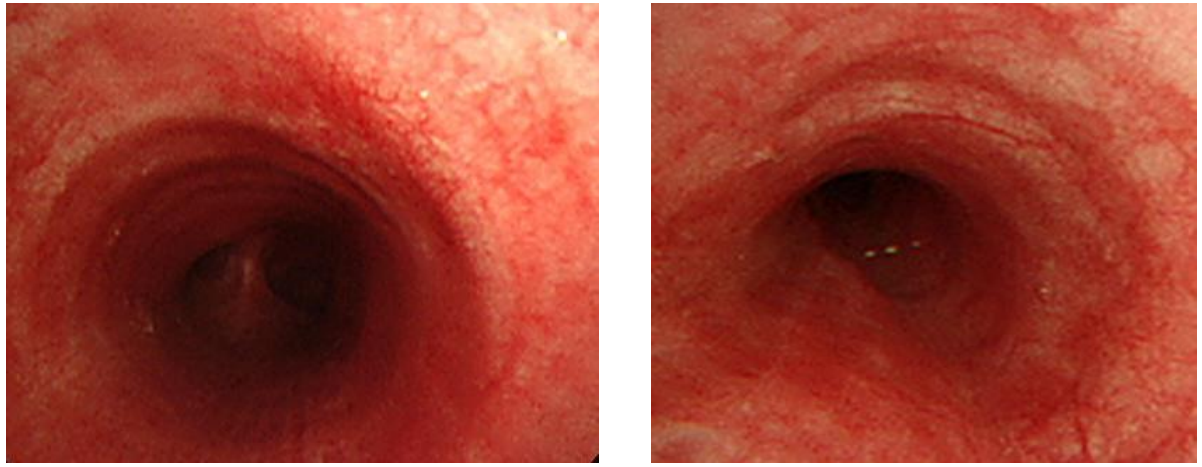



Seretide 250 evohaler 2PU BID
Spiriva Respimat 2.5mcg 2PU QD
Singulair 10mg 1 tab QD
Compresolone 5mg 2 tab BID
Famotidine 20mg 1 tab BID
Allegra 60mg 1 tab BID

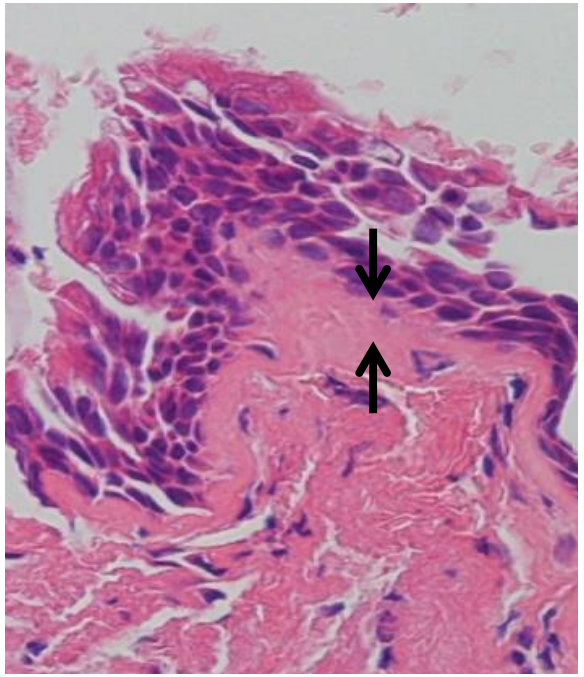
# 2017-08

## Bronchoscopy

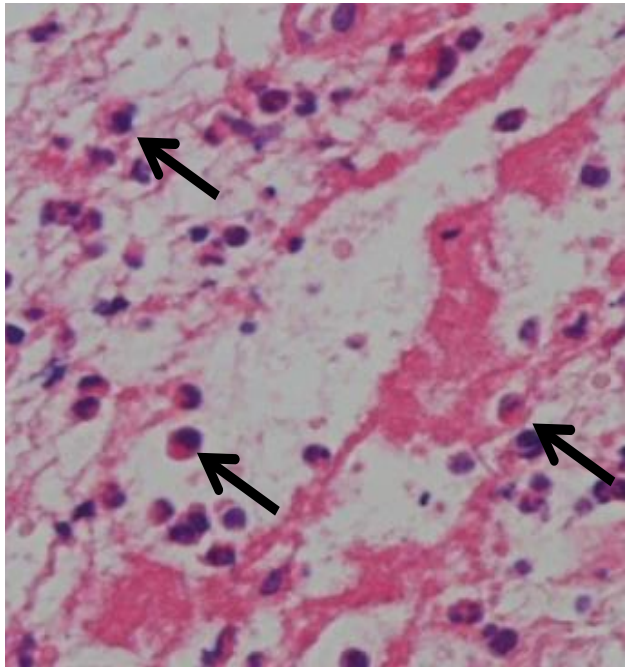


**Hyperemia**
**Bronchial biopsy of subsegment of RLL**

**Thickened basement membrane**



**Eosinophils infiltration**



**Bronchoalveolar lavage**

WBC: 171/uL
Neutrophil: 1%
Lymphocyte: 12%
**Eosinophil: 3%**
Mesothelial + histocyte: 85%

**Bronchoalveolar lavage**

TB/Fungus/Aerobic culture: negative

**Blood**

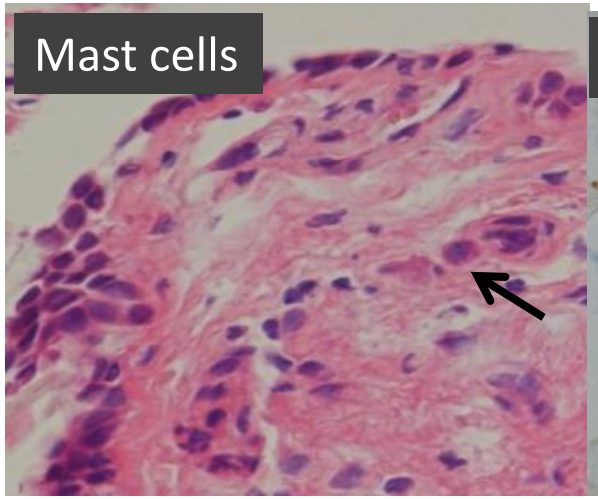
Eos count: 747/uL
Total IgE: 84.20 Ku/L
CAP test (+)

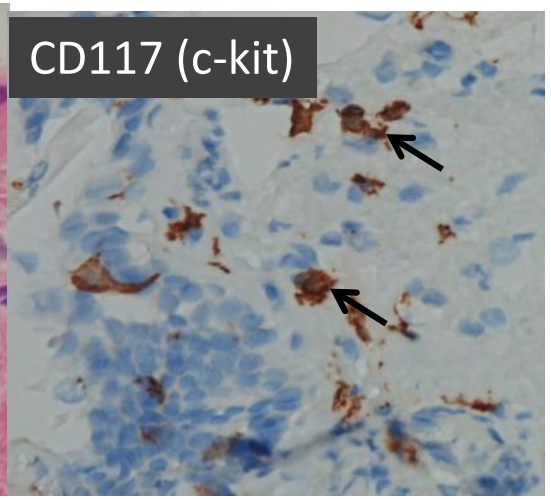
ACT: 16

Almost every month before xolair

AE required hospitalization

OPD medication




| 2017-09 | 2017-10 | 2017-11 | 2017-12 | 2018-01 | 2018-02 | 2018-03 | 2018-04 | 2018-05 | 2018-06 |
|---|---|---|---|---|---|---|---|---|---|
| Eos: 747 | | Eos: 520 | Eos: 554 | | | | | | |
| Xolair | Xolair | Xolair | Xolair | | | | | | |
| | | | | Nucala | Nucala | Nucala | Nucala | Xolair | Xolair & Nucala |
| | | | | Eos: 8 | | | Eos: 40 | Eos: 24 | Eos: 34 |

ACT: 19

ACT: 25

# Integrated Safety Information

**Adverse reactions with mepolizumab 100 mg SC with ≥3% incidence and more common than placebo in MENSA and SIRIUS studies.**

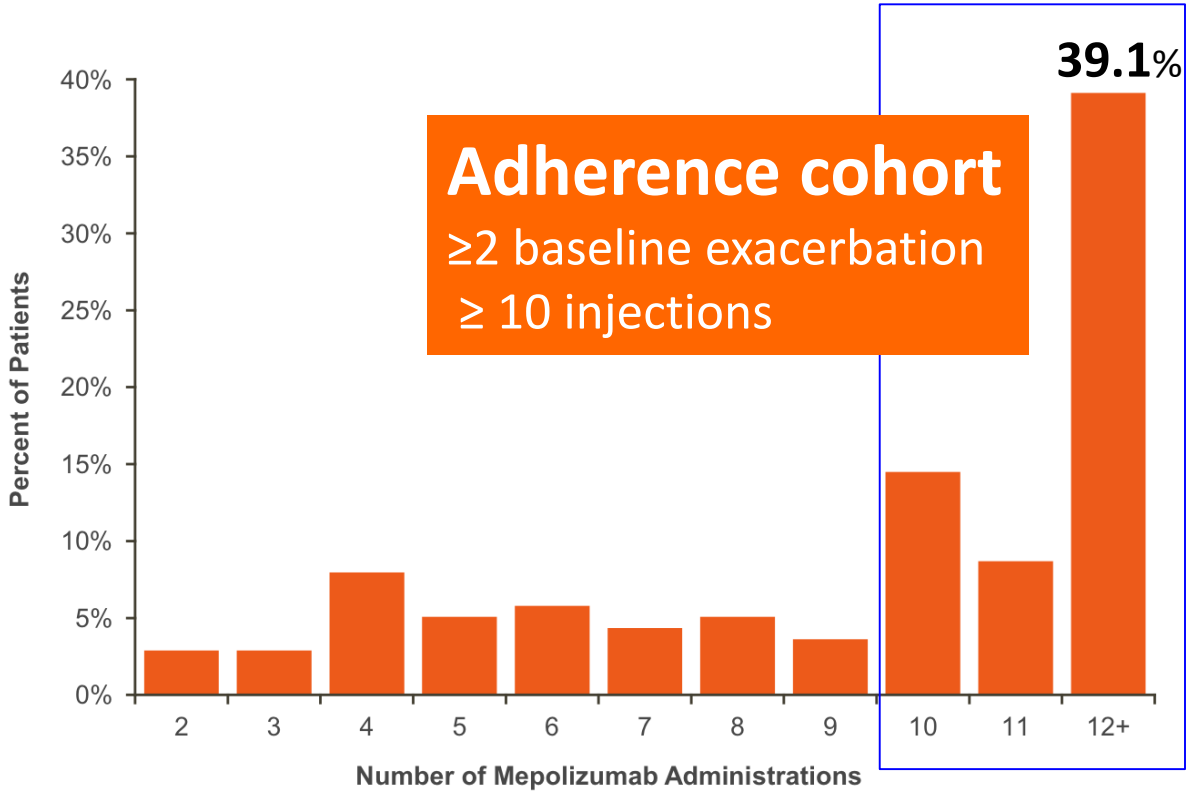
| Adverse Reaction | Mepolizumab 100 mg SC (n=263) % | Placebo (n=257) % |
|---|---|---|
| Headache | 19 | 18 |
| Injection site reaction | 8 | 3 |
| Back pain | 5 | 4 |
| Fatigue | 5 | 4 |
| Influenza | 3 | 2 |
| Urinary tract infection | 3 | 2 |
| Abdominal pain upper | 3 | 2 |
| Pruritus | 3 | 2 |
| Eczema | 3 | <1 |
| Muscle spasms | 3 | <1 |

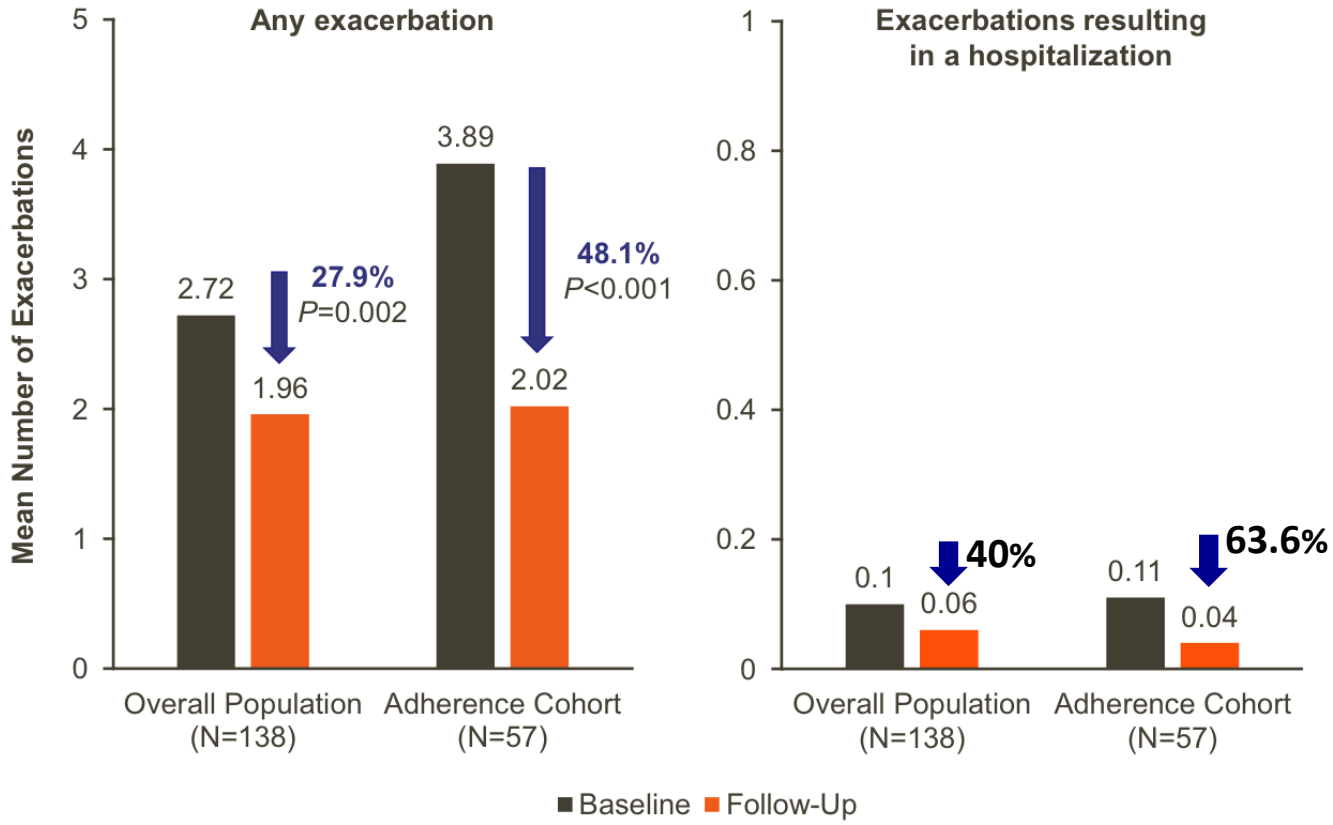
Systemic reactions including hypersensitivity have been reported at an overall incidence comparable to that of placebo.

# Real World Impact of Mepolizumab on Asthma Exacerbations

## Adherence Matters

a retrospective cohort design (n=138)
electronic medical records and pharmacy claims data (Nov 1, 2015 and Sep 30, 2016
**the IBM Watson Health MarketScan Commercial Database**



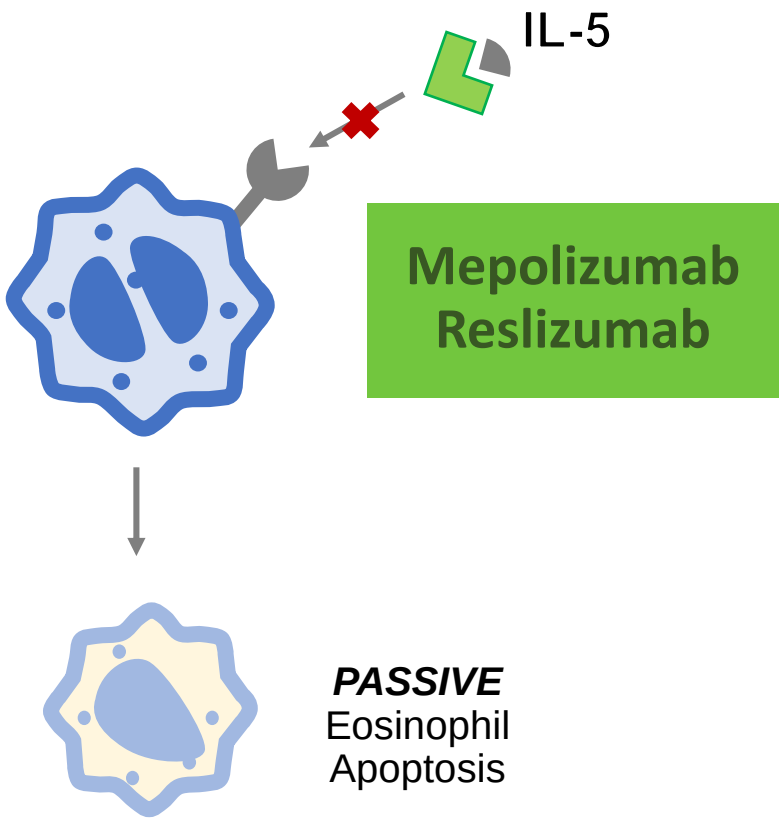




(GSK ID HO-18-19166/209019)

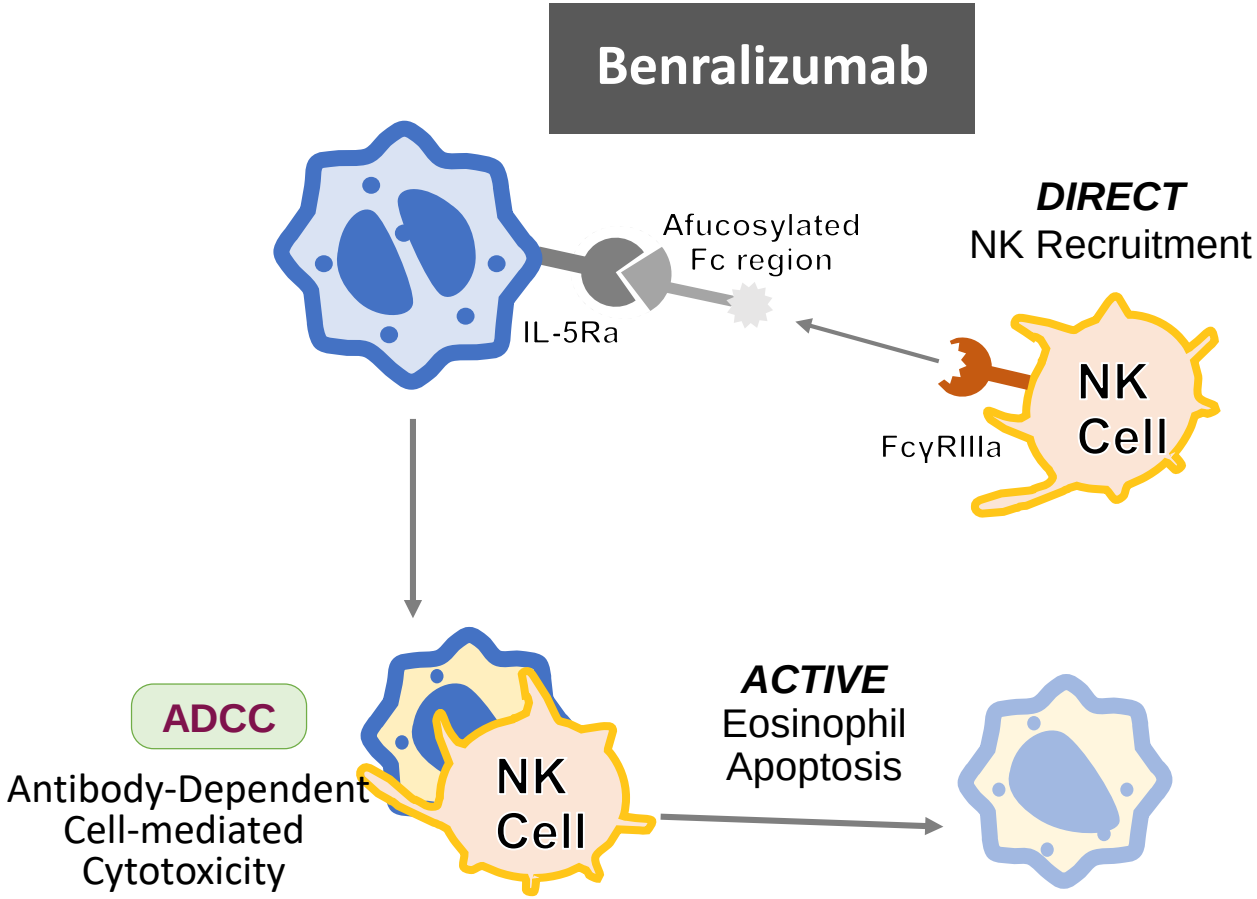
Hahn B, ATS International Conference, Dallas, TX, USA, May 17–22, 2019

# Mechanism of action: IL-5 cytokine- vs. IL-5 receptor- targeted therapy

## Anti-IL-5 MOA[1-4]
***indirect***




## Anti-IL-5Ra MOA[5-7]
***Enhanced ADCC***




*Benralizumab induces eosinophil apoptosis within 6 hours *in vitro*[7]; blood eosinophils were depleted within 24 hours in a clinical study[6]
IL-5 = interleukin 5; IL-5Ra = interleukin 5 receptor alpha; MOA = mechanism of action; NK = natural killer.

1. Patterson MF, et al. *J Asthma Allergy*. 2015;8:125-134; 2. Busse WW, et al. In: Lee JJ, Rosenberg HF, eds. Eosinophils in Health and Disease. London, UK: Academic Press; 2013: 587-591; 3. Flood-Page P, et al. *Am J Respir Crit Care Med.* 2003.167:199-204; 4. Sehmi R et al. *Clin Exper Allergy.* 2016;793-802; 5. Kolbeck R et al. *JACI* 2010;125:1344-1353; 6. Laviolette M et al. *J Allergy Clin Immunol.* 2013;132:1086-1096; 7. Dagher R et al. International Eosinophil Society 10th Biennial Symposium, Gothenburg, Sweden, Friday, 21 July 2017

# Anti–IL-5 treatments in patients with severe asthma by blood eosinophil thresholds: Indirect treatment comparison

Busse W, J Allergy Clin Immunol 2019;143:190-200.

| Mepolizumab (100mg Q4W SC) | Reslizumab (3mg/kg Q4W IV) | Benralizumab (30mg Q8W SC) |
|---|---|---|
| MENSA (NCT01691521)[1]<br>MUSCA (NCT02281318)[2] | Castro M et al. *Am J Respir Crit Care Med* 2011[5]<br>NCT01270464[6]<br>NCT01508936[7]<br>NCT01287039[8]<br>NCT01285323[8] | SIROCCO (NCT01928771)[3]<br>CALIMA (NCT01914757)[4] |

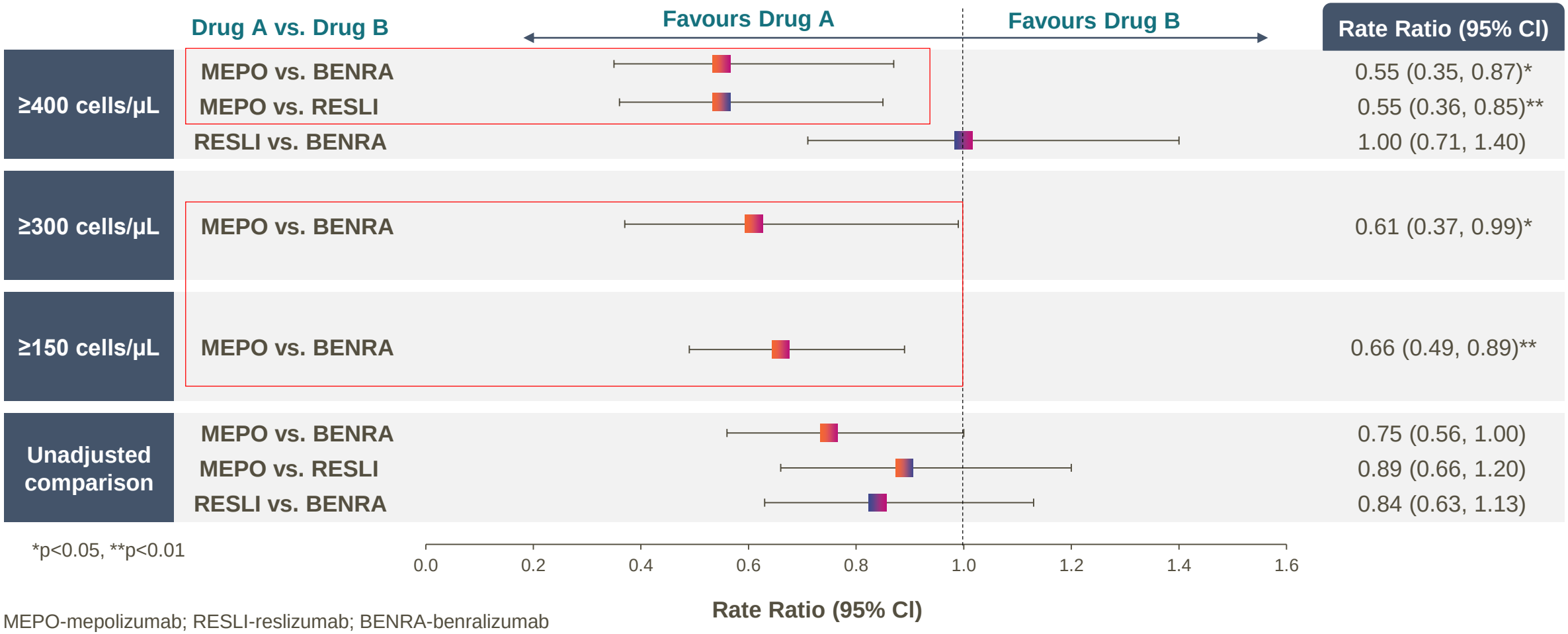
In addition, two meta-analyses were identified including subgroup analyses relevant for this analyses, but not reported in the individual study publications:

- a meta-analysis of SIROCCO and CALIMA[9]
- a meta-analysis of NCT01287039 (Study 1) and NCT01285323 (Study 2)[10]

1. Ortega HG et al. N Engl J Med. 2014;371:1198–207; 2. Chupp GL et al. Lancet Respir Med. 2017;5:390-400; 3. Bleecker ER et al. Lancet. 2016; 388: 2115–27; 4. FitzGerald JM et al. Lancet. 2016; 388: 2128–41; 5. Castro M et al. Am J Respir Crit Care Med 2011;184:1125–32; 6. Bjermer L et al. Chest. 2016 ;150(4):789-98; 7. Corren J et al. Chest. 2016;150(4):799-810; 8. Castro M et al. Lancet Respir Med. 2015 ;3(5):355-66; 9. FitzGerald JM et al. Lancet Respir Med. 2018 ;6(1):51-64; 10. Brusselle G et al. ERJ Open Res. 2017;3(3): 00004-2017. doi: 10.1183/23120541.00004-2017

# Clinically significant exacerbations (similar trend for ACQ)

Comparisons of the rate of clinically significant exacerbations by baseline blood eosinophil subgroups and in the ITT population




MEPO-mepolizumab; RESLI-reslizumab; BENRA-benralizumab

Busse W, J Allergy Clin Immunol 2019;143:190-200.

# Heterogeneity between studies

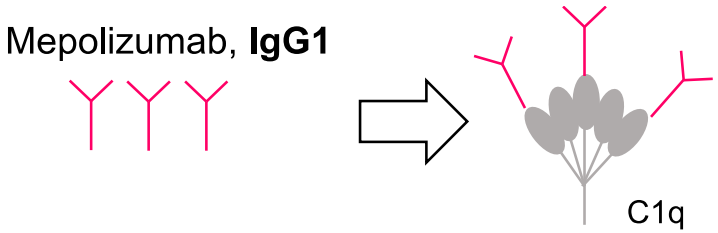
Key differences in study inclusion criteria

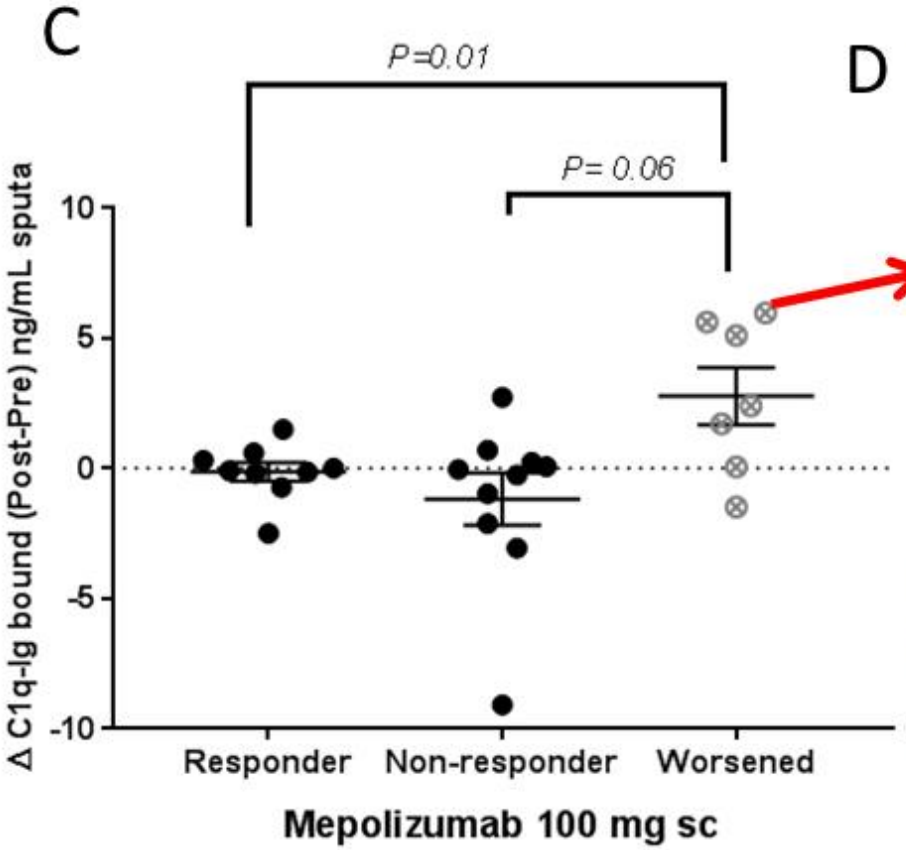
| Characteristic | Mepolizumab | Reslizumab | Benralizumab |
|---|---|---|---|
| **Baseline blood eosinophils** | **≥150 cells/μL or ≥300 cells/μL in past year** | **≥400 cells/μL** | **≥300 cells/μL*** |
| **Exacerbation history** | ≥2 exacerbations in past year | ≥1 exacerbation in past year | ≥2 exacerbations in past year |
| **ICS dose** | **High** (≥18 years: ≥880 μg/day fluticasone; ≥12 and ≤17 years: ≥440 μg/day fluticasone or equivalent) | **Medium-high** (≥440 μg/day fluticasone or equivalent) | **High** (≥500 μg/day fluticasone dry powder formulation or equivalent) |
| **Maintenance OCS use** | Allowed, any dose | Allowed, ≤10mg prednisolone/day | Allowed, any dose |
| **%predicted $FEV_1$** | <80% (<90% for age <18) | Not required | <80% (<90% for age <18) |
| **ACQ score** | Not required | ACQ-7 ≥1.5 | ACQ-6 ≥1.5 |

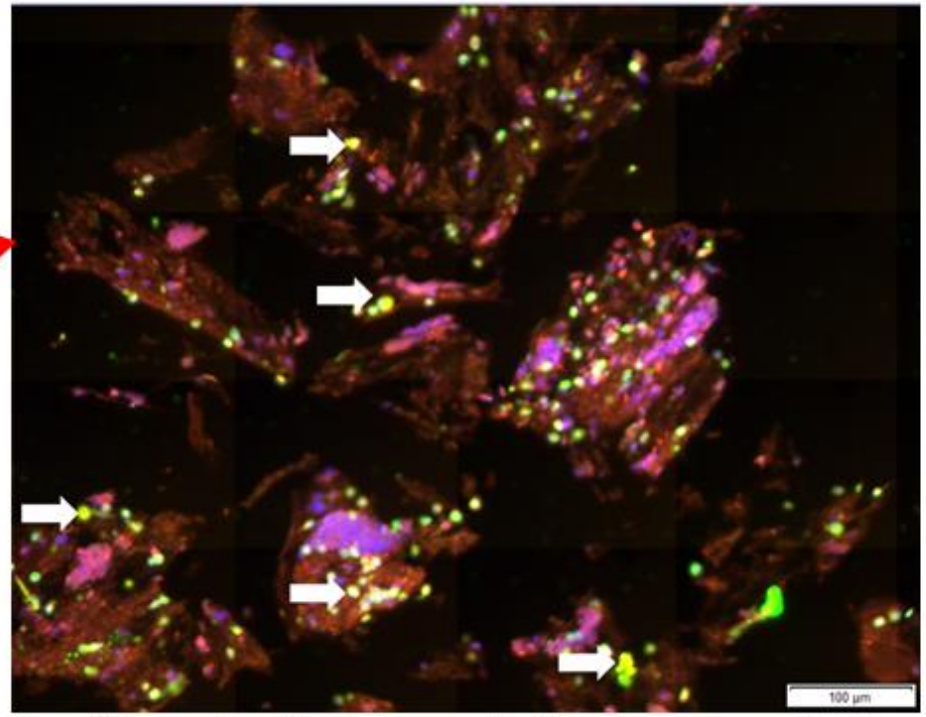
*Inclusion criteria for benralizumab studies were wider for blood eosinophil and ICS dose. However, results were reported for the ≥300 cells/μL and high ICS dose patient population

Busse W, J Allergy Clin Immunol 2019;143:190-200.

# Airway autoimmune responses in severe eosinophilic asthma following low-dose Mepolizumab therapy



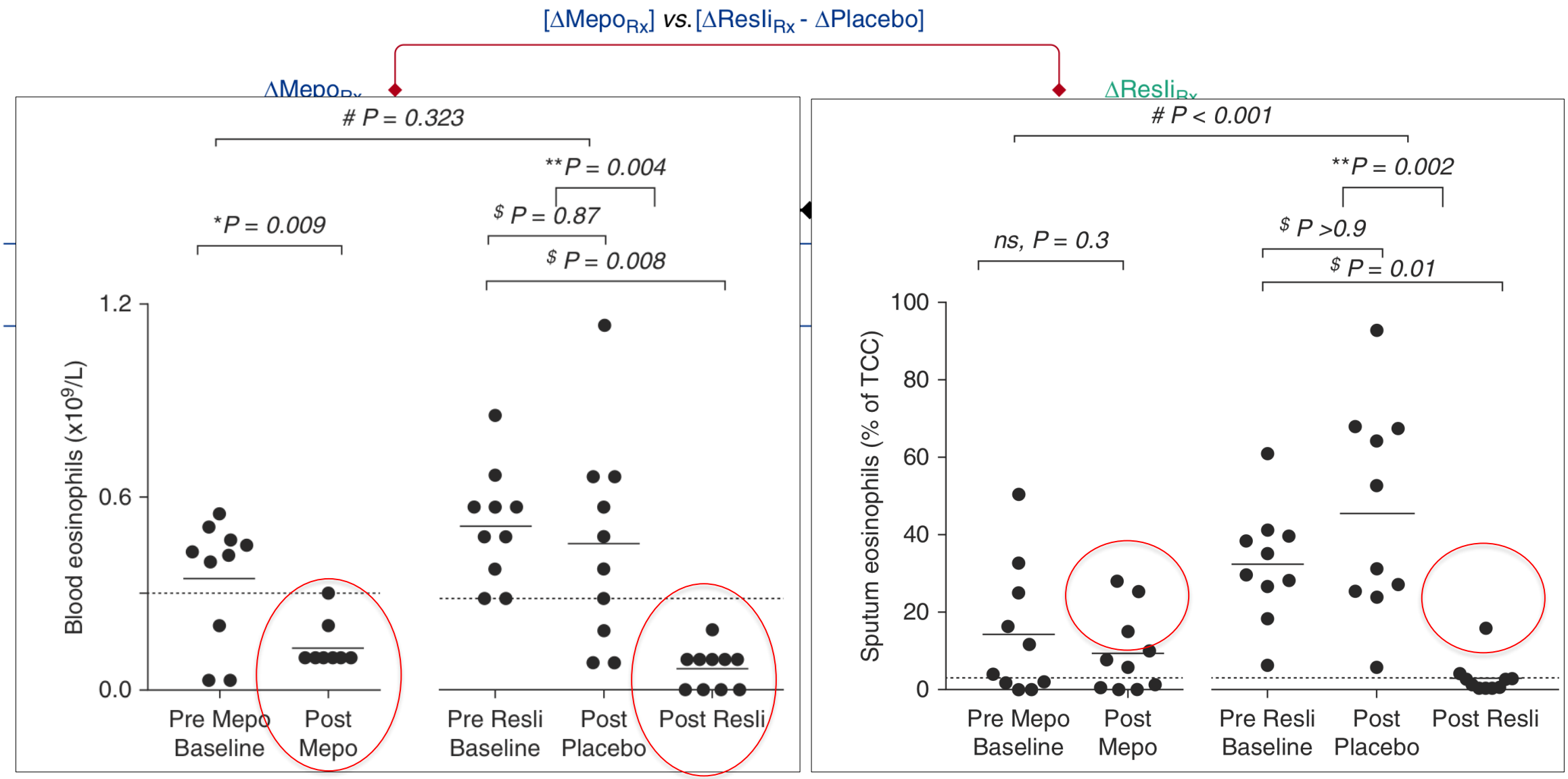




**Airway eosinophilia**

**Paraffin embedded, formalin fixed sputum plugs**
**Staining index: C1q (green), IgG (red), DAPI (blue)**
**White arrows indicating focal points of co-localisation**
**Bar: 100 µm**

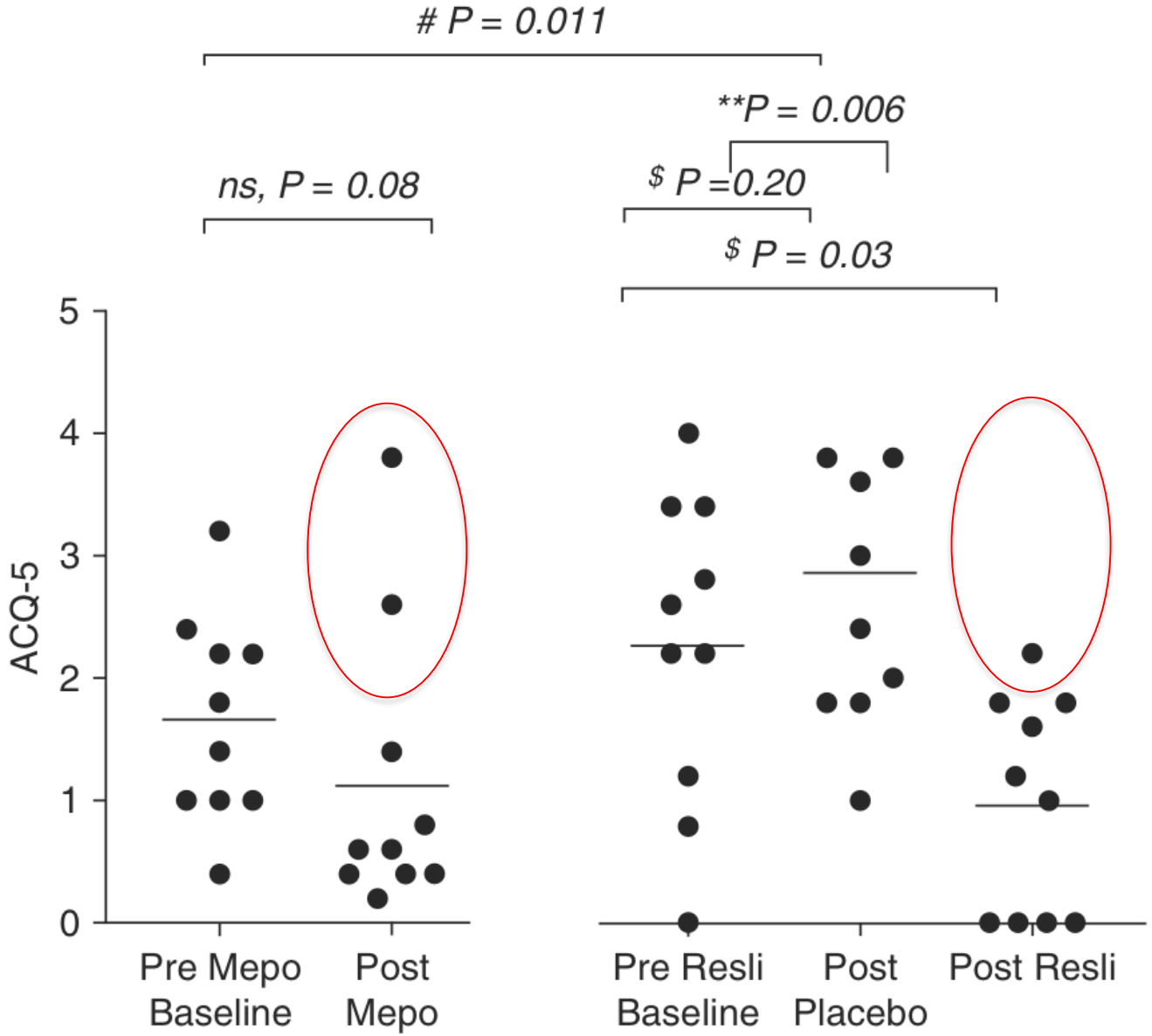
Mukherjee M et al, 2019 ATS, May 22, Room D222-D224

# Weight-adjusted Intravenous Reslizumab in Severe Asthma with Inadequate Response to Fixed-Dose Subcutaneous Mepolizumab



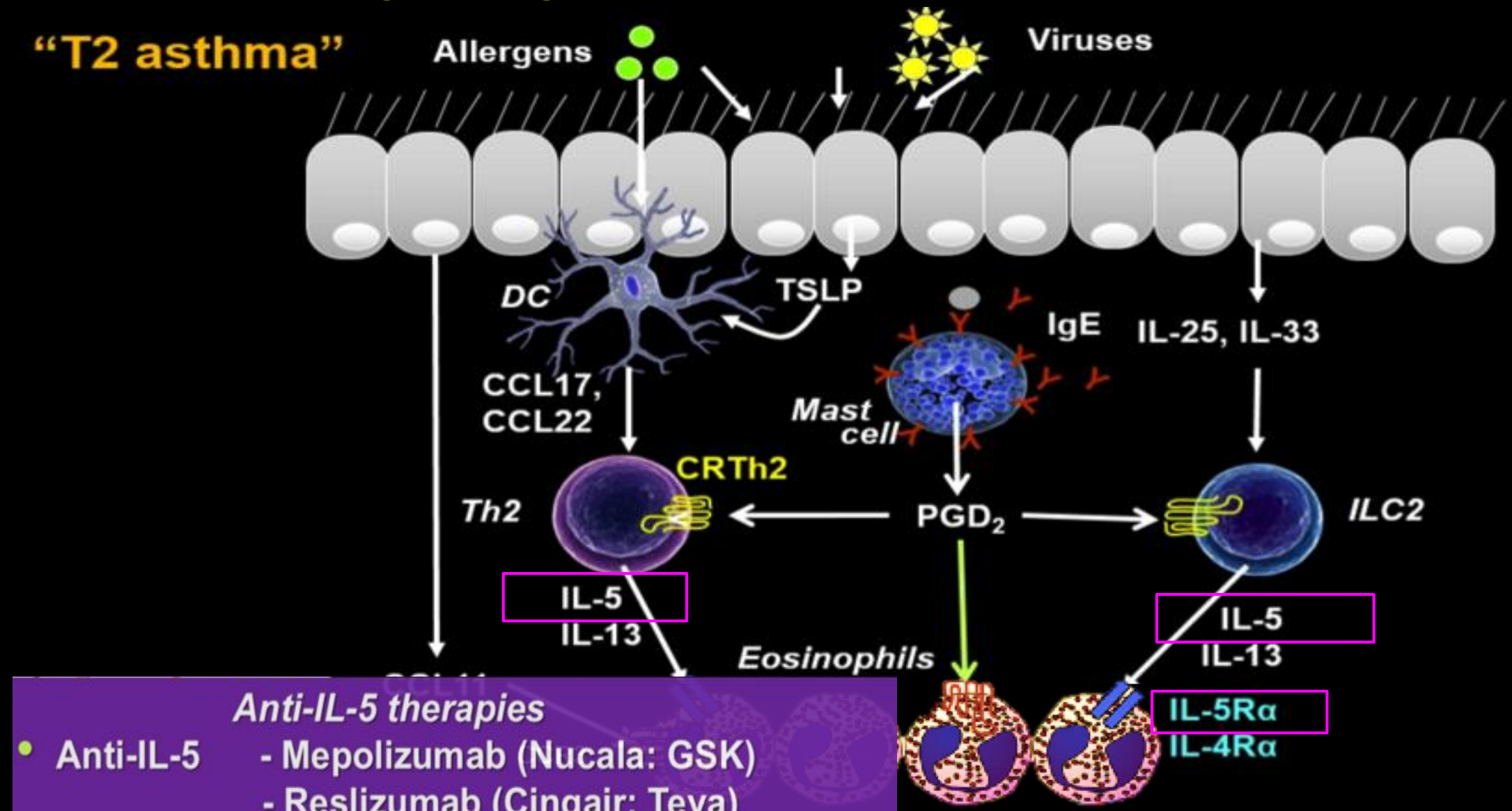

Mukherjee M,Am J Respir Crit Care Med Vol 197, Iss 1, pp 38–46, Jan 1, 2018

# Weight-adjusted Intravenous Reslizumab in Severe Asthma with Inadequate Response to Fixed-Dose Subcutaneous Mepolizumab



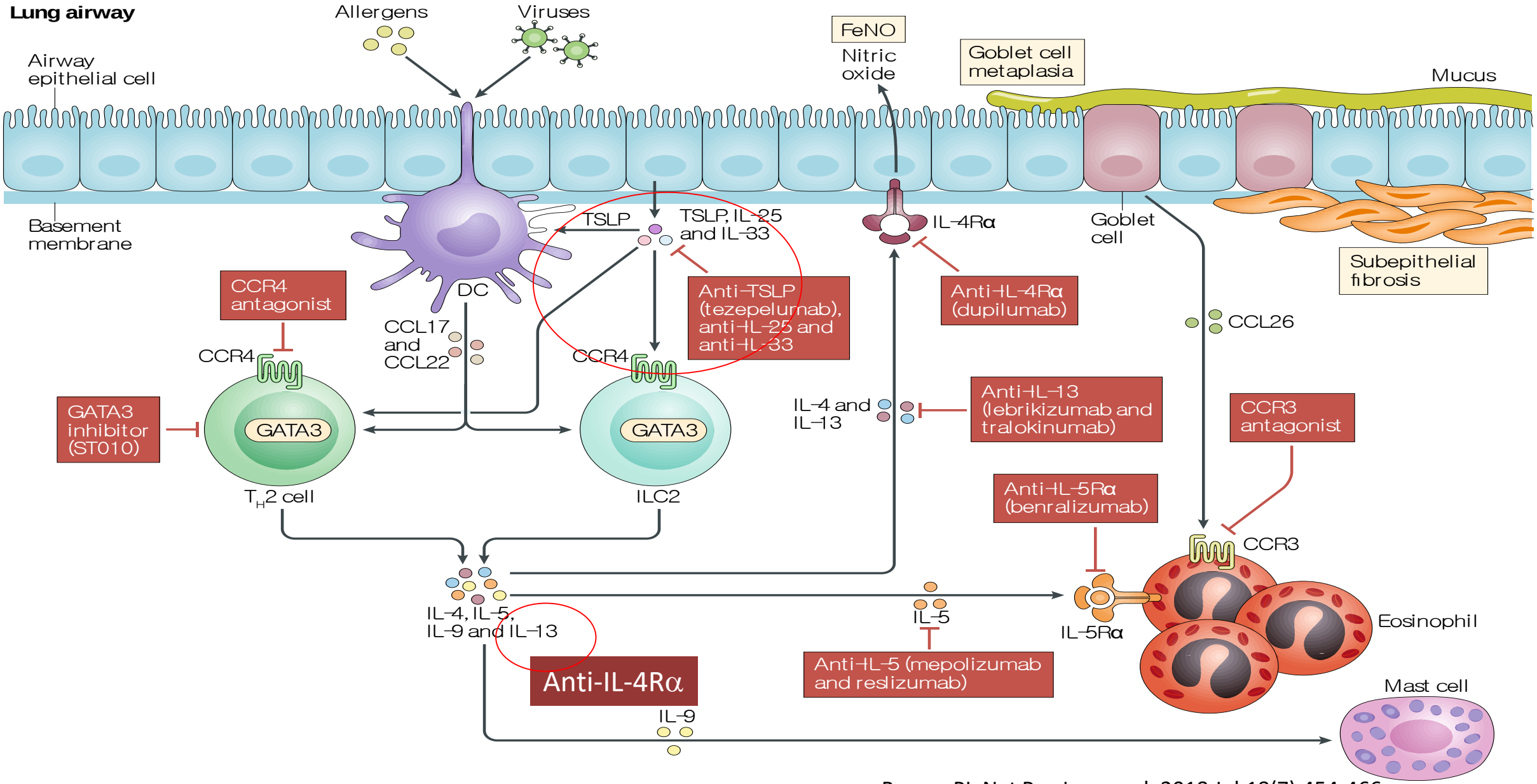

Mukherjee M,Am J Respir Crit Care Med Vol 197, Iss 1, pp 38–46, Jan 1, 2018

# Targeting Eosinophilic Inflammation



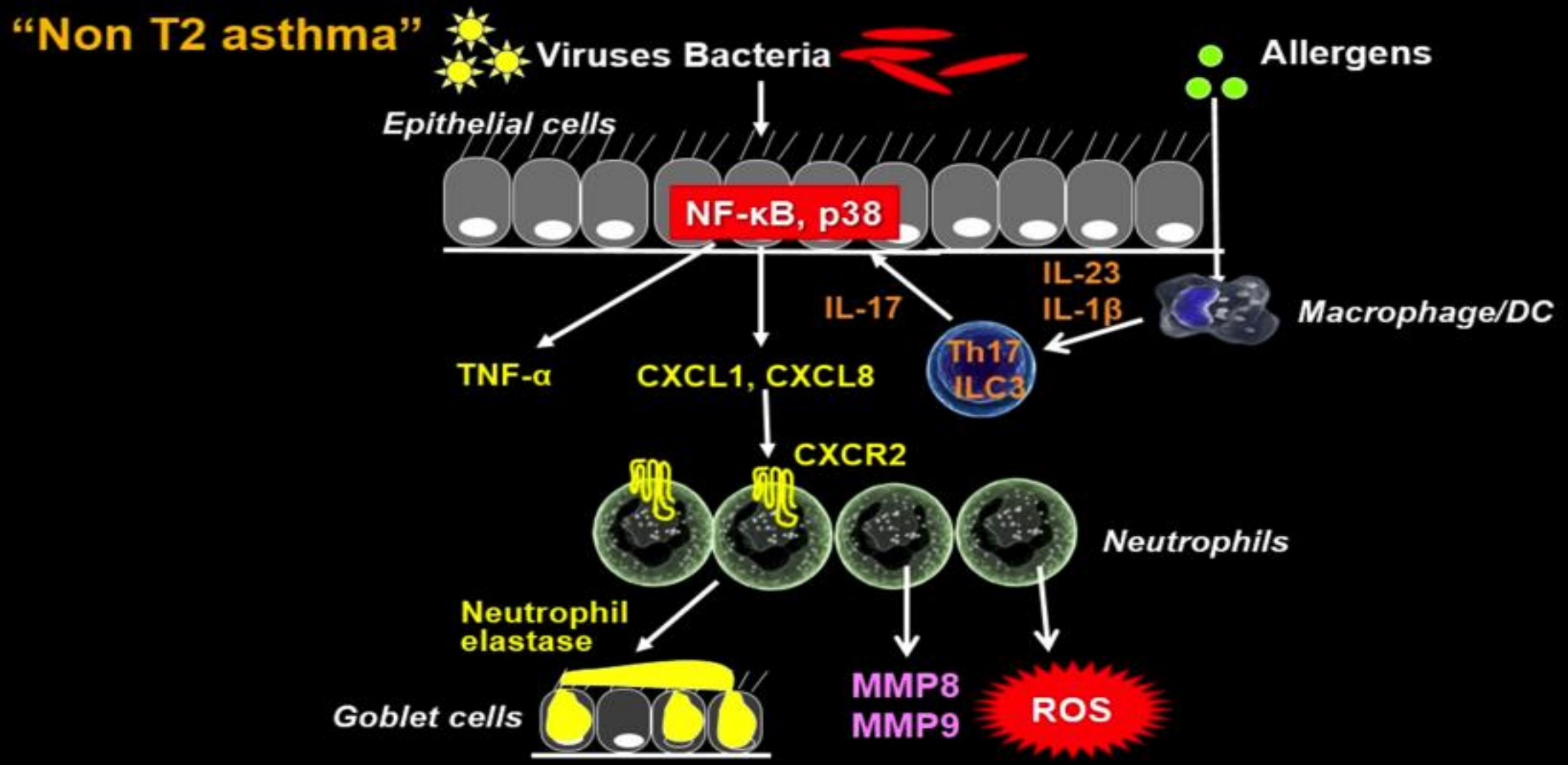

J Allergy Clin Immunol 2015;136:531-45.

# Eosinophilic Airway Diseases




Barnes PJ, Nat Rev Immunol. 2018 Jul;18(7):454-466.

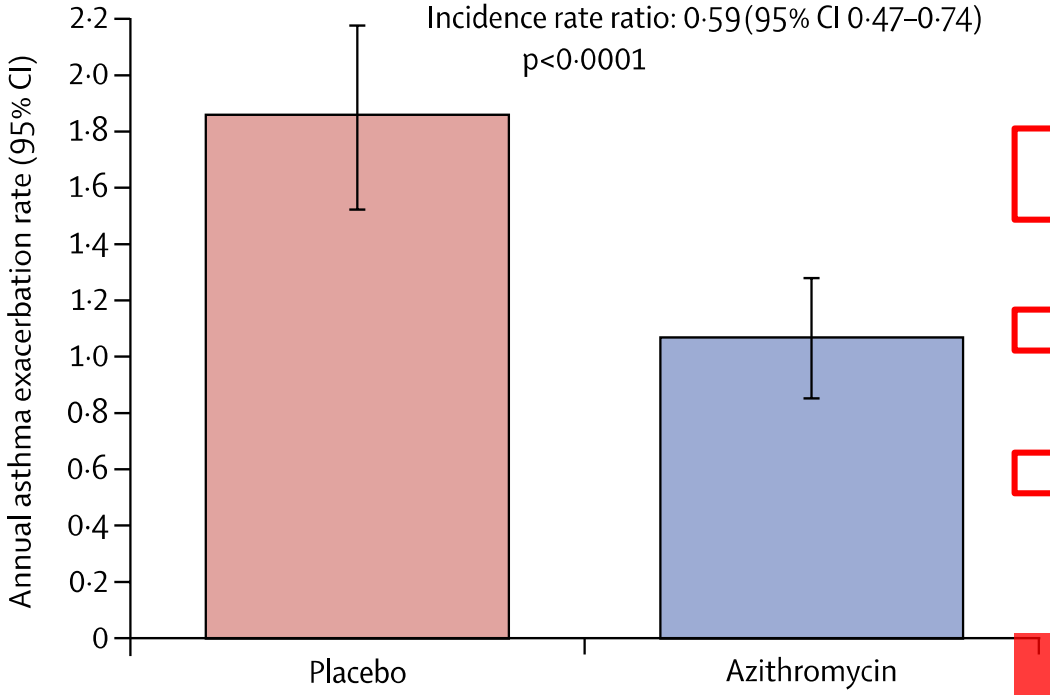
# Targeting Neutrophil Inflammation




J Allergy Clin Immunol 2015;136:531-45.

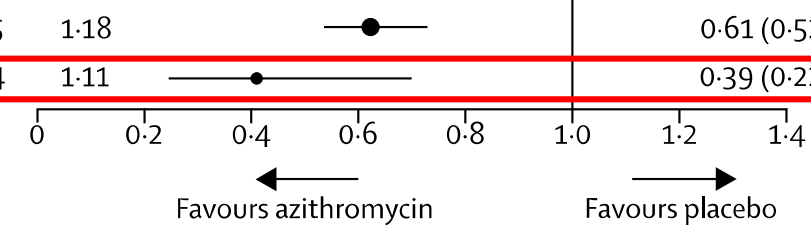
# Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES)

moderate to severe asthma
symptomatic (ACQ6 ≥ 0·75)
despite treatment with maintenance ICS/LABA




## Targeting bacteria or neutrophil?

| | Number | Exacerbations per person-year | | Incidence rate ratio (95% CI) |
|---|---|---|---|---|
| | | Placebo | Azithromycin | |
| Non-eosinophilic asthma | 224 | 1·74 | 1·15 | 0·66 (0·47–0·93) |
| Eosinophilic asthma | 196 | 1·98 | 0·96 | 0·52 (0·29–0·94) |
| Inhaled corticosteroid dose adjustment | 420 | 1·86 | 1·07 | 0·58 (0·46–0·74) |
| Frequent exacerbators | 140 | 2·79 | 1·47 | 0·55 (0·41–0·73) |
| Cough and sputum VAS | 48 | 1·72 | 0·79 | 0·49 (0·26–0·95) |
| Bacteria–negative | 188 | 1·85 | 1·18 | 0·61 (0·52–0·72)* |
| Bacteria–positive | 48 | 2·64 | 1·11 | 0·39 (0·22–0·69)* |




## biomarkers of airways dysbiosis

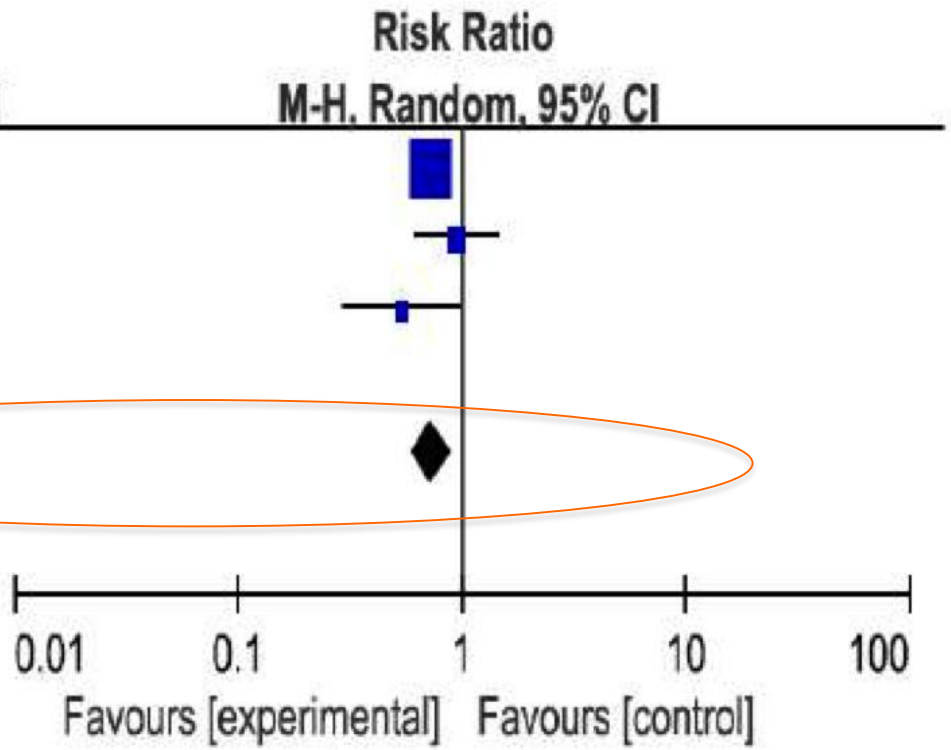
Gibson PG, Lancet 2017; 390: 659–68

# Azithromycin for Acute Exacerbation Reduction in Severe Asthma

| Study or Subgroup | Azithromycin Events | Total | Placebo Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| AMAZES 2017 | 94 | 213 | 127 | 207 | 67.1% | 0.72 [0.60, 0.87] |
| AZALEA 2016 | 28 | 97 | 31 | 102 | 21.3% | 0.95 [0.62, 1.46] |
| AZISAST 2013 | 9 | 27 | 18 | 29 | 11.6% | 0.54 [0.29, 0.98] |
| **Total (95% CI)** | | **337** | | **338** | **100.0%** | **0.74 [0.59, 0.92]** |
| Total events | 131 | | 176 | | | |

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 2.47$, $df = 2$ ($P = 0.29$); $I^2 = 19\%$

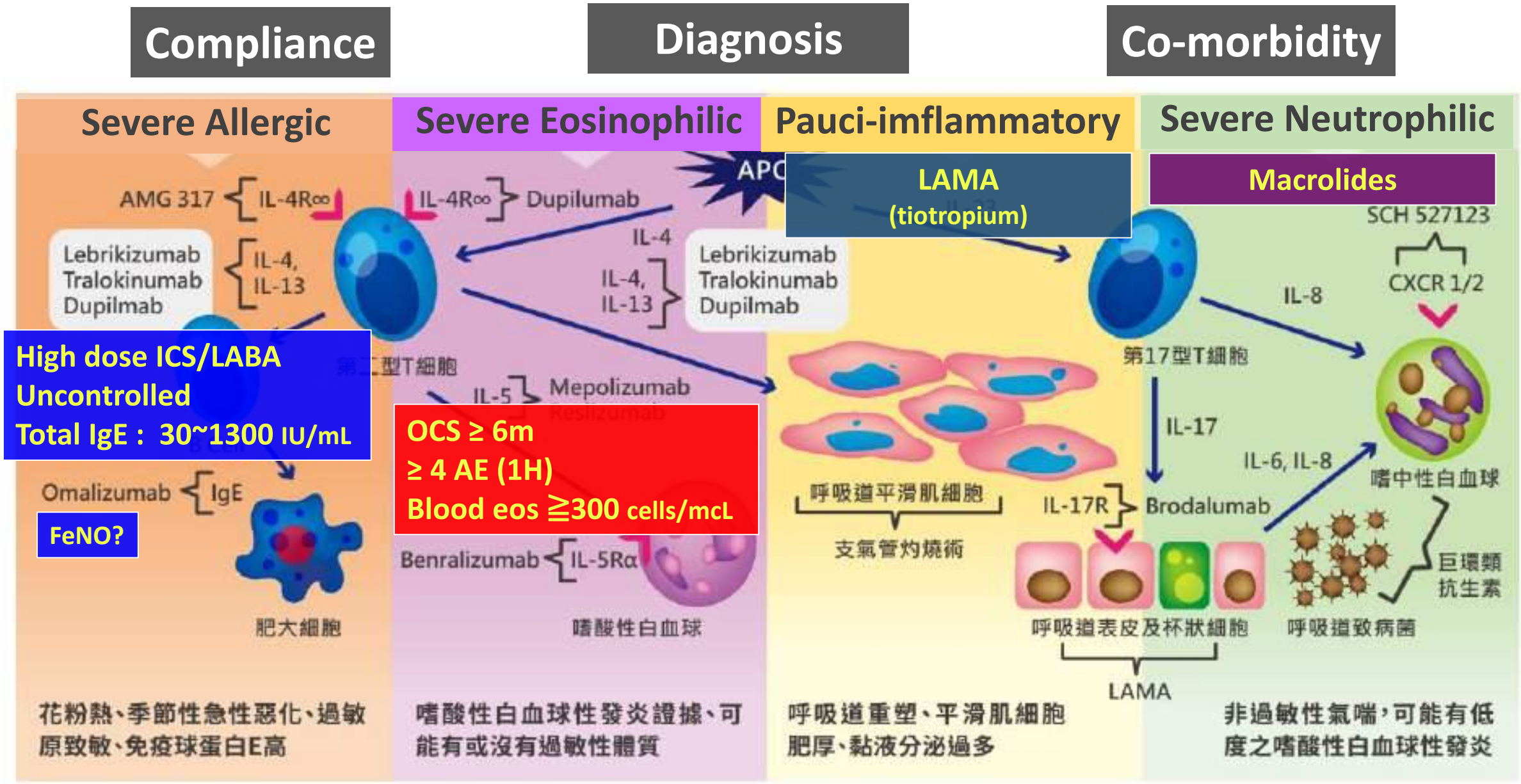
Test for overall effect: $Z = 2.76$ ($P = 0.006$)




**GRADE 2C**, weak recommendation (high heterogeneity)

Taiwan Asthma Guideline, TSPCCM, 20

# Phenotype-guided therapy for Severe Asthma




Taiwan Asthma Guideline, TSPCCM, 2018

# Thank you for your attention