



Asma severo: i nuovi target di terapia e i nuovi farmaci

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The definition of severe asthma (according to ERS/ATS 2014) (7)

During treatment with:

- High-dose ICS + at least one additional controller (LABA, montelukast, or theophylline) or
- Oral corticosteroids >6 months/year

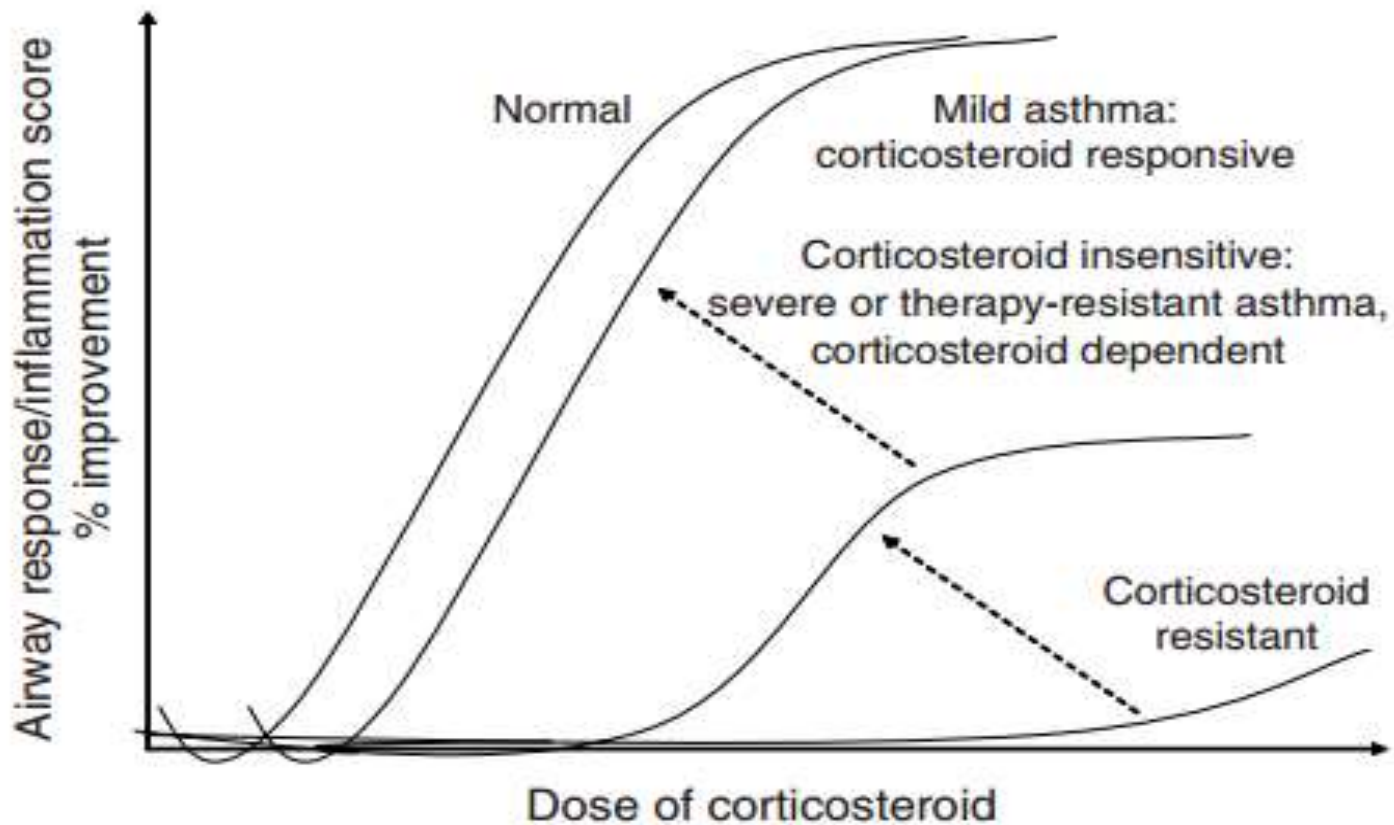
...at least one of the following occurs or would occur if treatment would be reduced:

- ACT <20 or ACQ >1.5
- At least 2 exacerbations in the last 12 months
- At least 1 exacerbation treated in hospital or requiring mechanical ventilation in the last 12 months
- $FEV_1 < 80\%$ (if FEV_1/FVC below the lower limit of normal)

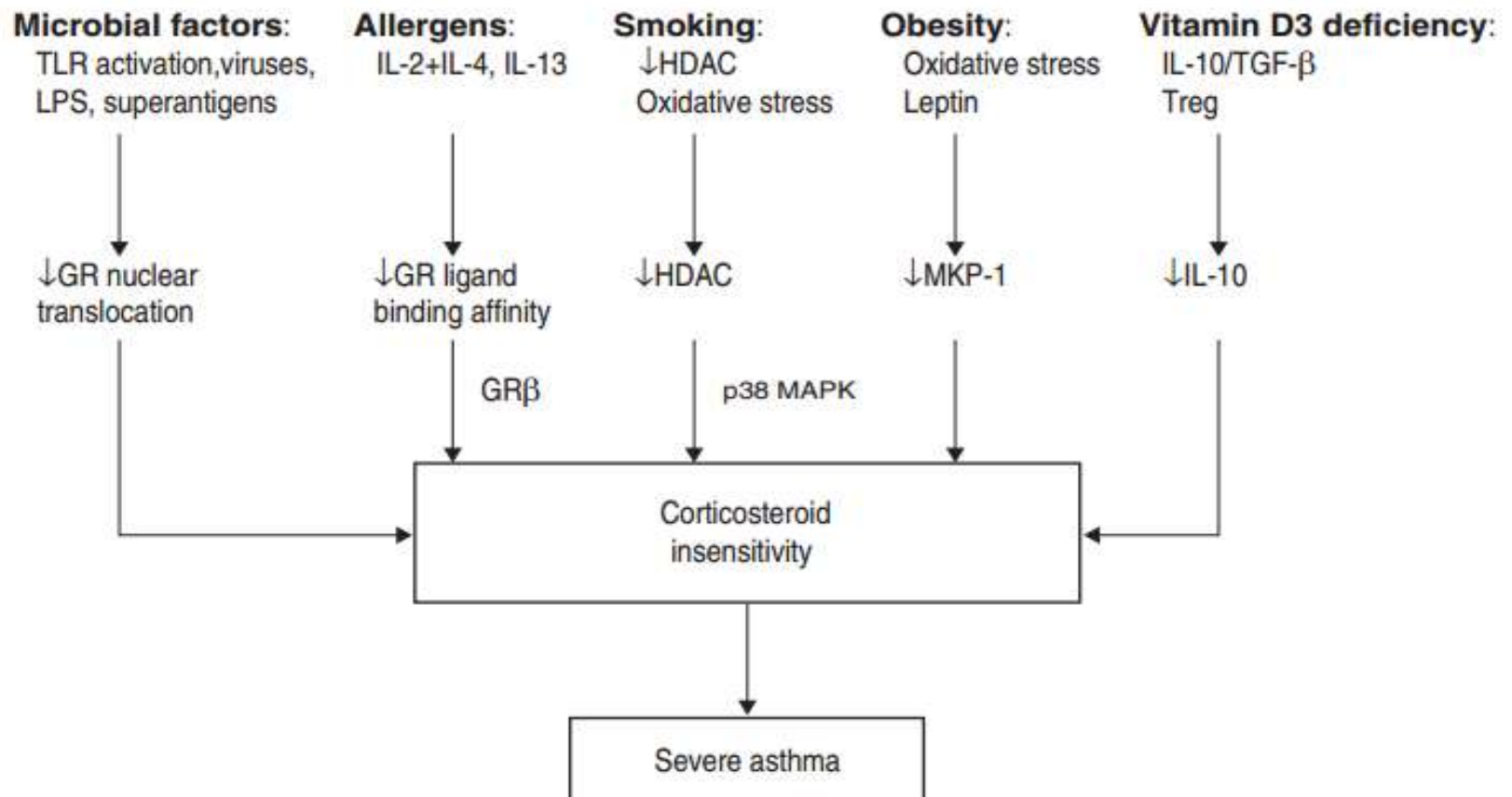
The lower limit of normal (LLN) for FEV_1/FVC can be calculated using appropriate spirometer software (www.lungfunction.org). Current recommendations advocate a $FEV_1/FVC < LLN$ to detect airway obstruction (40). However, if LLN is unknown, in our opinion the formerly universal limit ($FEV_1/FVC < 70\%$ for adults, $FEV_1/FVC < 75\%$ for children) can still be used.

ICS: Inhaled corticosteroid; ACT, Asthma Control Test; ACQ: Asthma Control Questionnaire; FEV_1 : Forced expiratory volume in one second; FVC: Forced vital capacity; ERS: European Respiratory Society; ATS: American Thoracic Society; LABA: Long-acting β_2 agonist

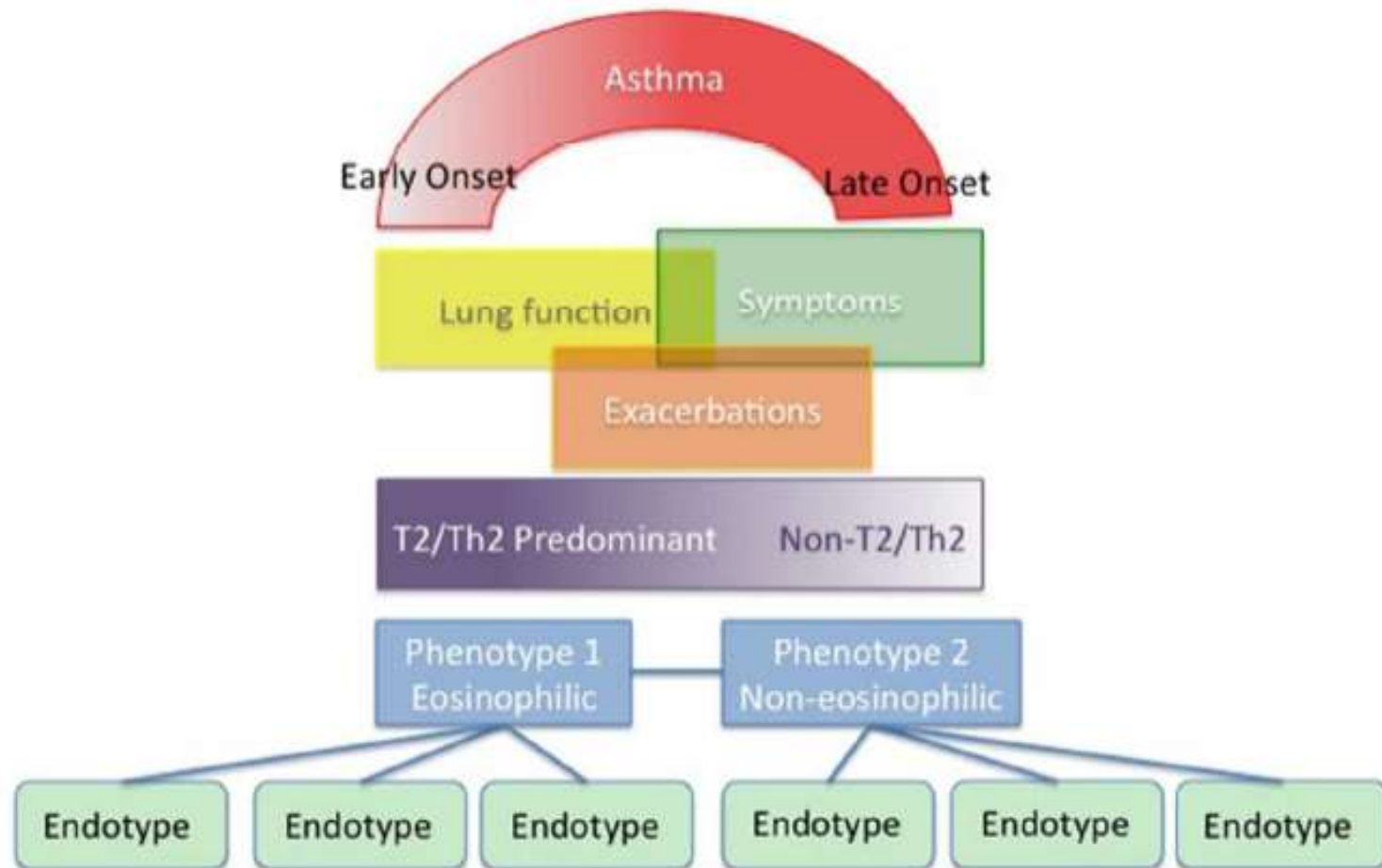
CS insensitivity



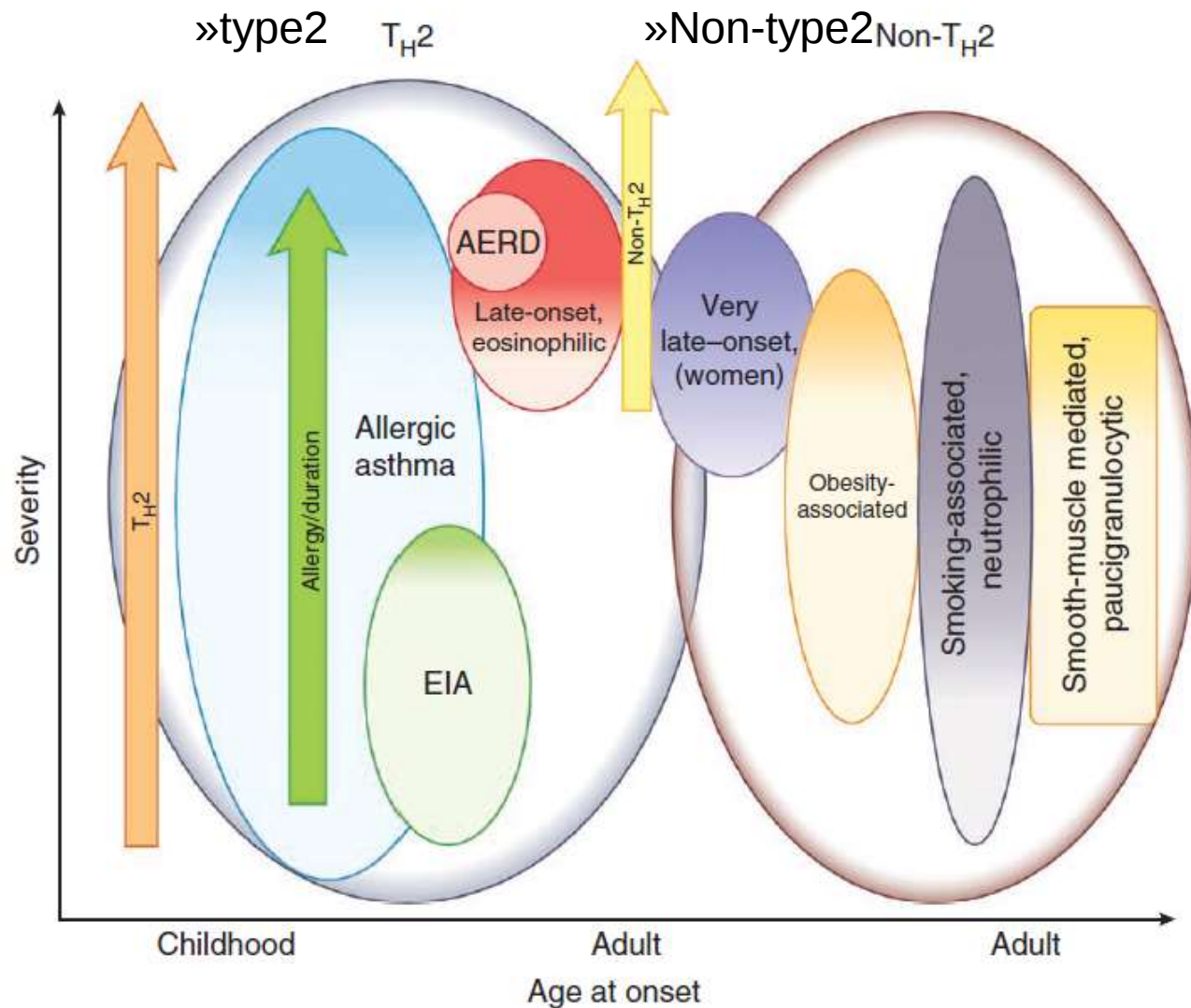
Mechanisms of CS insensitivity in severe asthma



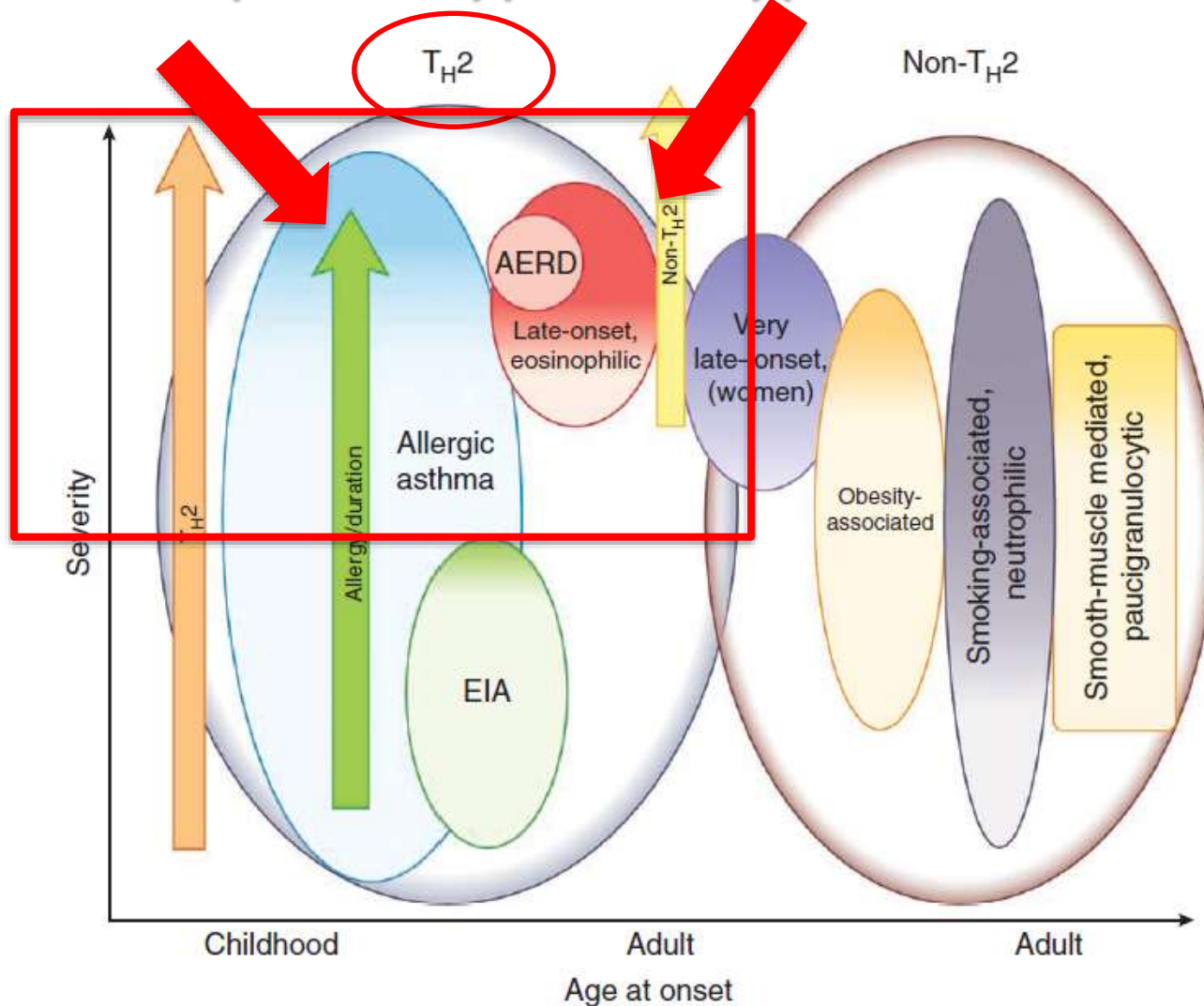
The spectrum of phenotypes in asthma



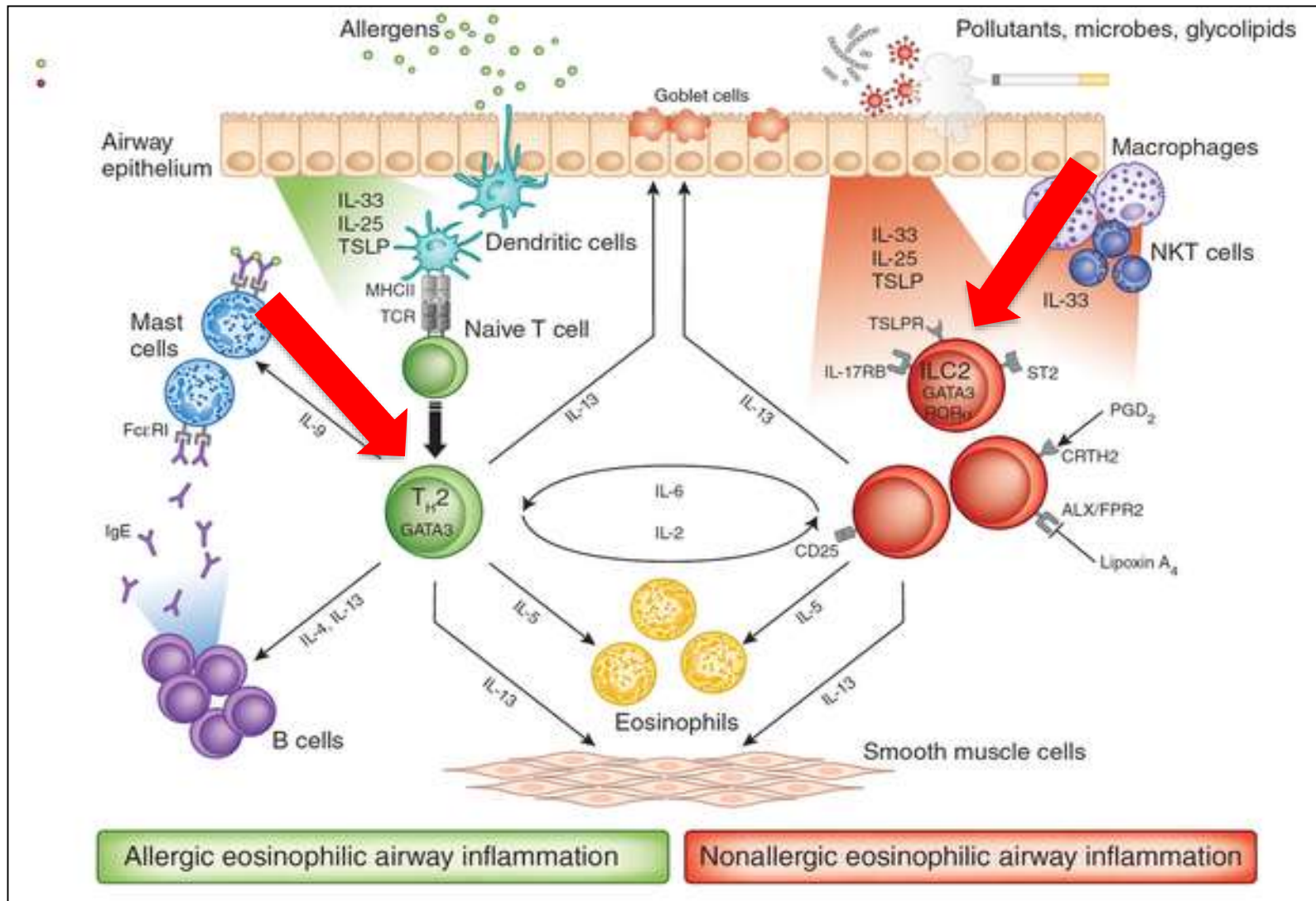
Asthma phenotypes



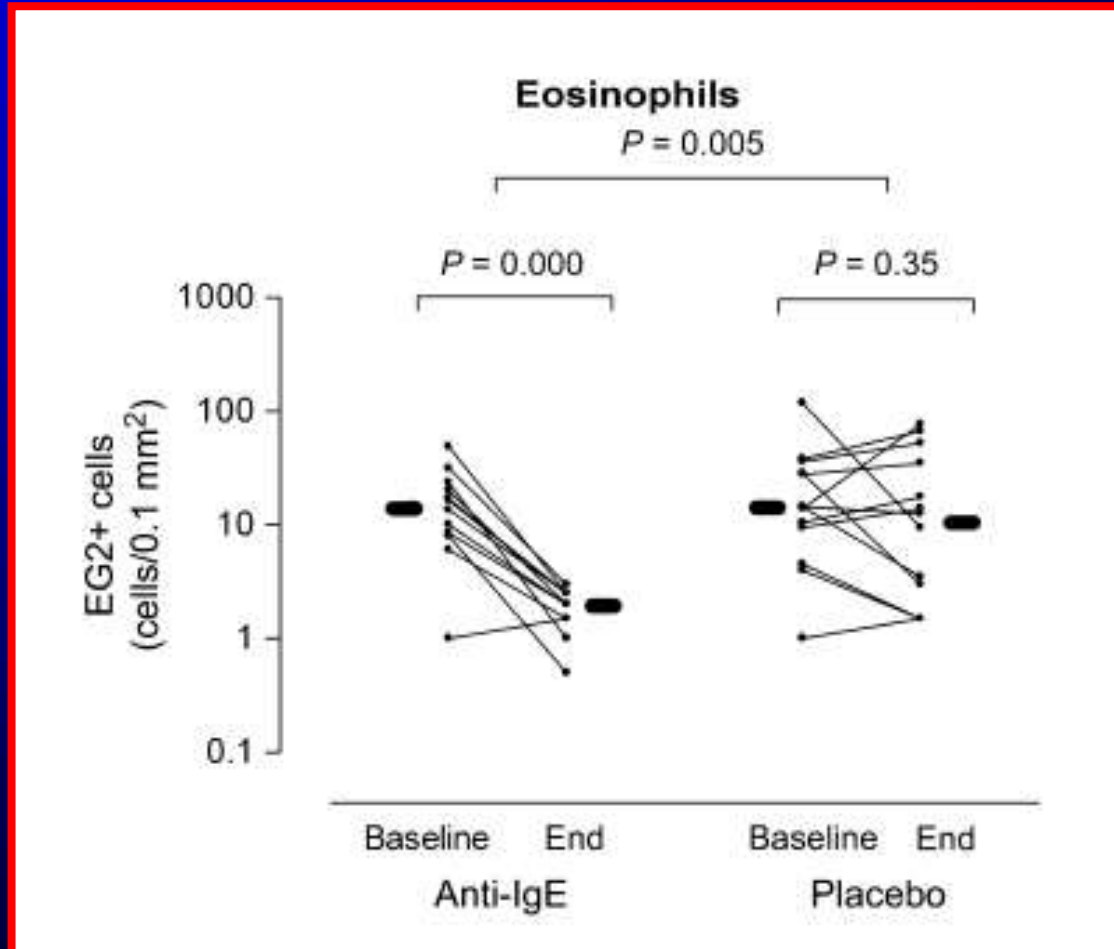
Two phenotypes of type 2 asthma



Two phenotypes of type 2 asthma



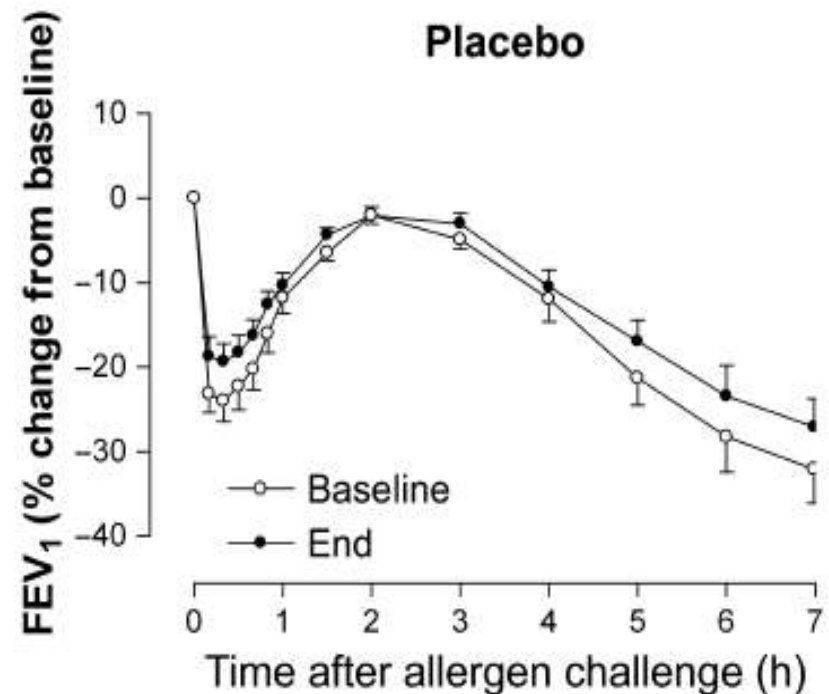
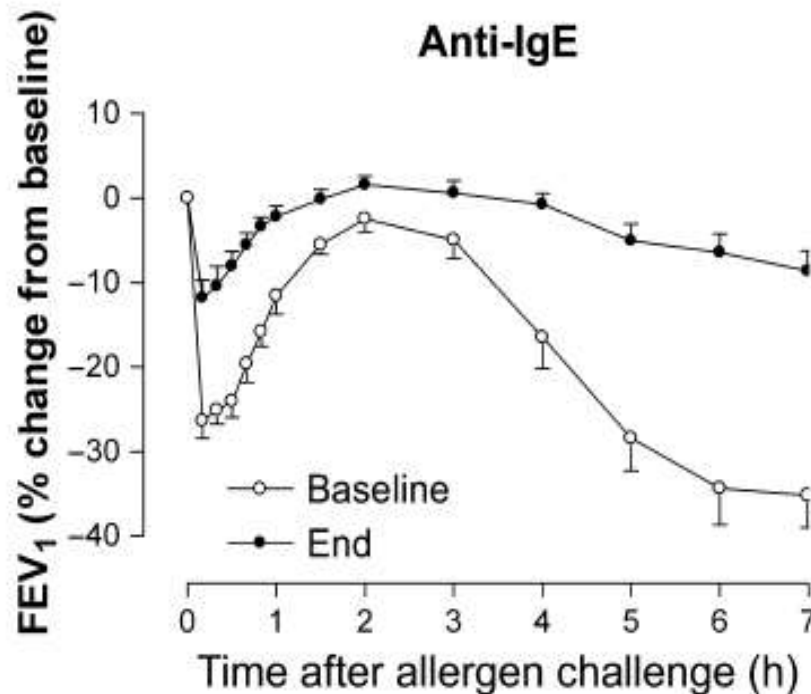
Eosinophils in bronchial biopsies after omalizumab



Omalizumab for 12 weeks

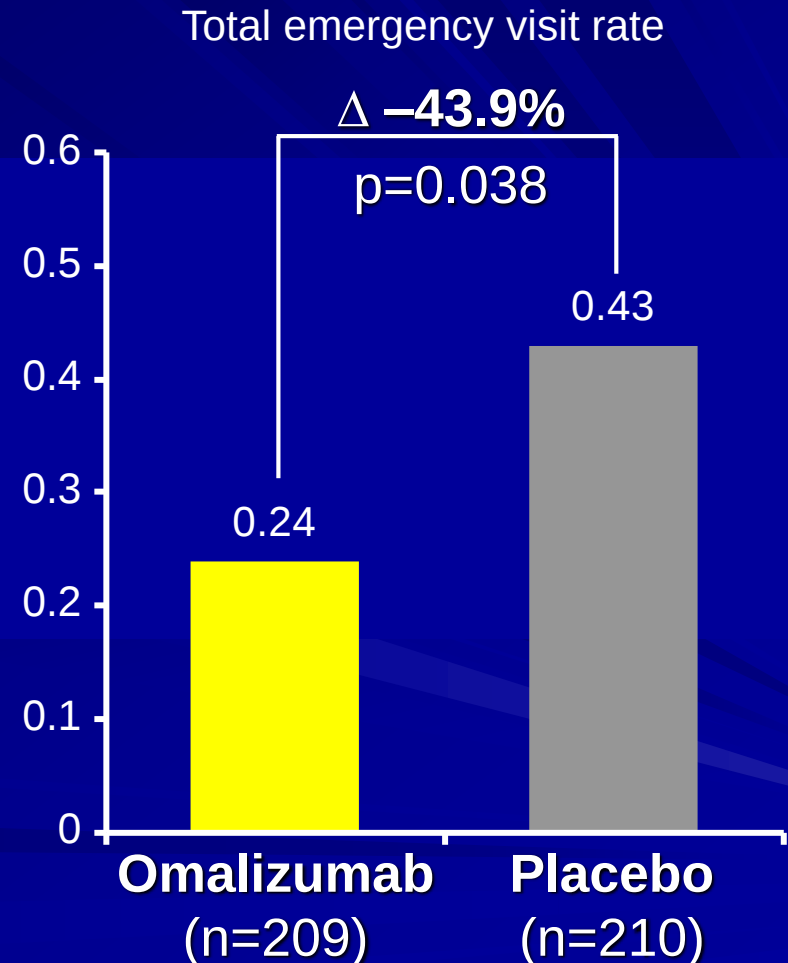
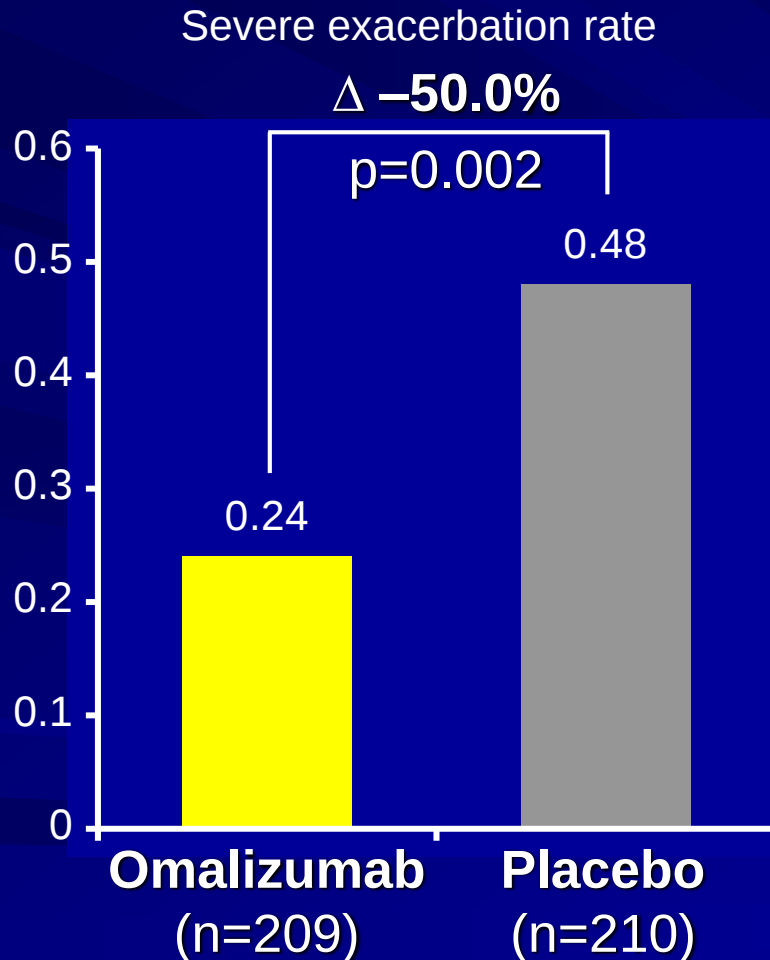
Van Rensen et al. Allergy 2009;64: 72-80.

Airway responses to inhaled allergen after omalizumab



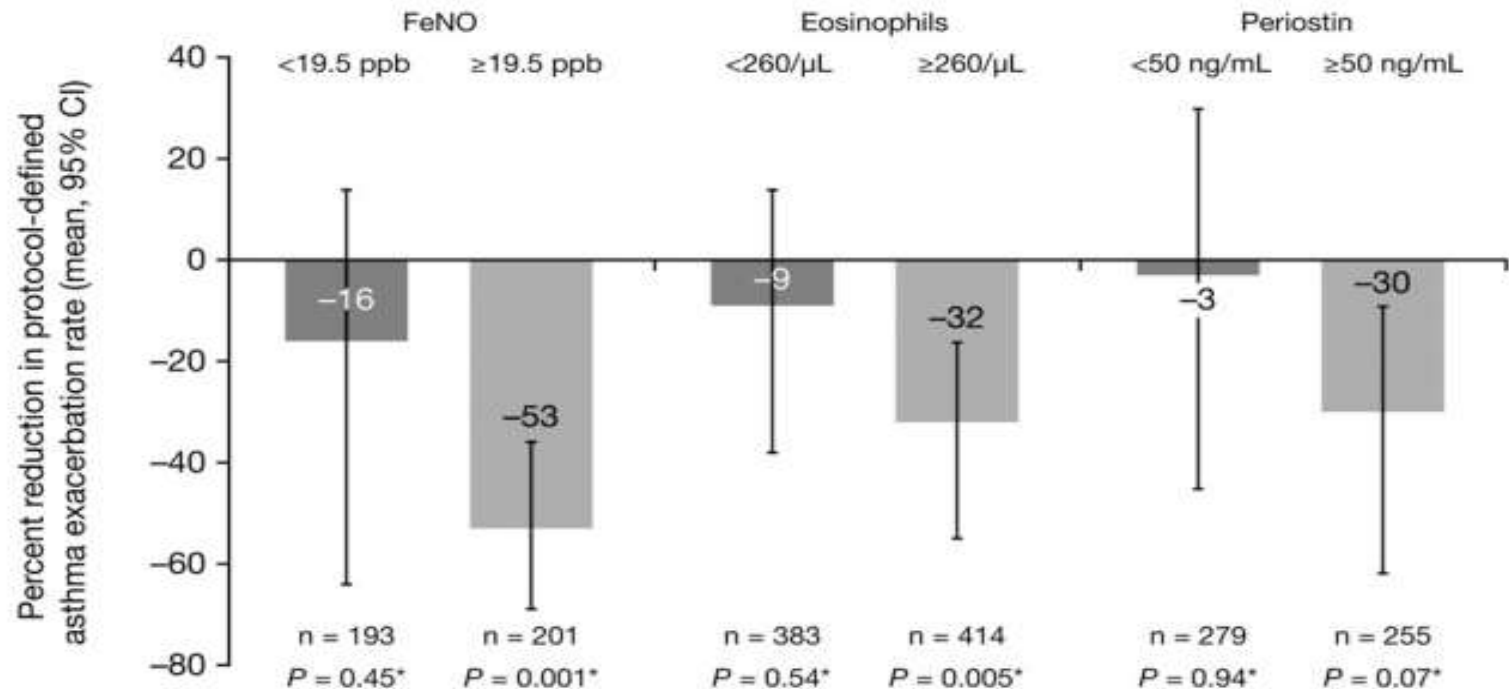
Omalizumab for 12 weeks

INNOVATE study: Omalizumab reduces severe exacerbations and emergency visits



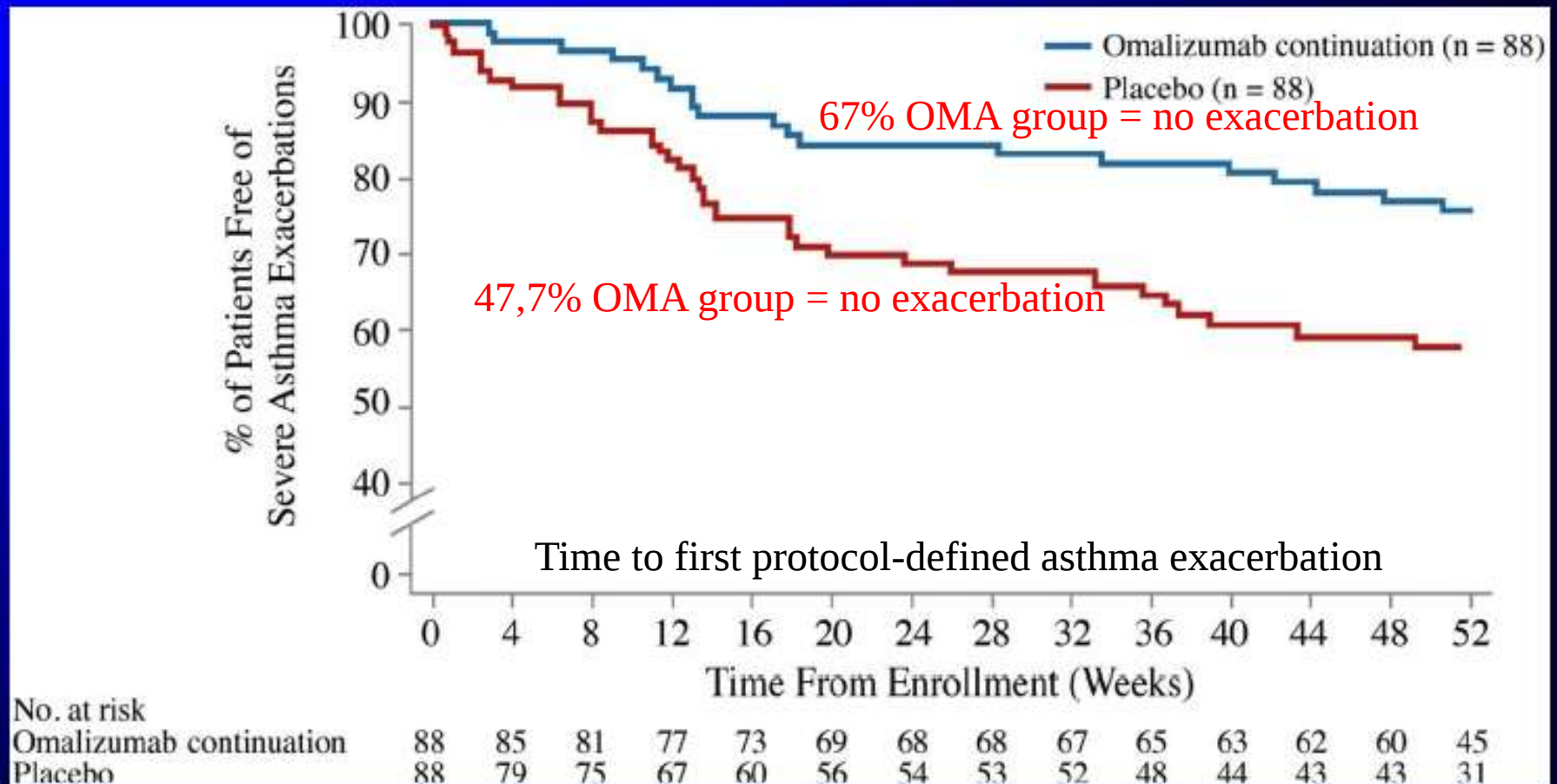
Humbert M. et al. Allergy 2005.

Biomarkers as predictors for omalizumab



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

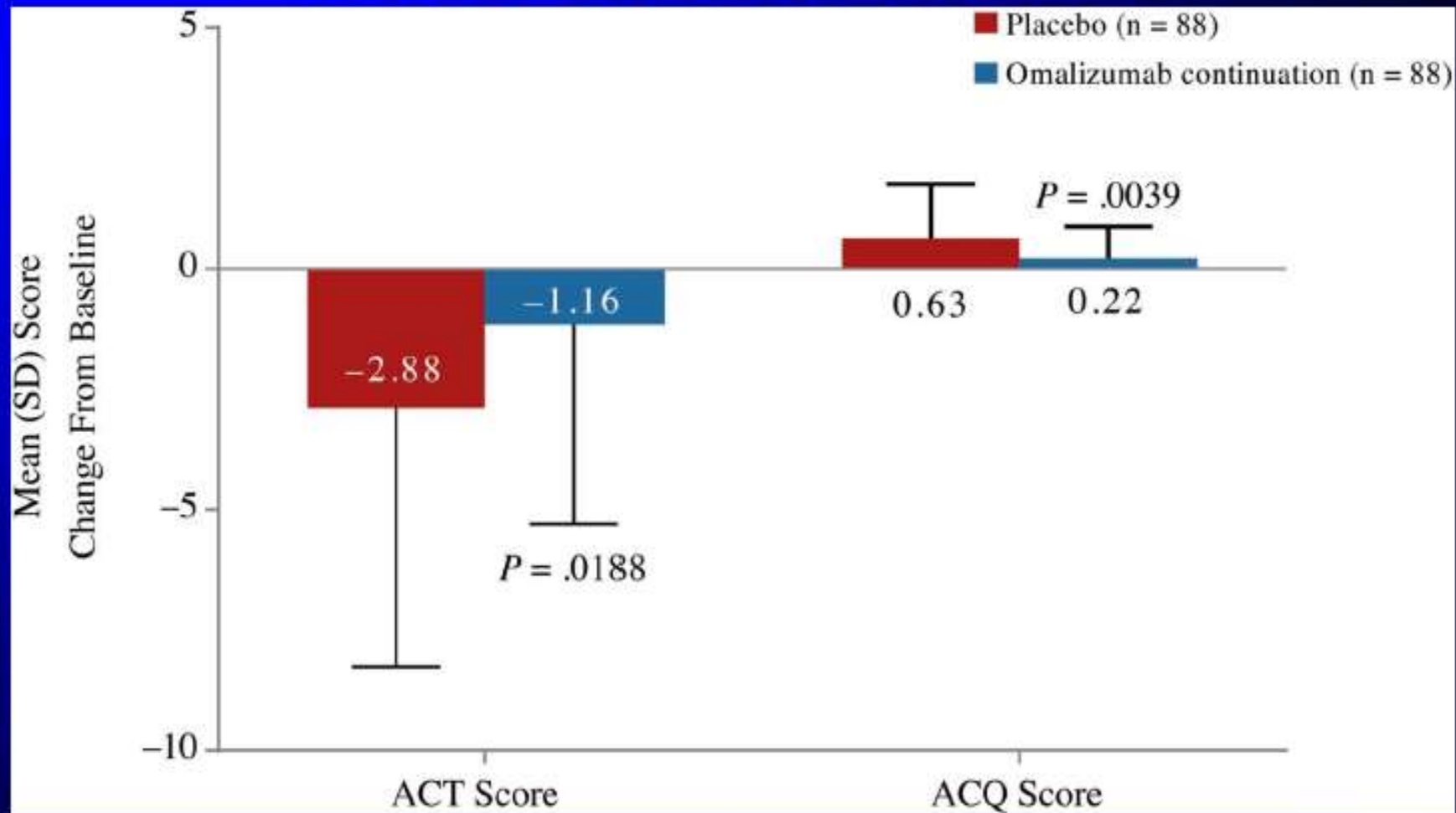
Time to first asthma exacerbation (XPORT Study)



Long term (5 years) treatment before randomization

Ledford D, et al. *J Allergy Clin Immunol* 5:1362-1370, 2017

Changes in ACT and ACQ scores from baseline to week 52



Ledford D, et al. *J Allergy Clin Immunol* 5:1362-1370, 2017

Omalizumab: disease modulation

Anti-IgE Therapy with Omalizumab Decreases Endothelin-1 in Exhaled Breath Condensate of Patients with Severe Persistent Allergic Asthma

Zietkowski et al. Respiration. 2010;80(6):534-42.

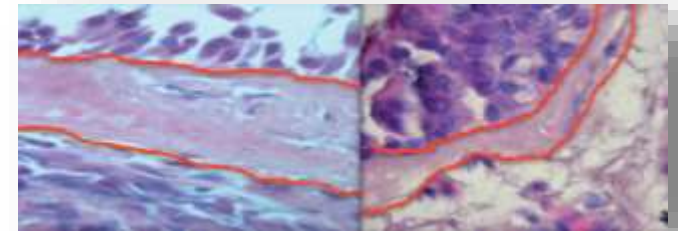
Riduzione dei livelli di endotelina

Correlazione significativa tra ↓endotelina e ↓ FeNO
E conta degli eosinofili

Omalizumab riduce l'ispessimento della membrana reticolare basale e l'infiltrato di eosinofili

OMALIZUMAB MODULATES BRONCHIAL RETICULAR BASEMENT MEMBRANE THICKNESS AND EOSINOPHIL INFILTRATION IN SEVERE PERSISTENT ALLERGIC ASTHMA PATIENTS

Riccio et al. Int J Immunopathol Pharmacol. 2012 Apr-Jun;25(2):475-84.



Pre

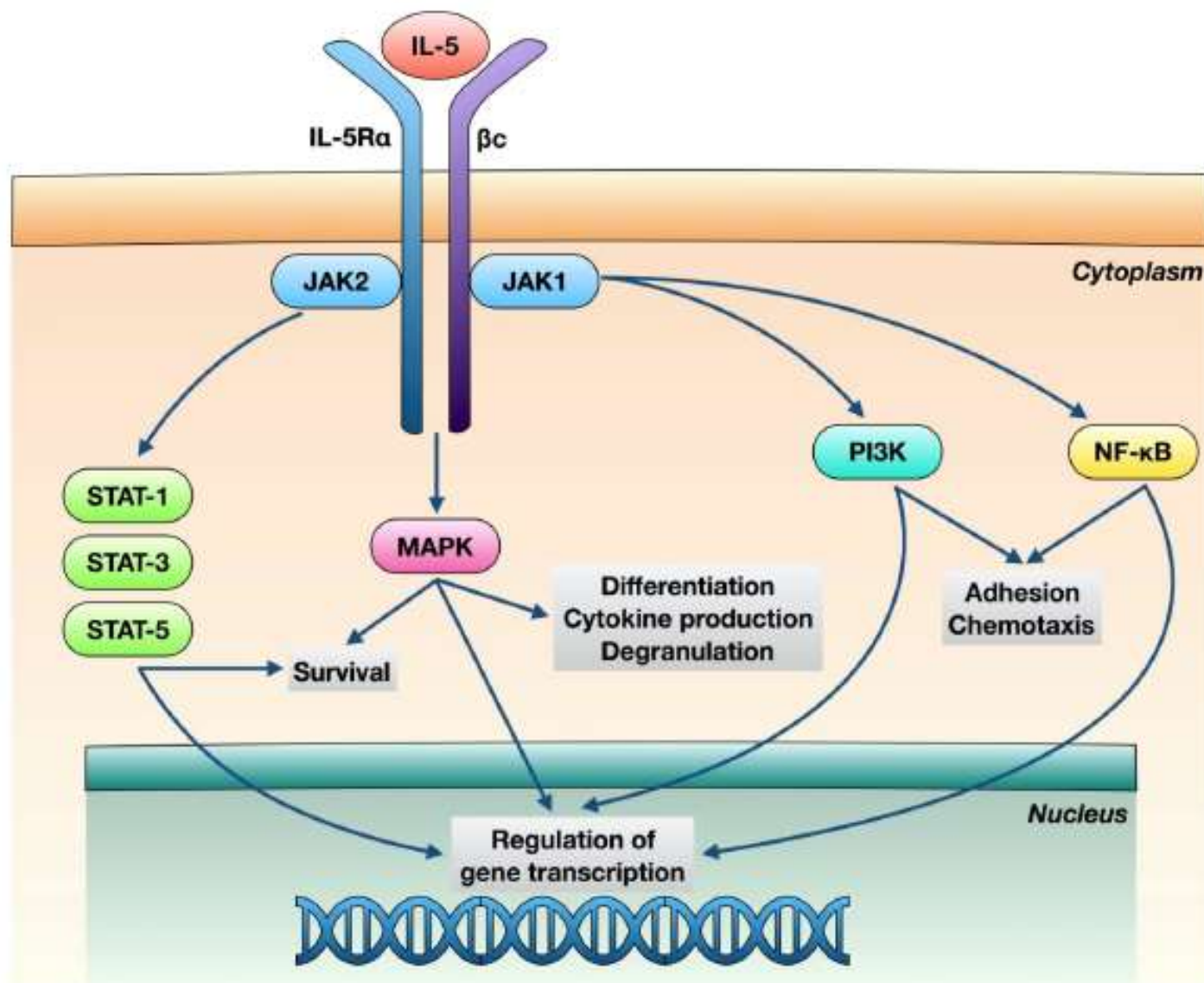
Post

Effects of Adding Omalizumab, an Anti-Immunoglobulin E Antibody, on Airway Wall Thickening in Asthma

Hoshino et al. Respiration. 2012;83(6):520-8.

Omalizumab riduce l'infiammazione delle vie aeree e lo spessore della parete nei pazienti con asma grave

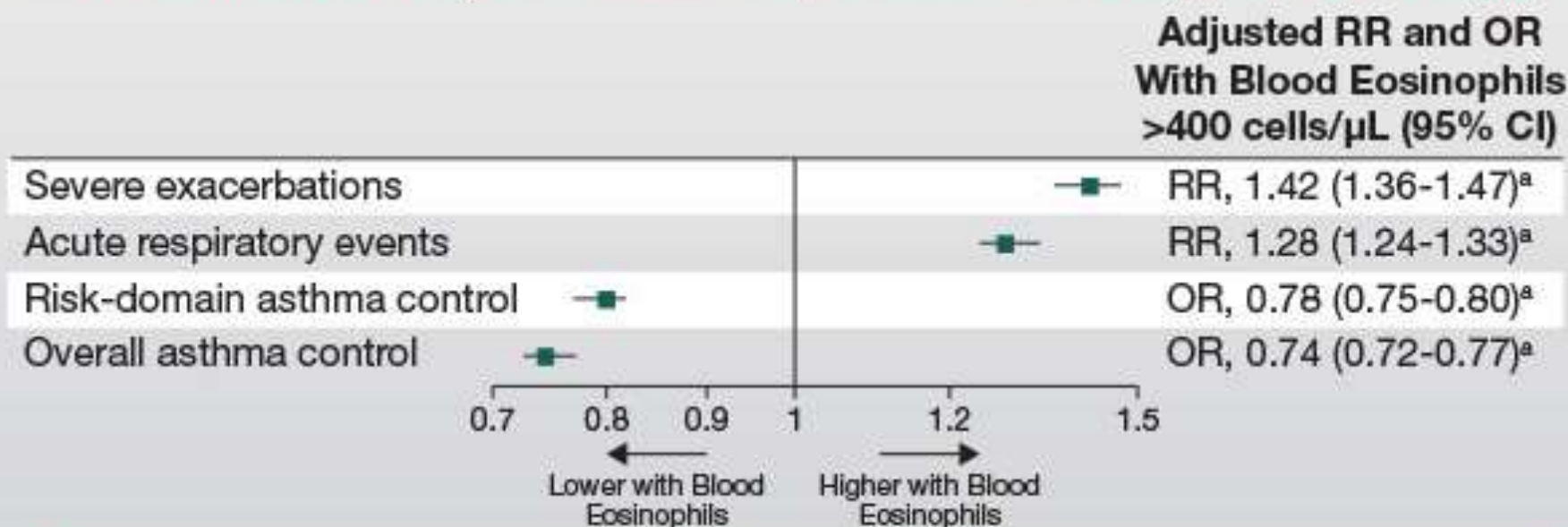
SIGNAL TRANSDUCTION PATHWAYS UNDERLYING THE BIOLOGICAL ACTIONS EXERTED BY IL-5 ON EOSINOPHILS



Pelaia C, Vatrella A, Busceti MT, Gallelli L, Pelaia G.
Drug Des Devel Ther 11:3137-3144, 2017

Association Between Blood Eosinophil Levels and Overall Disease Burden¹

Adjusted RRs for Severe Exacerbations and Acute Respiratory Events and ORs for Asthma Control (Patients With Peripheral Blood Eosinophils >400 cells/ μ L)



Blood eosinophil counts >400 cells/ μ L compared with $\leq$ 400 cells/ μ L associated with greater rate of asthma exacerbations and lower odds of achieving asthma control

^a 20,929 (16%) of 130,248 patients had blood eosinophil counts >400 cells/ μ L. $P < .0001$ for all comparisons. Adjusted for age, sex, BMI, smoking status, and Charlson comorbidity index score.

Mepolizumab: Published Clinical Trials In Asthma

First author/year	Disease Severity	N	Dosage/Delivery	Outcome summary
Flood-Page et al, 2003 ¹	Mild asthma	11	750 mg i.v. every 4 weeks for 3 months	↓Blood Eos; ↓Airway Eos only by 50%=PEF, FEV ₁ , bronchial hyperresponsiveness
Flood-Page et al, 2007 ²	Moderate persistent asthma	362	3x 250 or 750 mg at monthly intervals	↓Blood+Sputum Eos; no significant changes in clinical endpoints
Halder et al, 2009 ³	Eosinophilic asthma	61	750 mg i.v. every 4 weeks for 1 year	↓Blood+Sputum Eos; ↓Severe exacerbations; ↑QoL=FEV ₁ , bronchial hyperreactivity
Nair et al, 2009 ⁴	Prednisone-dependent asthma	9	750 mg i.v. every 4 weeks for 5 months	↓Blood+Sputum Eos; ↓Exacerbations; Prednisone sparing effect
Pavord et al, 2012 ⁵ DREAM	Severe eosinophilic asthma	462	75–250–750 mg i.v. every 4 weeks for 13 infusions	↓Blood+Sputum Eos; ↓Exacerbations=FEV ₁ , AQLQ, and ACQ scores
Bel et al, 2014 ⁶	Severe eosinophilic asthma	135	100 mg s.c. every week for 20 weeks	Glucocorticoid sparing effect; ↓Exacerbations; Improvement ACQ-5 score
Ortega et al, 2014 ⁷ MENSA	Severe eosinophilic asthma	385	75 mg i.v. or 100 mg s.c. every 4 weeks for 32 weeks	↓Blood+Sputum Eos; ↓Exacerbations; ↑FEV ₁ ; ↑ACQ-5 score
Ortega et al, 2016 ⁸	Severe eosinophilic asthma	1192	DREAM: 75 mg, 250 mg, or 750 mg i.v. MENSA: 75 mg i.v. or 100 mg s.c.	↓Exacerbations; ↑FEV ₁ ; ↑ACQ-5 score above MCID

ACQ-5=asthma control questionnaire 5-item version; AQLQ=asthma quality of life questionnaire; Eos=eosinophils; FEV₁=forced expiratory volume in 1 second; i.v.=intravenous; MCID=minimal clinically important difference; s.c.=subcutaneous.

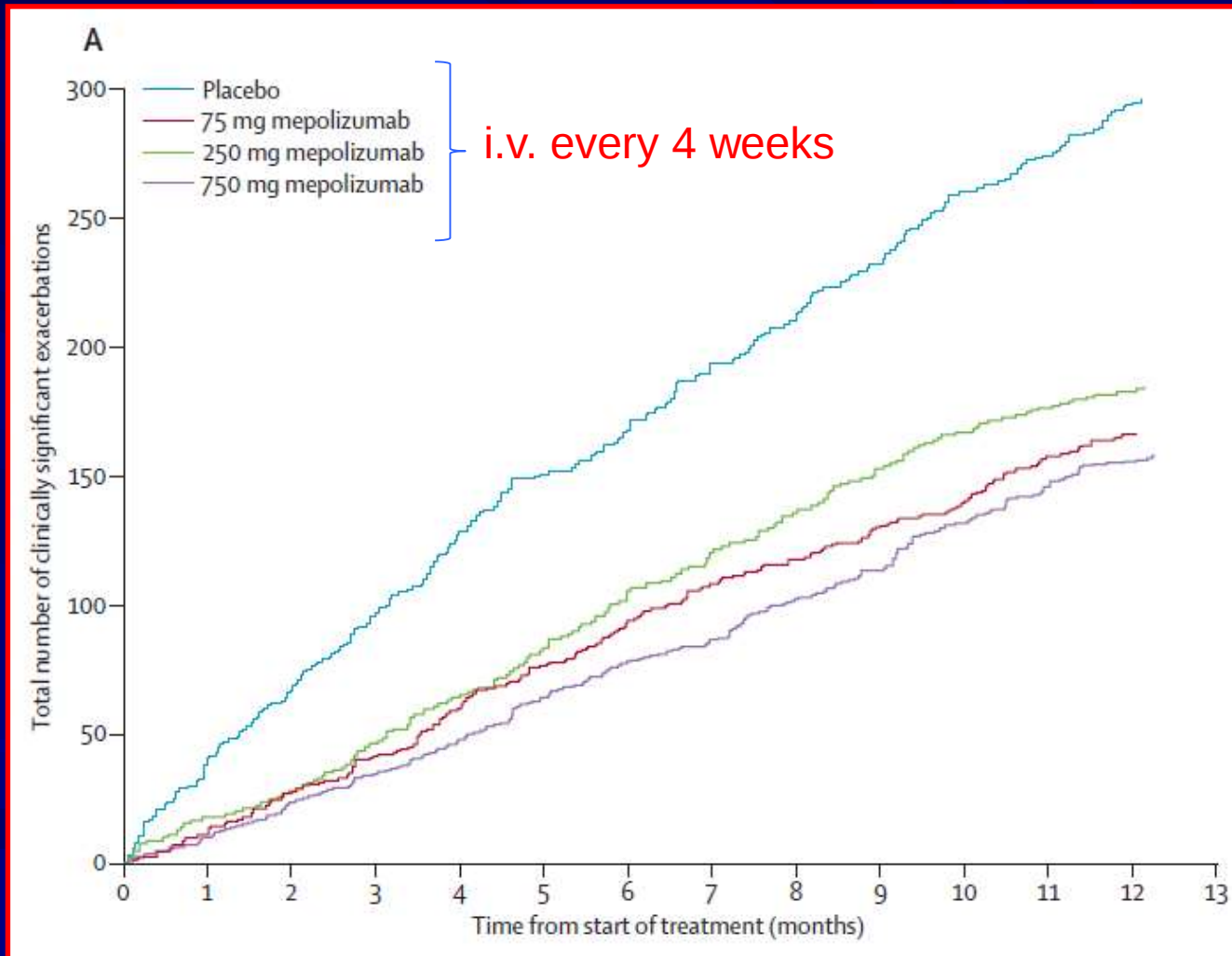
1. Flood-Page P et al. *Am J Respir Crit Care Med*. 2003;167:199-204. 2. Flood-Page P et al. *Am J Respir Crit Care Med*. 2007;176:1062-1071. 3. Halder P et al. *N Engl J Med*. 2009;360:973-984. 4. Nair P et al. *N Engl J Med*. 2009;360:985-993. 5. Pavord ID et al. *Lancet*. 2012;380:651-659. 6. Bel EH et al. *N Engl J Med*. 2014;371(13):1189-1197. 7. Ortega HG et al. *New Engl J Med*. 2014;371:1198-1207. 8. Ortega HG et al. *Lancet Respir Med*. 2016;4(12):1000-1009.

DREAM study: inclusion criteria

- Age 12-74 years
- Clinical diagnosis of asthma (refractory)
- History of two or more exacerbations / year
- **Evidence of eosinophilic inflammation:**
 - 1) sputum eosinophil count $\geq 3\%$, *or*
 - 2) blood eosinophil count $\geq 300/\mu\text{L}$, *or*
 - 3) $\text{FE}_{\text{NO}} \geq 50$ ppb.

DREAM study: Mepolizumab in severe eosinophilic asthma: impact on exacerbations

N=621
patients



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

MENSA study in severe eosinophilic asthma with frequent exacerbations

N=576 patients

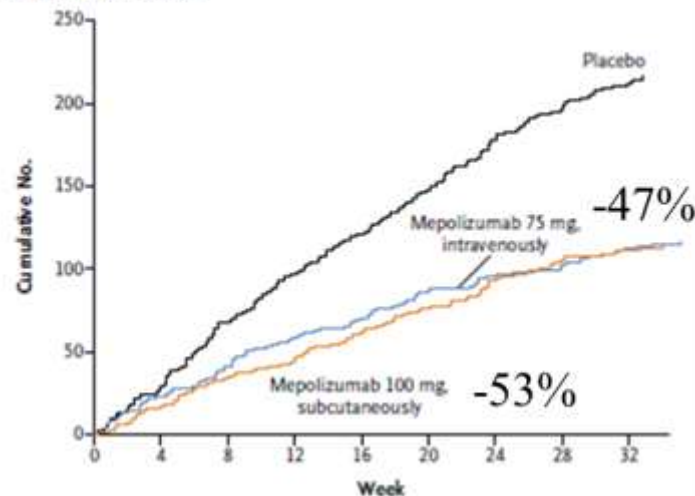
A

Run-in Period
(1–6 wk before
randomization)

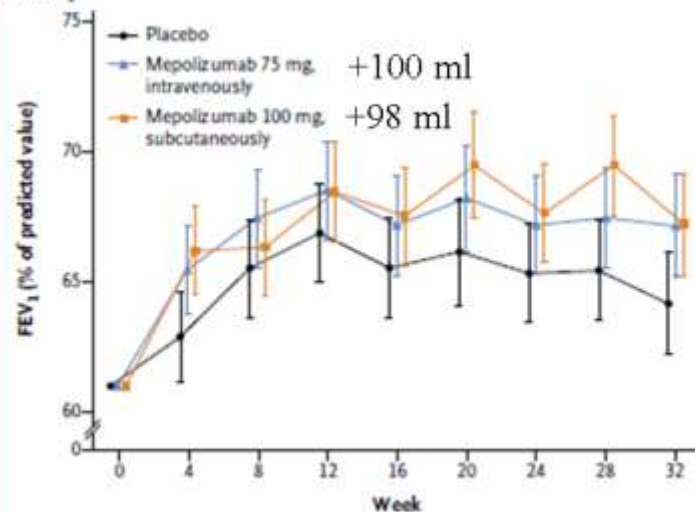
Visit 1
Screening

Visit 2
Randomization
1:1:1

A Asthma Exacerbations



B FEV₁



40
ow-up

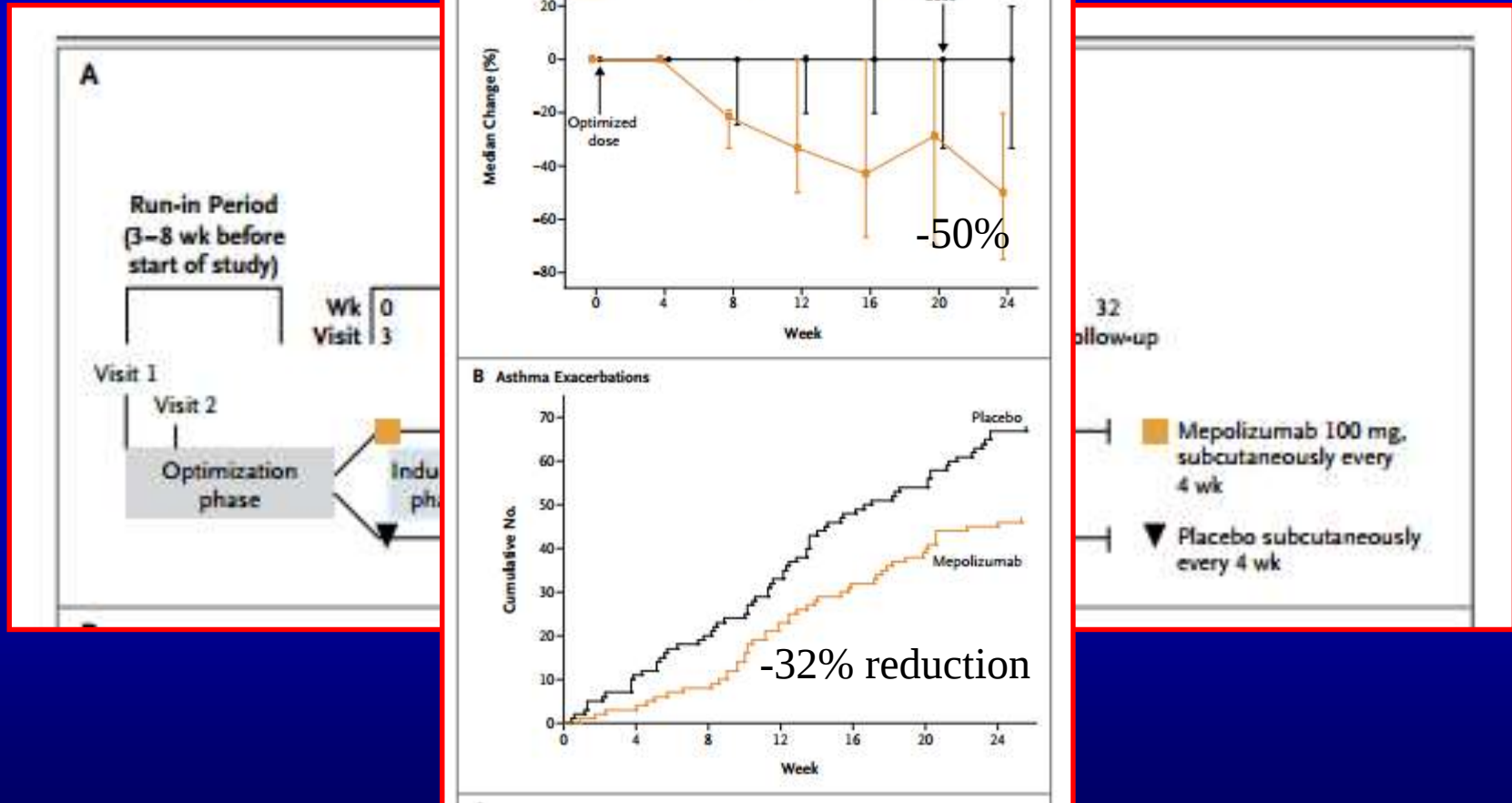
▲ Mepolizumab 75 mg i.v.

■ Mepolizumab 100 mg
S.C.

▼ Placebo

Ortega et al. NEJM 2014

Oral GC-sparing effect of mepolizumab in eosinophilic asthma



Reslizumab: Published Clinical Trials in Asthma until the end of 2016¹⁻⁵

First author/year	Disease Severity	N	Dosage/Delivery	Outcome summary
Kips et al, 2003 ¹	Severe asthmatics	18	0.03–1 mg/kg i.v. single dose	Safe; ↓Blood Eos
Castro et al, 2011 ²	Poorly controlled eosinophilic asthma	53	3 mg/kg i.v. every 4 weeks for 12 weeks	↓Blood Eos; ↑FEV ₁ ; ↑ACQ-5 score; Particularly in patients with nasal polyps ±30% patients had nasal polyps
Castro et al, 2015 ^{3,a}	Inadequately controlled asthma with elevated eosinophils	953 (N=477 in Study 1; N=476 in Study 2)	3 mg/kg i.v. every 4 weeks for 1 year	↓Exacerbation frequency
Bjermer et al, 2016 ⁴	Inadequately controlled asthma with elevated eosinophils	315	0.3 or 3.0 mg/kg every 4 weeks for 16 weeks	↑FEV ₁ ; ↑ACQ-5; ↑AQLQ
Corren et al, 2016 ⁵	Poorly controlled asthma with a range of eosinophil counts	492	3.0 mg/kg or placebo once every 4 weeks for 16 weeks	↑FEV ₁ ; ↑ACQ-7; ↓Rescue SABA use; no improvement in FEV ₁ with baseline eosinophil <400 cells/μL

Inclusion criteria: Blood EOS > 400/mcL

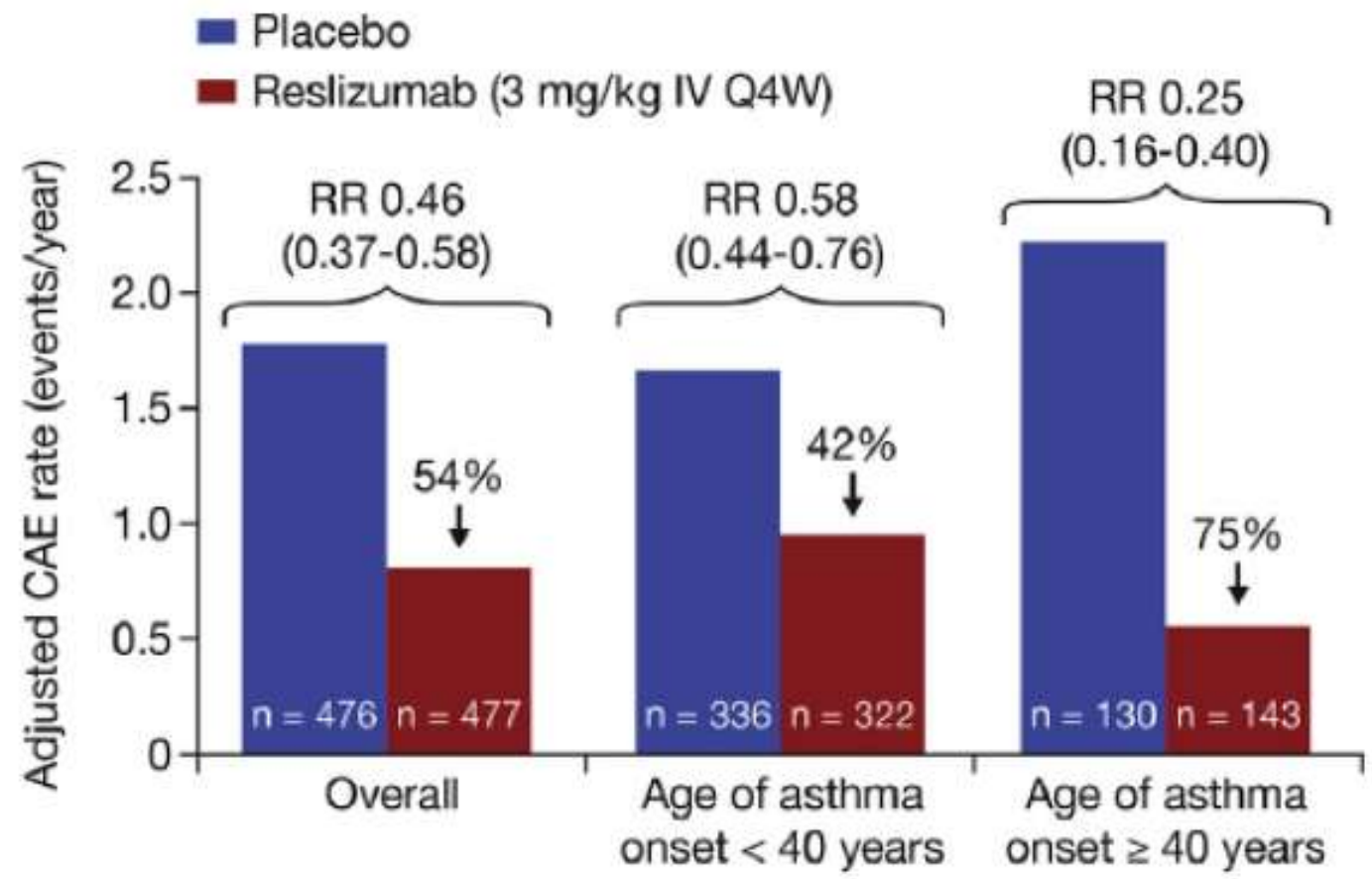
^aPooled analysis.

ACQ-5=asthma control questionnaire 5-item version; AQLQ=asthma quality of life questionnaire; Eos=eosinophils; FEV₁=forced expiratory volume in 1 second; SABA=short-acting beta agonist.

1. Kips JC et al. *Am J Respir Crit Care Med*. 2003;167:1655-1659. 2. Castro M et al. *Am J Respir Crit Care Med*. 2011;184:1125-1132. 3. Castro M et al. *Lancet Respir Med*. 2015;3:355-366. 4. Bjermer L et al. *CHEST*. 2016. doi: 10.1016/j.chest.2016.03.032. 5. Corren J et al. *CHEST*. 2016. doi: 10.1016/j.chest.2016.03.018. 6. Varricchi G et al. *Curr Opin Allergy Clin Immunol*. 2016;16:186-200.

CLINICAL ASTHMA EXACERBATION (CAE) RATE OVER 52 WEEKS

A higher proportion of patients in the late-onset asthma group had chronic sinusitis with nasal polyps



Brusselle G, Germinaro M, Weiss S, Zangrilli J.
Pulm Pharmacol Ther 43:39-45, 2017

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

Manali Mukherjee*, Fernando Aleman Paramo*, Melanie Kjarsgaard, Brittany Salter, Gayatri Nair, Nicola LaVigne, Katherine Radford, Roma Sehmi, and Parameswaran Nair

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

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Originally Published in Press as DOI: 10.1164/rccm.201707-1323OC on September 15, 2017

In this study, we tested the hypothesis that:

- reslizumab would be effective in severe prednisone-dependent eosinophilic asthma (sputum EOS > 3% and Blood EOS > 300/mcL)
- higher doses of anti-IL5 Mab would be more effective than lower doses to control airway eosinophilia and that this would be associated with better clinical outcomes

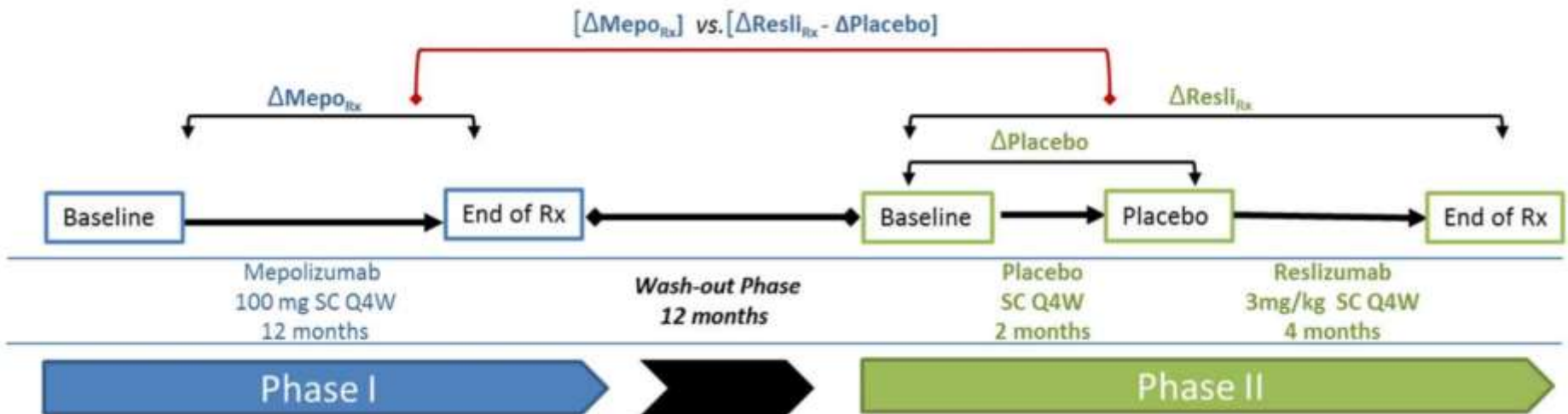
Weight-adjusted Intravenous Reslizumab in Severe Asthma with Inadequate Response to Fixed-Dose Subcutaneous Mepolizumab

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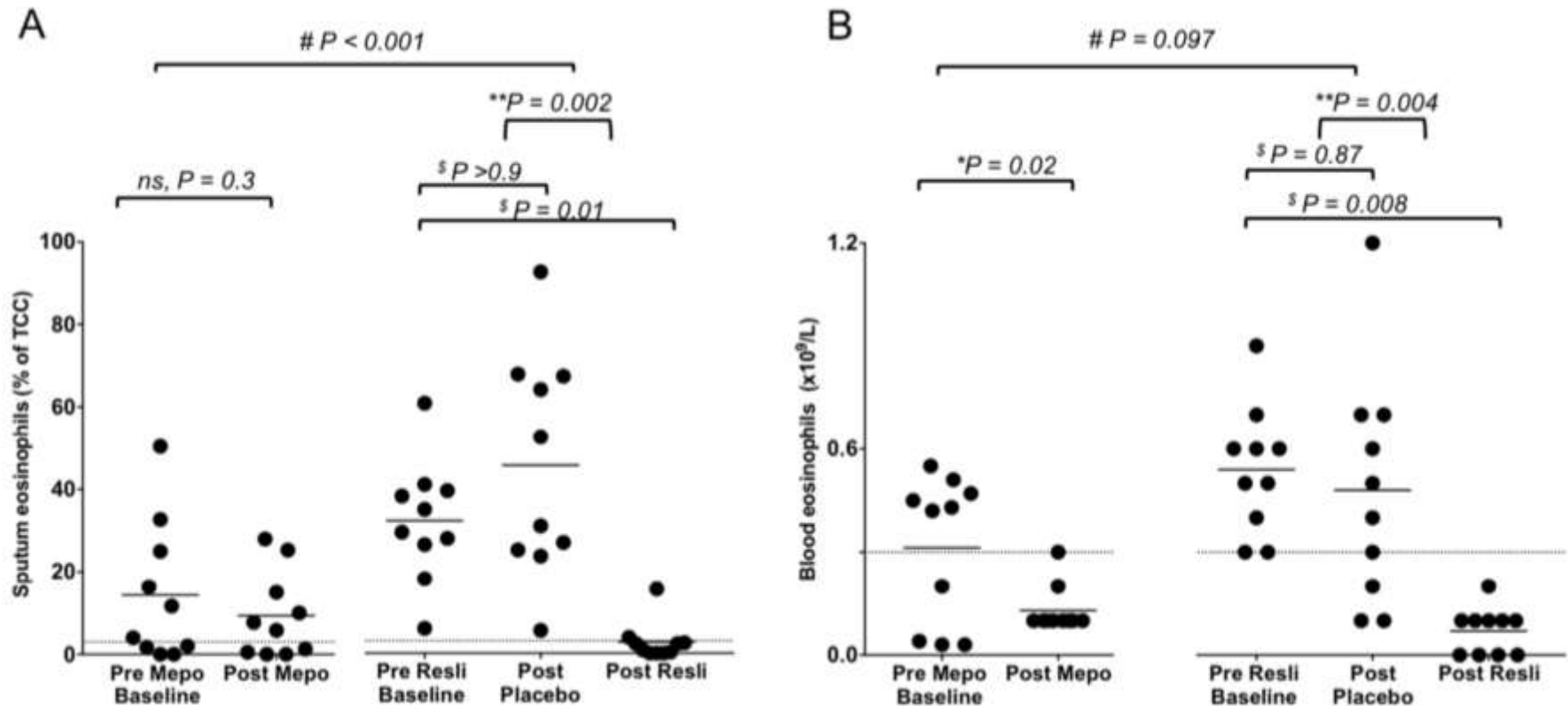
Am J Respir Crit Care Med Vol 197, Iss 1, pp 38–46, Jan 1, 2018

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Originally Published in Press as DOI: 10.1164/rccm.201707-1323OC on September 15, 2017



Changes in sputum and blood eosinophil levels over study period

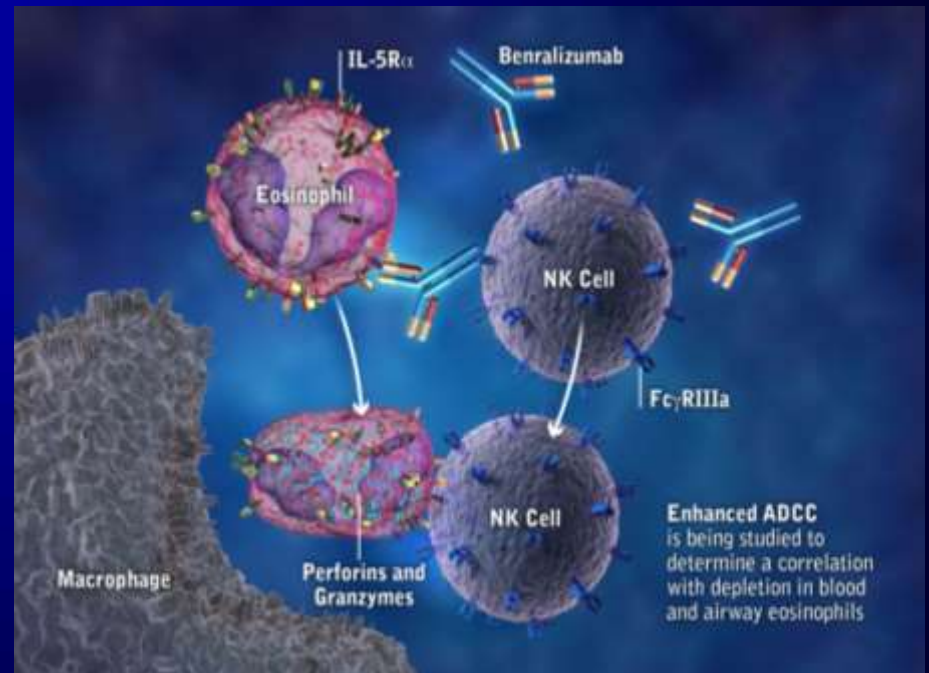


- 4 doses of IV reslizumab are effective in suppressing both sputum and blood eosinophilia
- This treatment effect is greater than that observed with 12 doses of 100 mg SC mepolizumab
- Suppression of airway eosinophilia was associated with a clinically meaningful improvement in asthma control and FEV1

Benralizumab depletes eosinophils: how does it work?

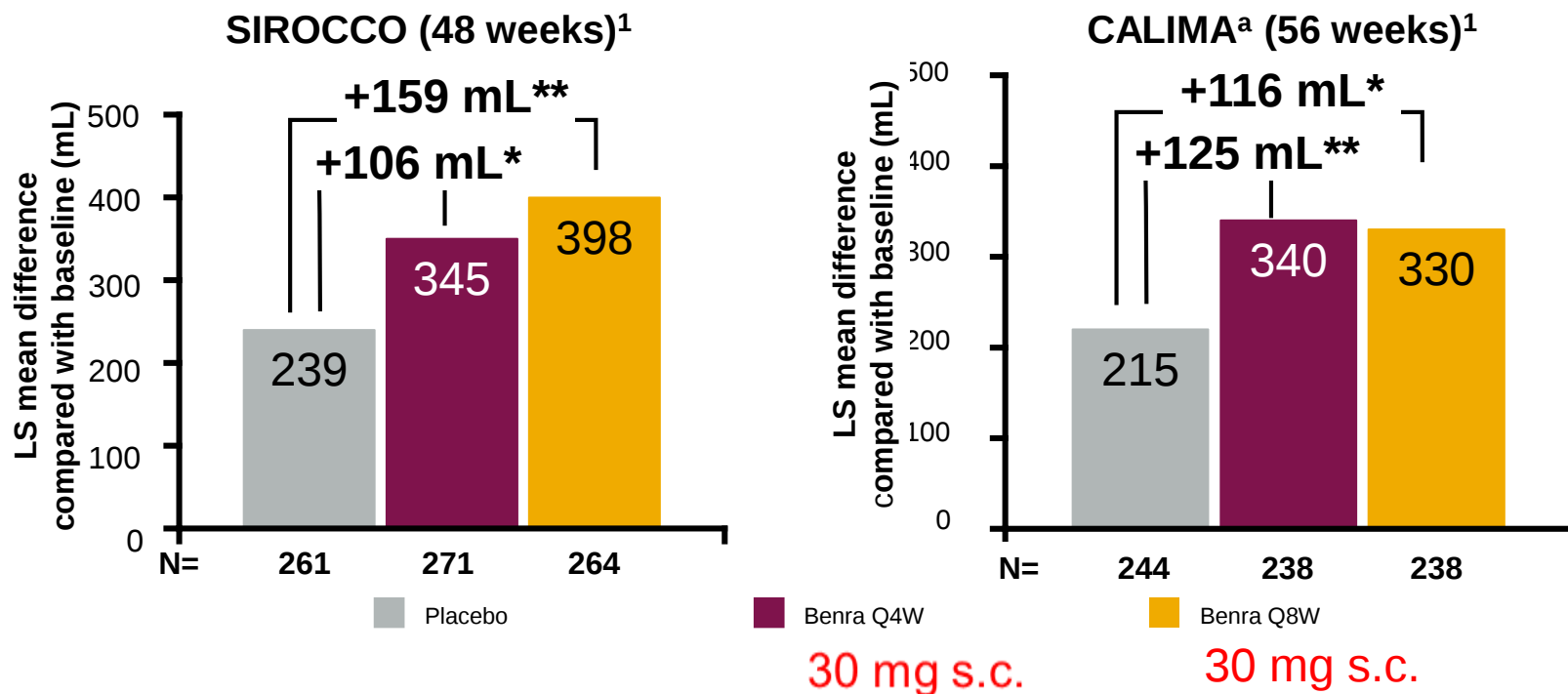
Benralizumab depletes eosinophils in a different way from anti-IL-5 antibodies:

- 1) Binds with high specificity to IL-5R α 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-5R α , interleukin-5 receptor α ; NK, natural killer

SIROCCO and CALIMA: Both Benralizumab Dosing Schedules Significantly Increased Pre-bronchodilator FEV₁ (FAS, eos ≥300/μL)



- Benralizumab led to a significant improvement in lung function at both dosing schedules compared to placebo in the SIROCCO and CALIMA trials

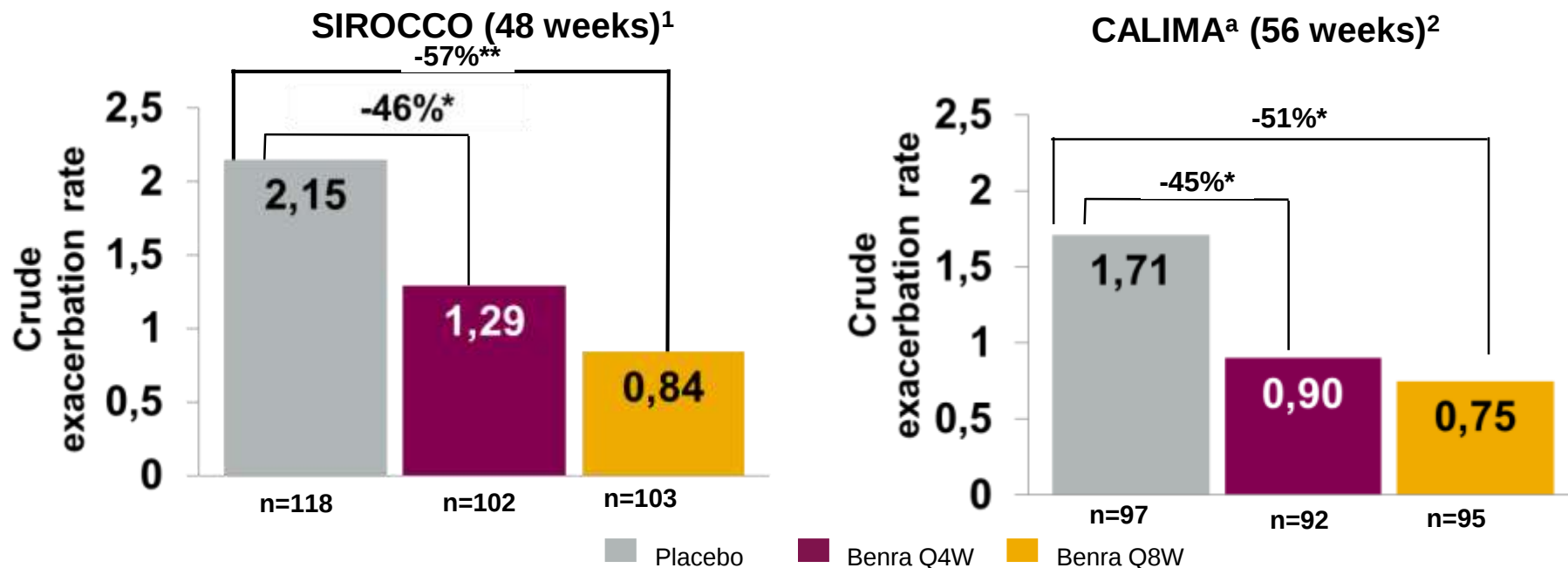
*P<0.05; **P<0.01. ^aData for the CALIMA study is from from high-dosage inhaled corticosteroid cohort.

Analysis via negative binomial adjusting for treatment, region, exacerbations in previous year, OCS (yes/no).

Benra = benralizumab; eos = baseline blood eosinophil count; FEV₁ = forced expiratory volume in one second; LS = least squares; OCS = oral corticosteroids; Q4W = every 4 weeks; Q8W = every 8 weeks.

1. Bleecker ER et al. *Lancet*. 2016; Accessed September 5, 2016; 2. FitzGerald JM et al. *Lancet*. 2016; Accessed September 5, 2016.

SIROCCO and CALIMA: AER in Patients with ≥ 3 Prior Exacerbations (eos $\geq 300/\mu\text{L}$)



- Benralizumab produced a similar magnitude of exacerbation reduction in similar, higher risk patients in both studies

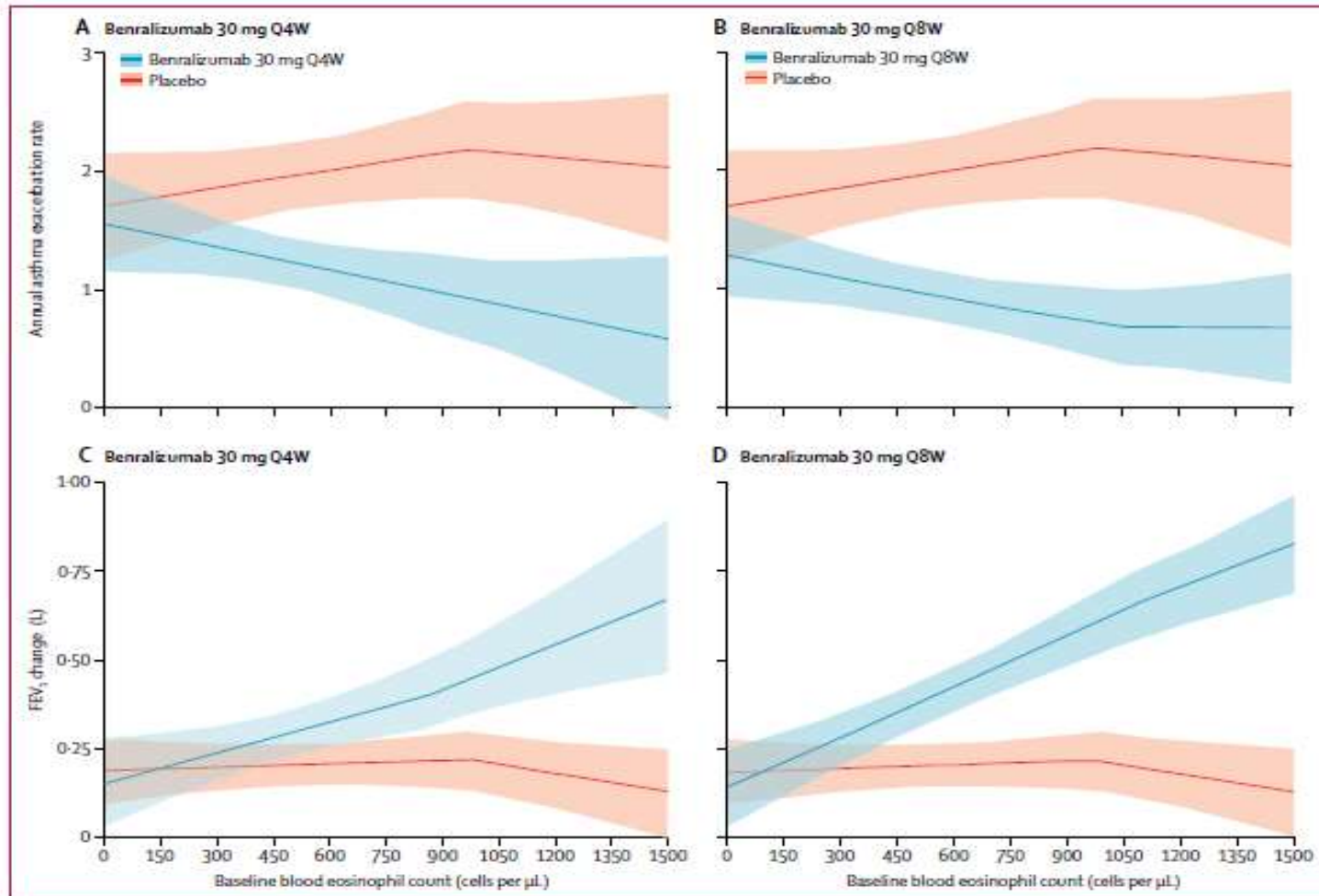
* $P \leq 0.005$; ** $P \leq 0.0005$. ^aData for CALIMA from high-dosage ICS cohort

Statistical analysis model: a negative binomial model including covariates treatment group, region, use of maintenance oral corticosteroids, and number of exacerbations in the previous year.

1. Bleecker ER et al. Supplementary appendix. *Lancet*. 2016; Accessed September 5, 2016; 2. FitzGerald JM et al. Supplementary appendix. *Lancet*. 2016; Accessed September 5, 2016.

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

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

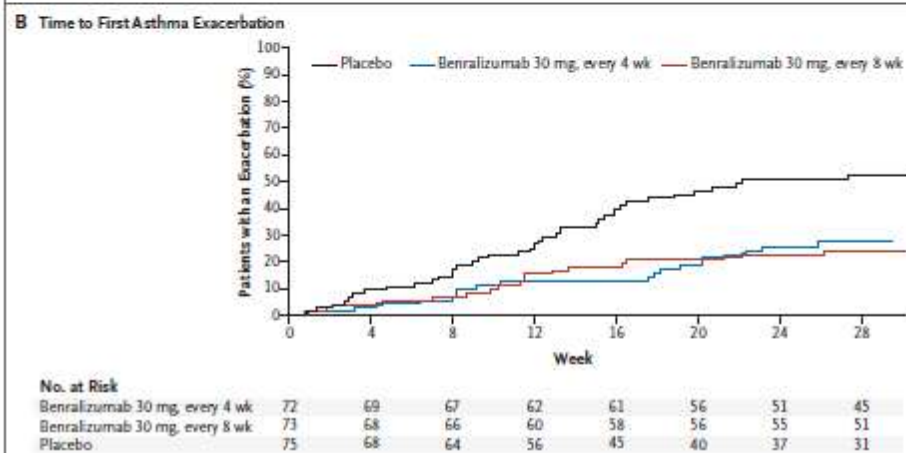
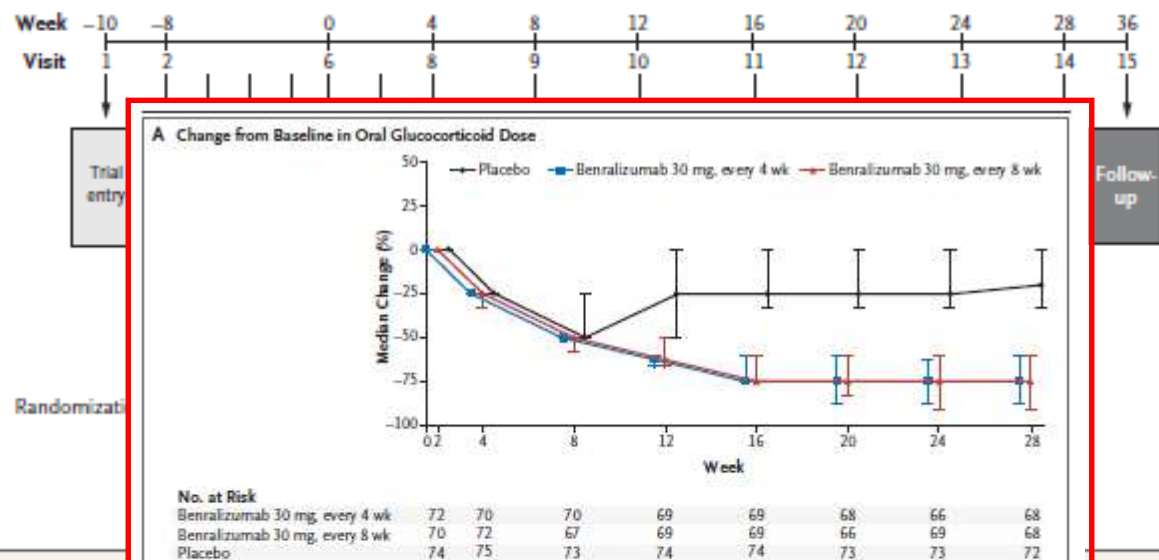


Patients with 3 or more exacerbations/year

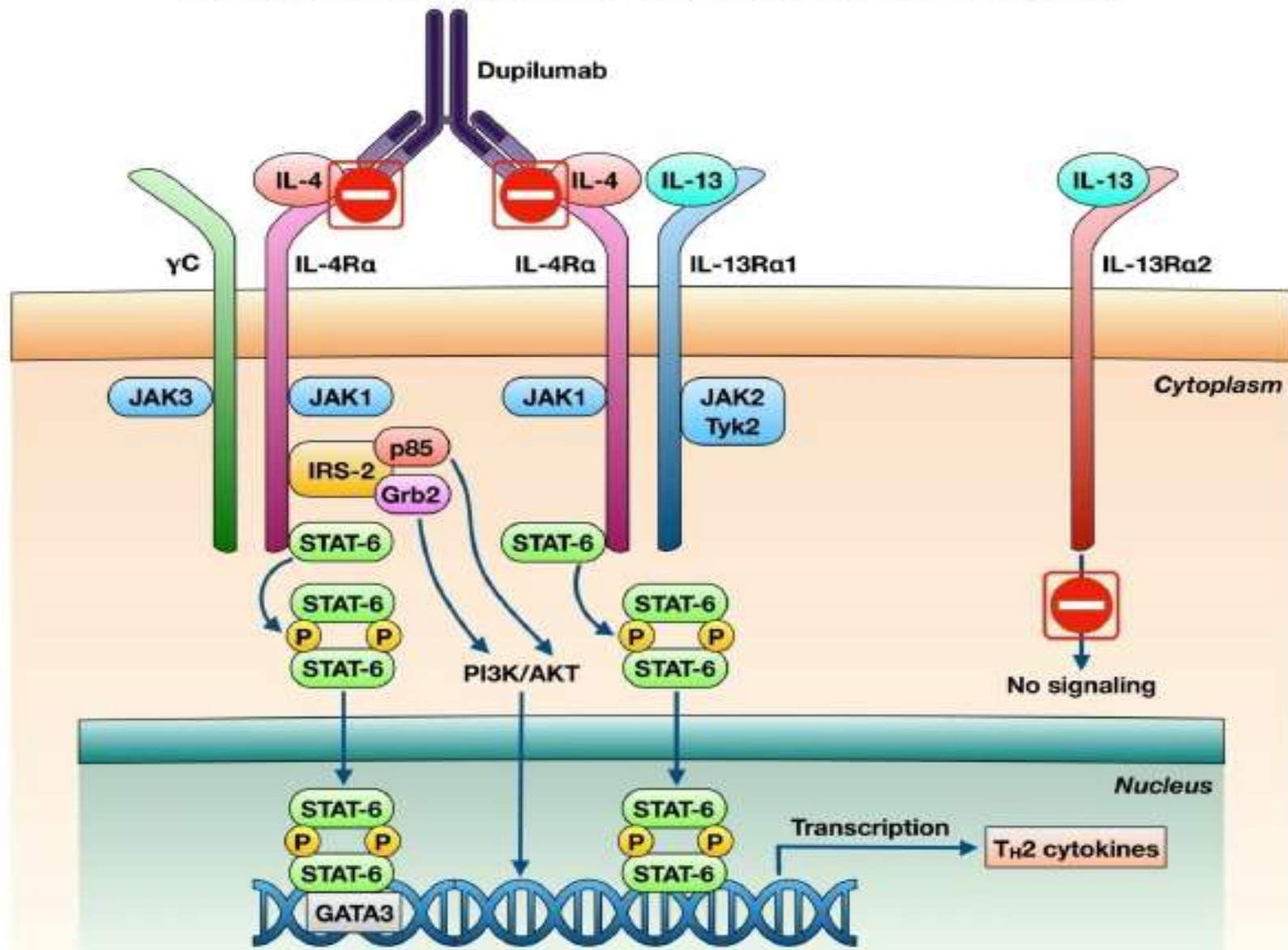
Lancet Respir Med 2017

Oral Glucocorticoid-Sparing Effect of Benralizumab in Severe Asthma

Parameswaran Nair, M.D., Ph.D., Sally Wenzel, M.D., Klaus F. Rabe, M.D., Ph.D., Arnaud Bourdin, M.D., Ph.D., Njira L. Lugogo, M.D., Piotr Kuna, M.D., Ph.D., Peter Barker, Ph.D., Stephanie Sproule, M.Math., Sandhia Ponnarambil, M.D., and Mitchell Goldman, M.D., for the ZONDA Trial Investigators*



DUPILUMAB: mechanism of action



Pelaia C, Vatrella A, Gallelli L, Navalesi P, Maselli R, Pelaia G.
Expert Opin Biol Ther 17;1565-1572, 2017

The NEW ENGLAND JOURNAL of MEDICINE

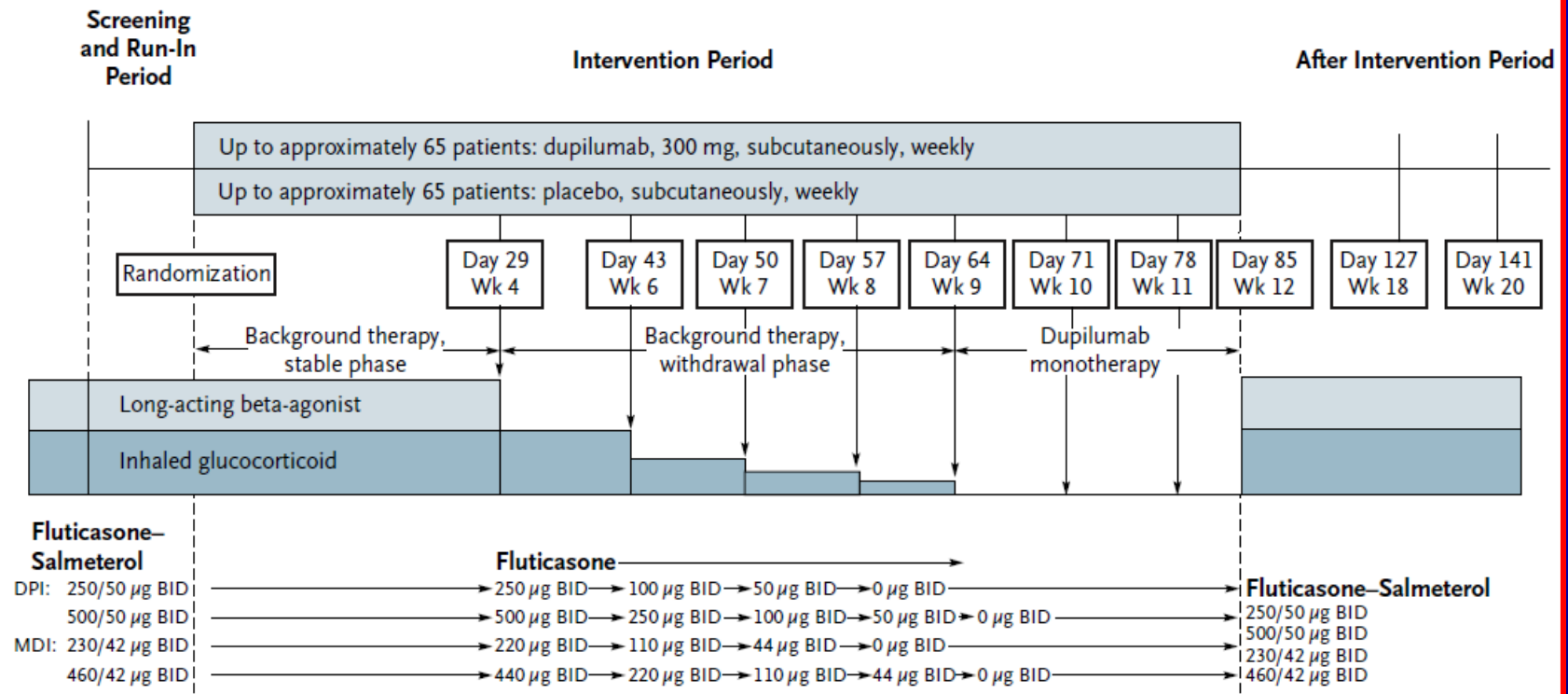
ESTABLISHED IN 1812

JUNE 27, 2013

VOL. 368 NO. 26

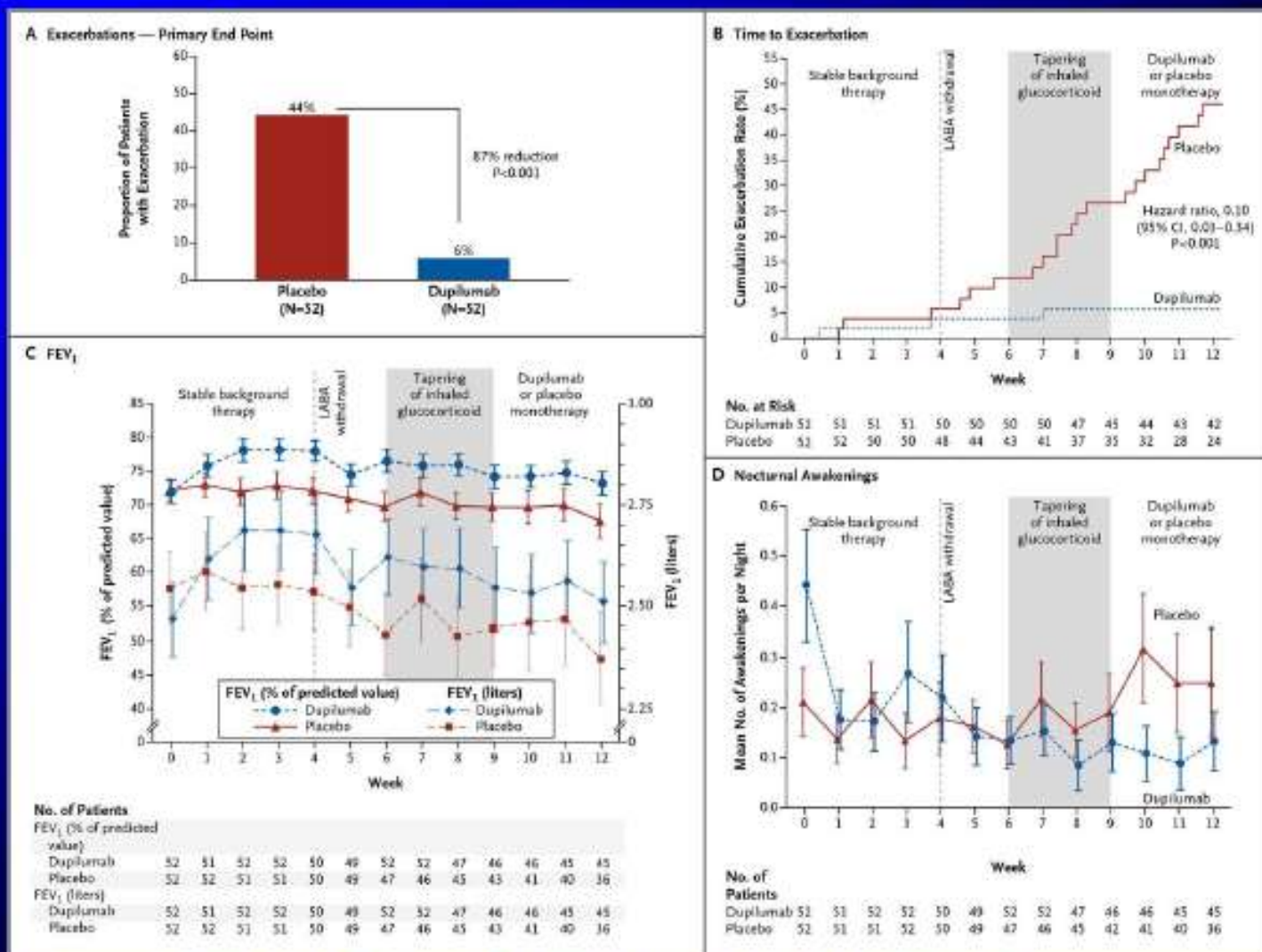
Dupilumab in Persistent Asthma with Elevated Eosinophil Levels

A



104 patients with persistent moderate-to-severe asthma and elevated blood/sputum eosinophilia

DUPILUMAB in persistent asthma with elevated eosinophil levels



Wenzel S et al. *N Engl J Med* 368:2455-2466, 2013



The NEW ENGLAND
JOURNAL of MEDICINE

Dupilumab in uncontrolled asthma: Phase 2b

Wenzel et al. Lancet 2016

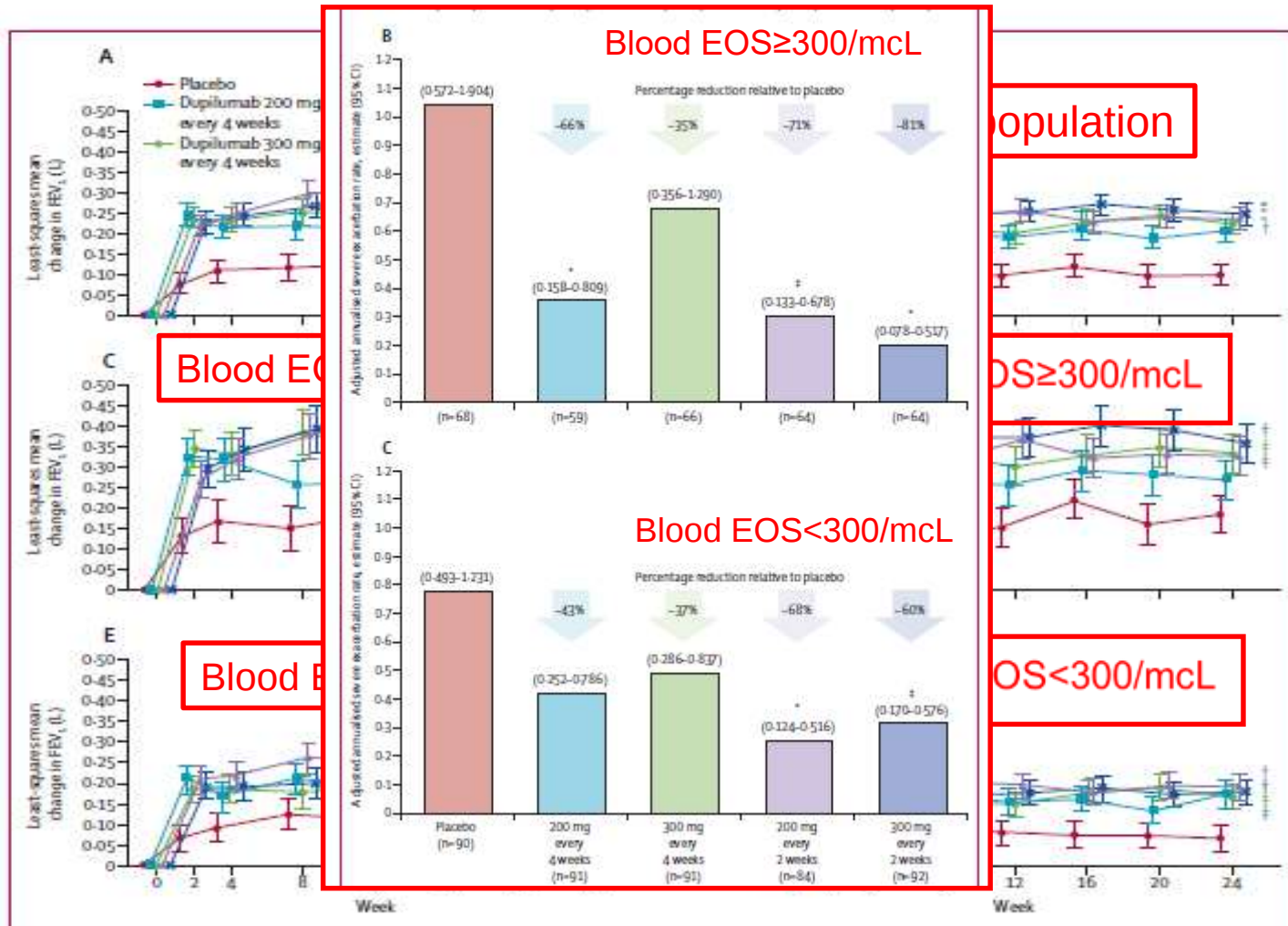


Figure 2: Improvement in FEV₁ in L (A, C, E) and percentage change (B, D, F) from baseline to week 24

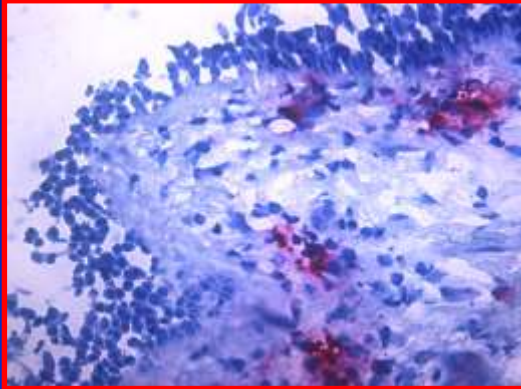
Data are in the overall population (A, B), patients with baseline blood eosinophil counts of at least 300 eosinophils per μ L (C, D), and patients with counts lower than 300 eosinophils per μ L (E, F). FEV₁=forced expiratory volume in 1 s. * $p<0.001$. † $p<0.01$. ‡ $p<0.05$. Error bars indicate SE.

Neutrophilic asthma is a feature of:

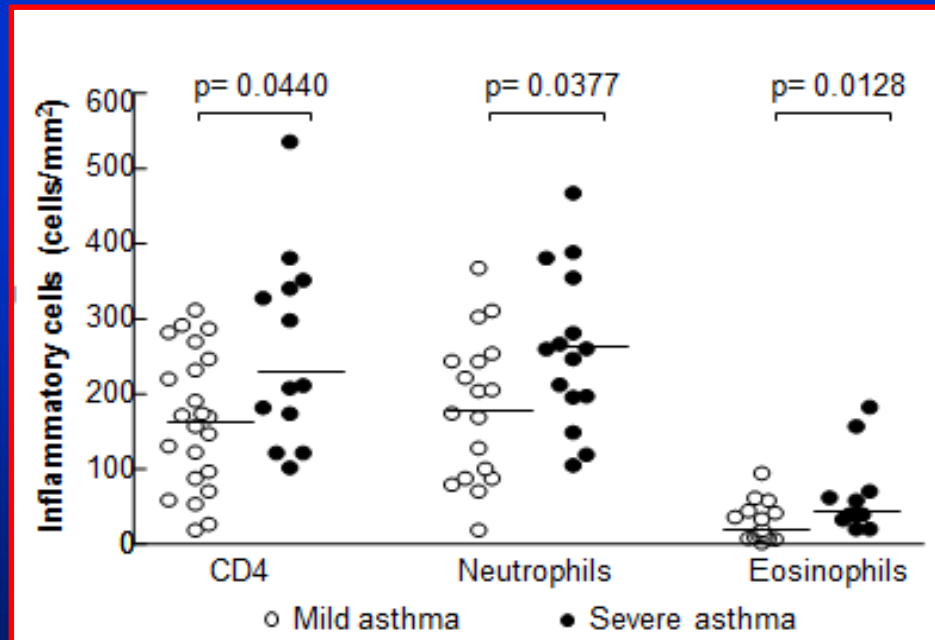
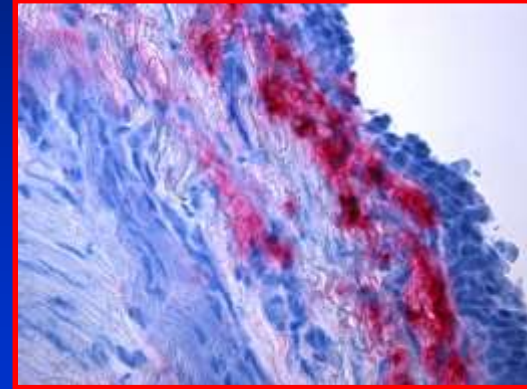
- Intrinsic asthma
- Asthma in the elderly
- Asthma in smokers
- Asthma with GER/Sinusitis
- Asthma exacerbation
- Near-fatal asthma (intubation)
- Sudden onset fatal asthma
- Severe asthma

Biopsies: Neutrophils in Severe Asthma

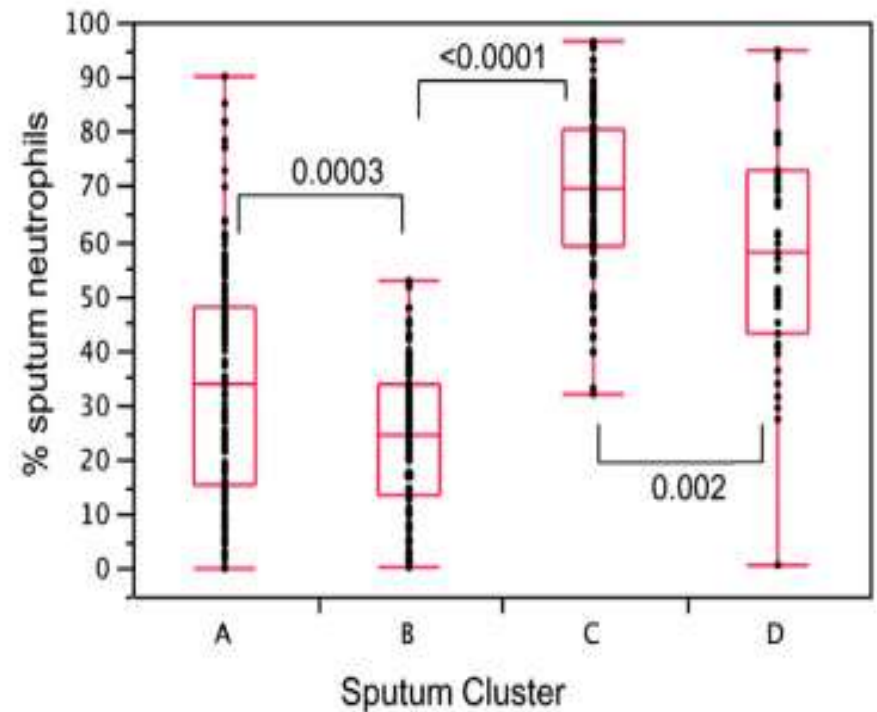
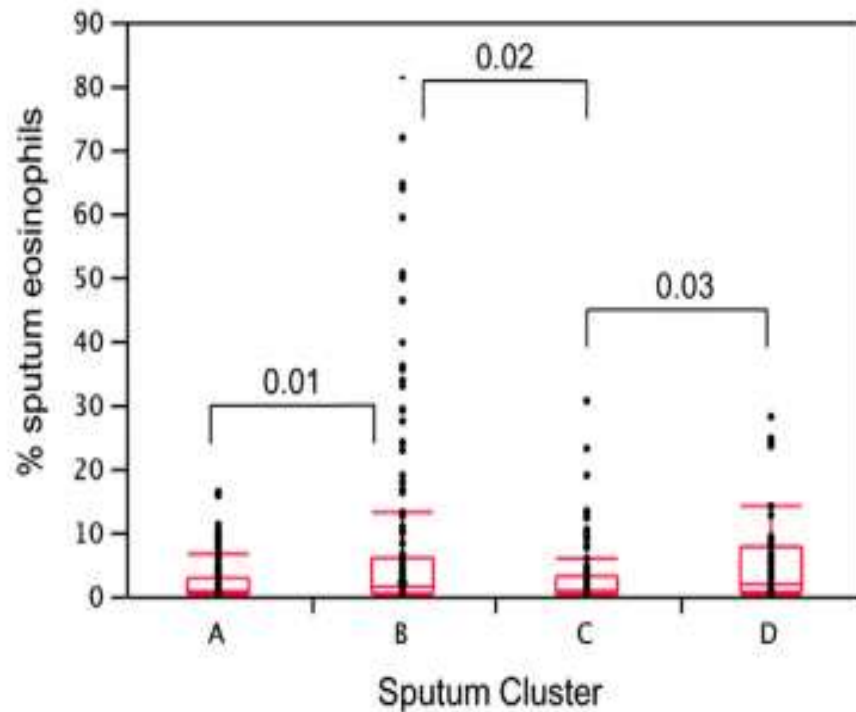
MILD ASTHMA



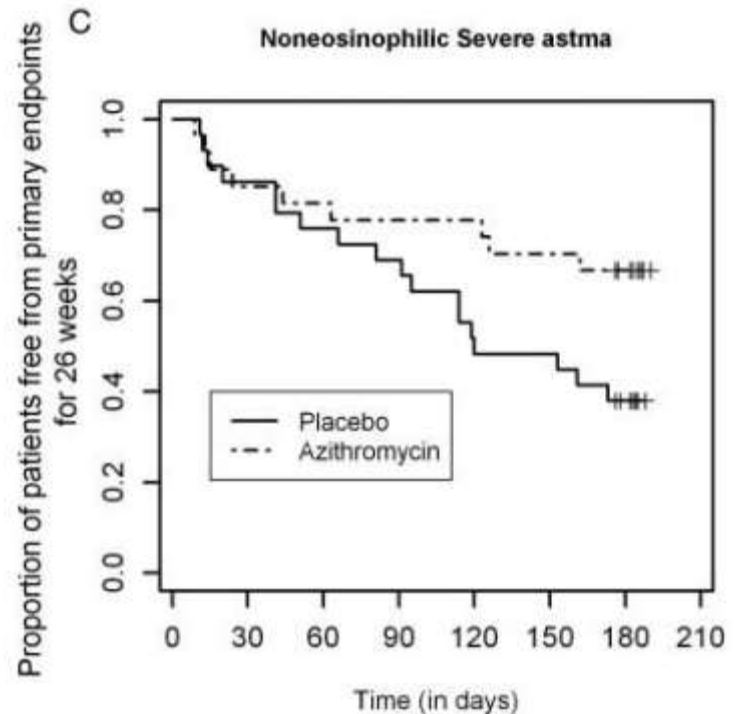
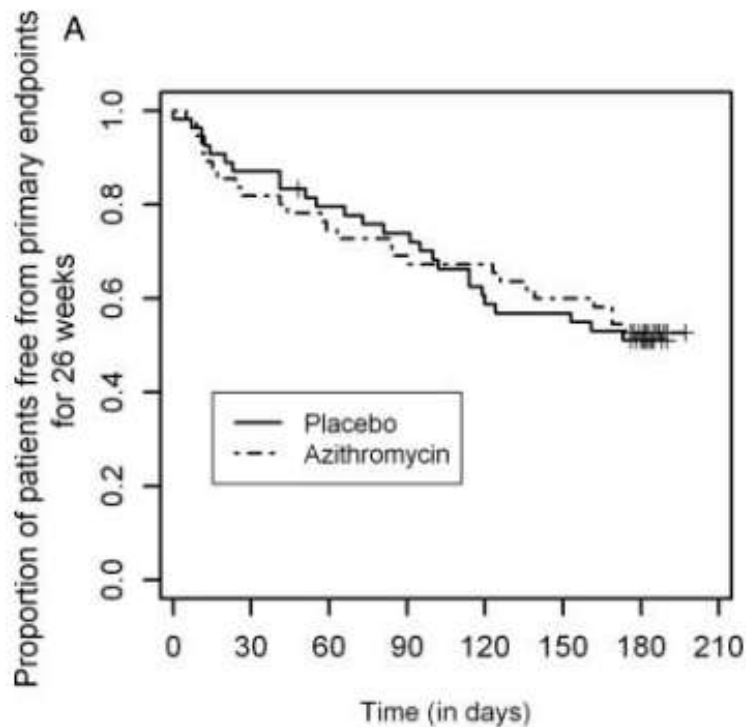
SEVERE ASTHMA



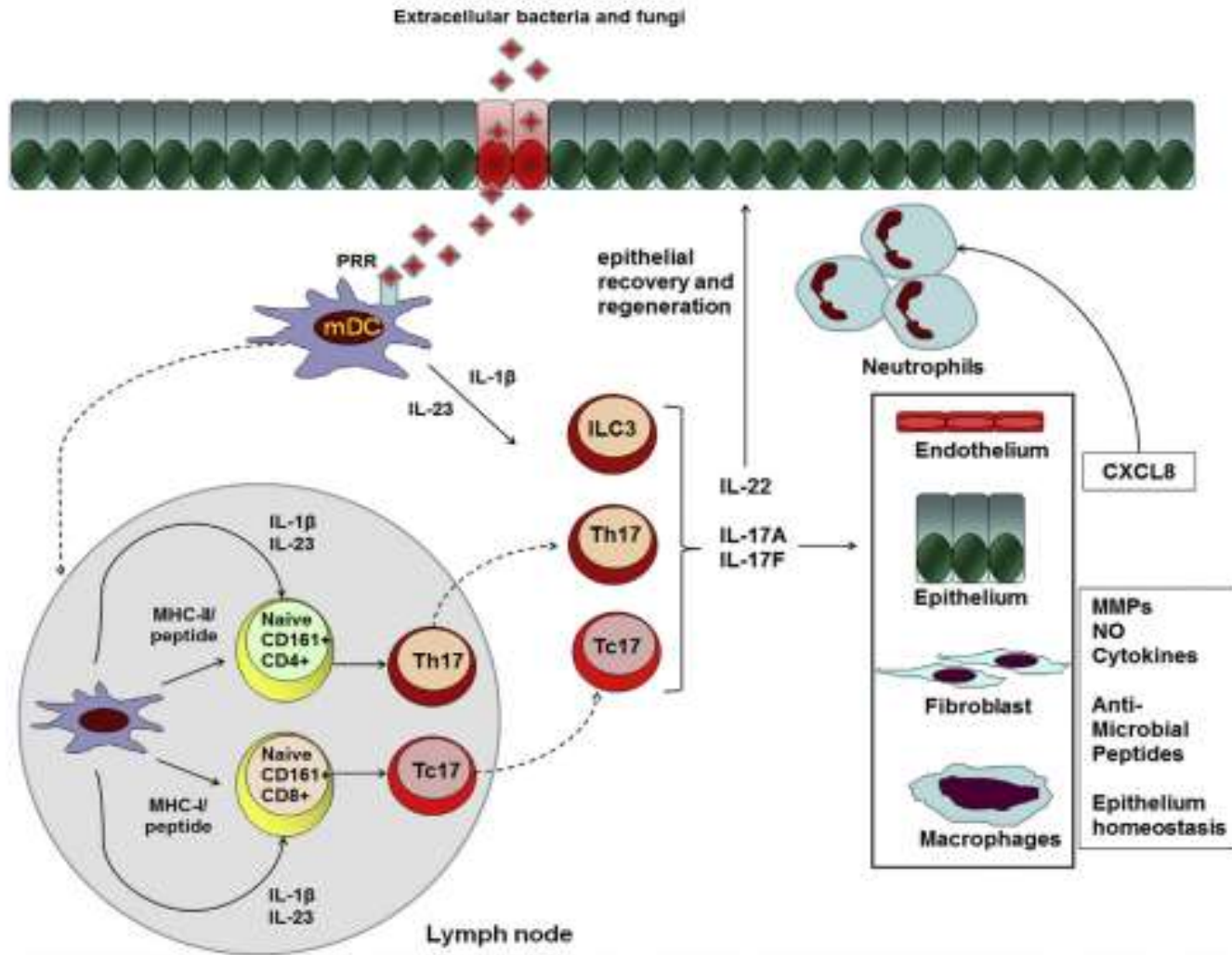
Cluster analysis: neutrophils in severe asthma



AZISAST: Azithromycin and exacerbations in severe asthma



Type 3 immunity

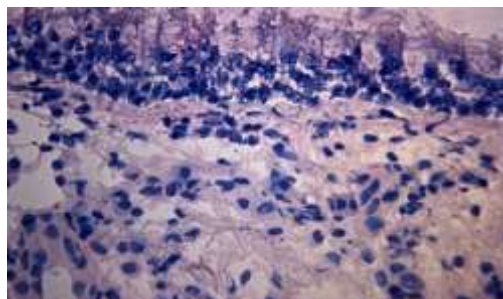


Identification of IL-17F/frequent exacerbator endotype in asthma

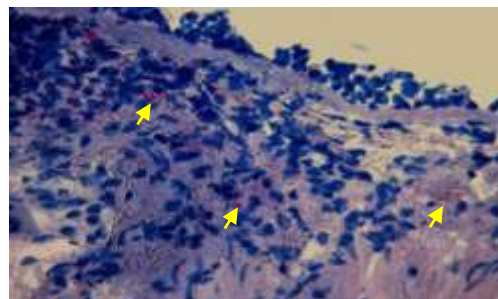


Fabio L. M. Ricciardolo, MD, PhD,^a Valentina Sorbello, PhD,^a Anna Folino, PhD,^a Fabio Gallo, MSc,^b Gian Mario Massaglia, MD,^c Gabriella Favatà, MD,^d Salvatore Conticello, MD,^d Davide Vallese, PhD,^e Federica Gani, MD,^c Mario Malerba, MD,^f Gert Folkerts, PhD,^g Giovanni Rolla, MD,^h Mirella Profita, PhD,ⁱ Thais Mauad, PhD,^j Antonino Di Stefano, PhD,^{k*} and Giorgio Ciprandi, MD^{k*}
Torino, Genova, Novara, Brescia, and Palermo, Italy; Utrecht, The Netherlands; and São Paulo, Brazil

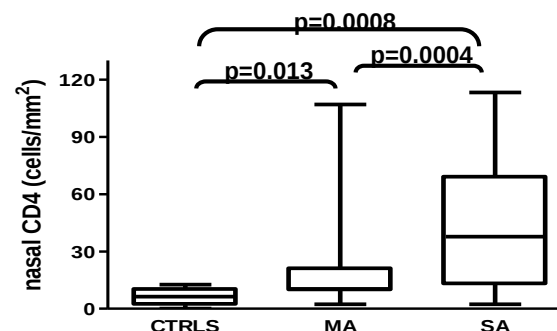
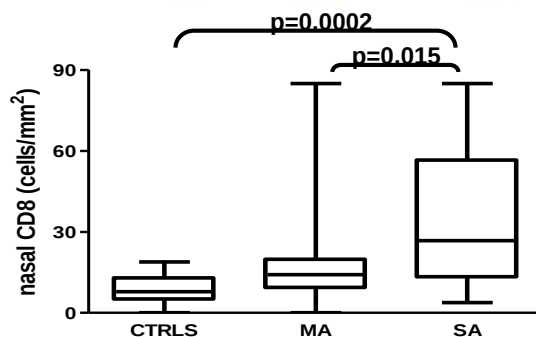
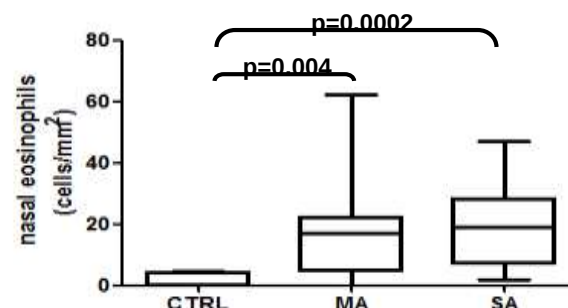
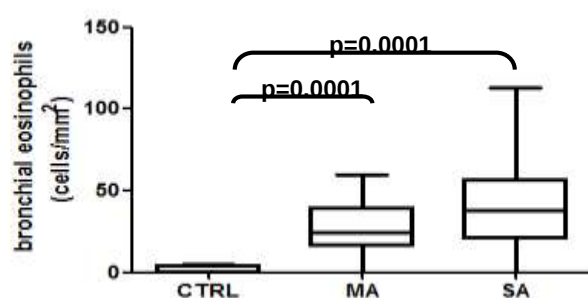
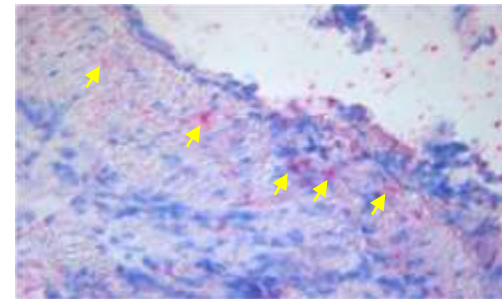
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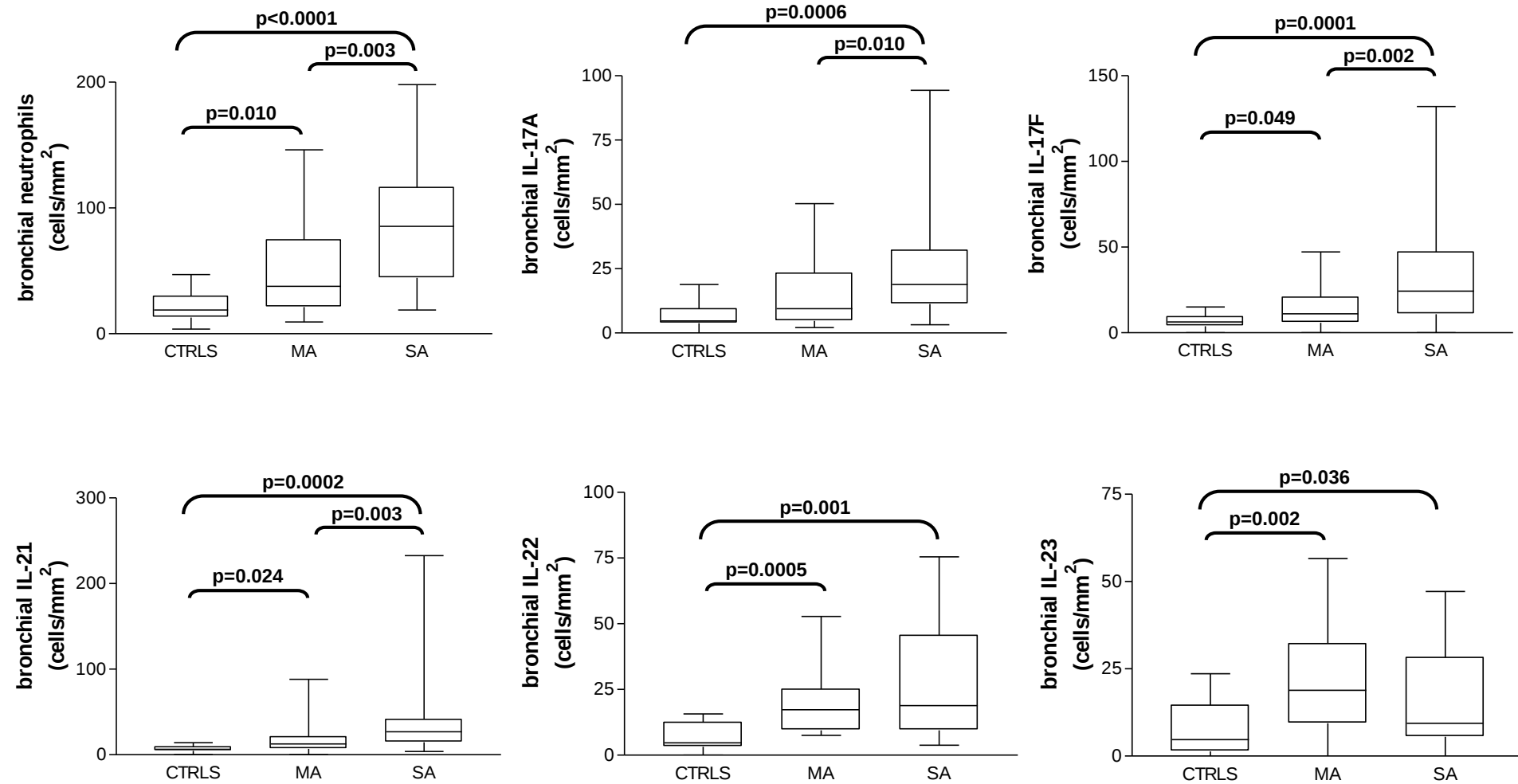
Mild Asthma



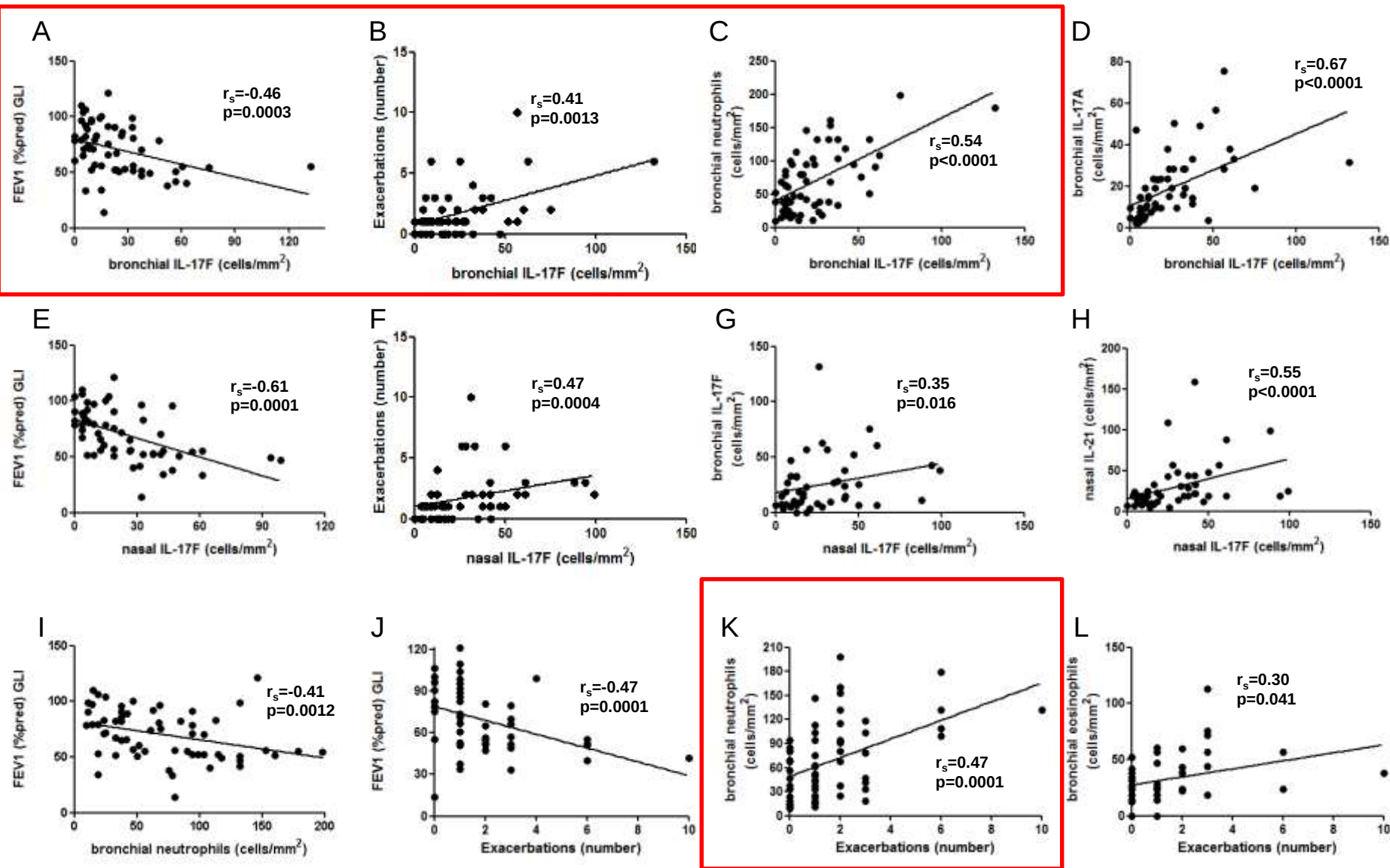
Severe Asthma



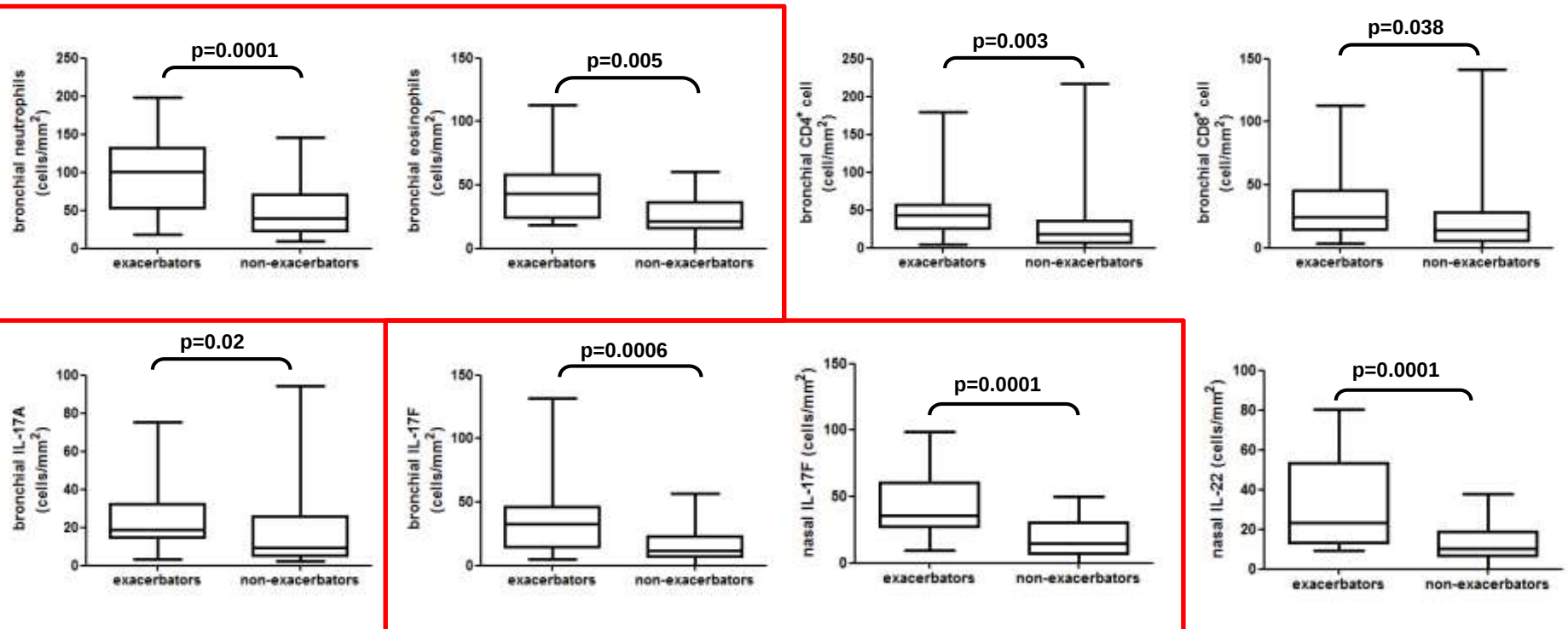
IL-17 related cytokines expression in bronchial mucosa of Severe Asthma



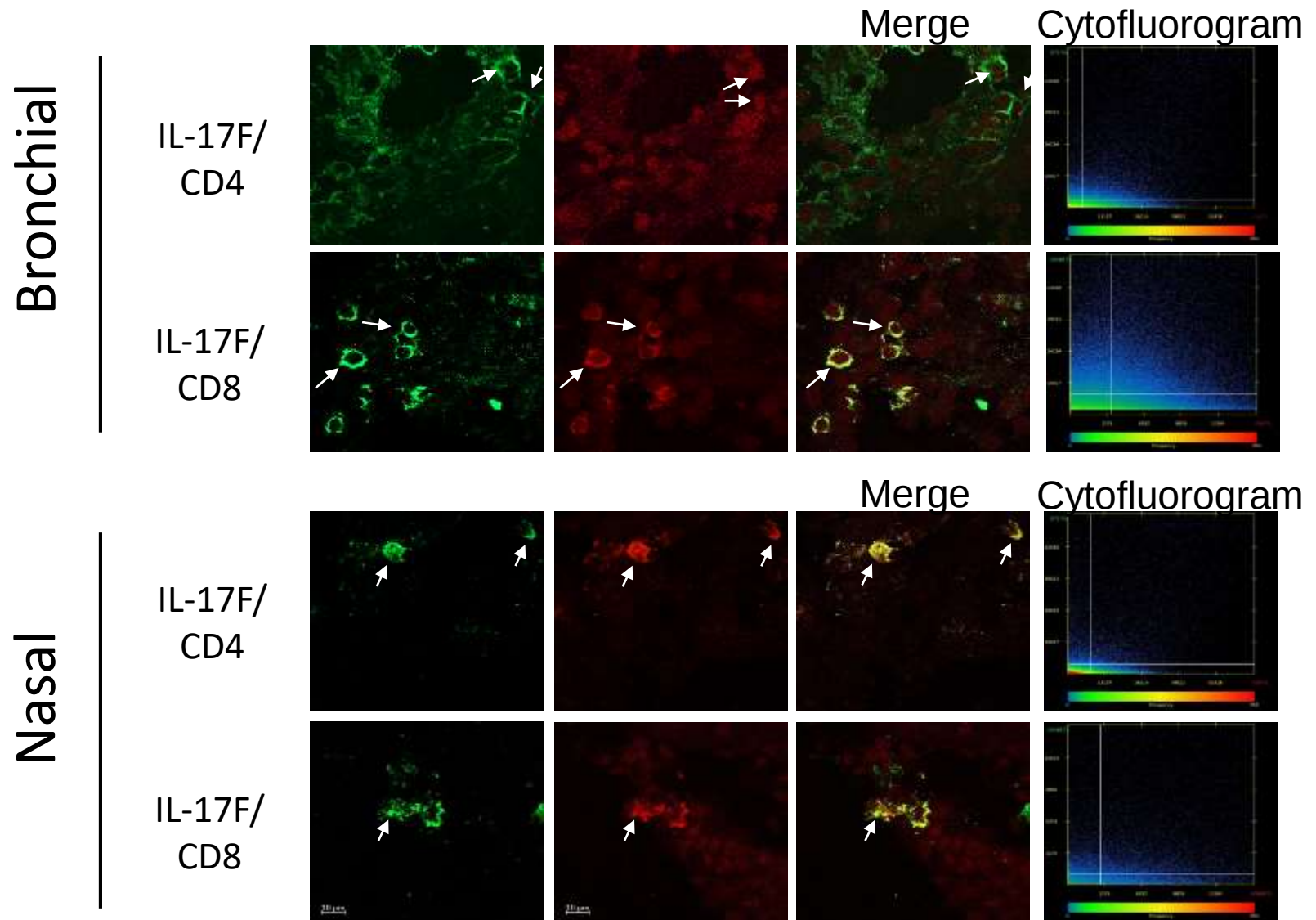
IL-17 related cytokines expression in bronchial mucosa of Severe Asthma



Identification of IL-17F/Frequent Exacerbator endotype in Asthma

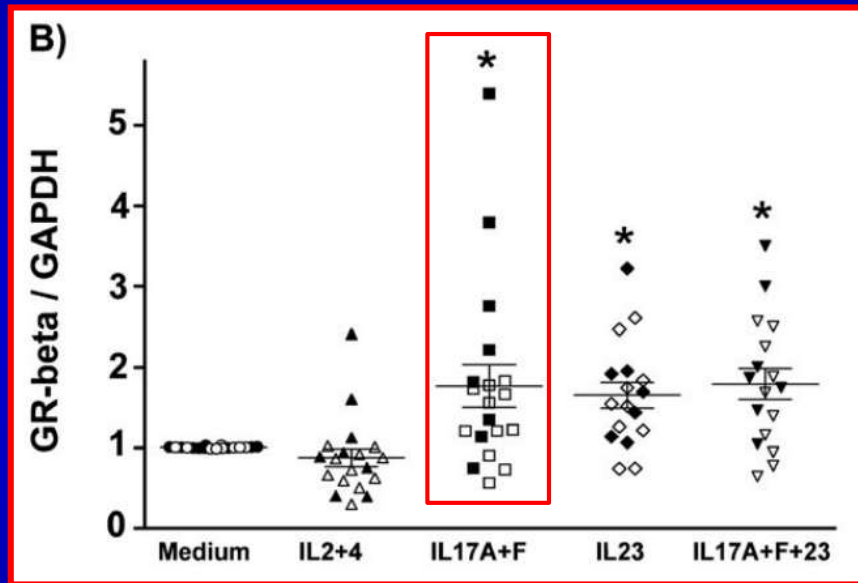


Identification of IL-17F/Frequent Exacerbator endotype in Asthma

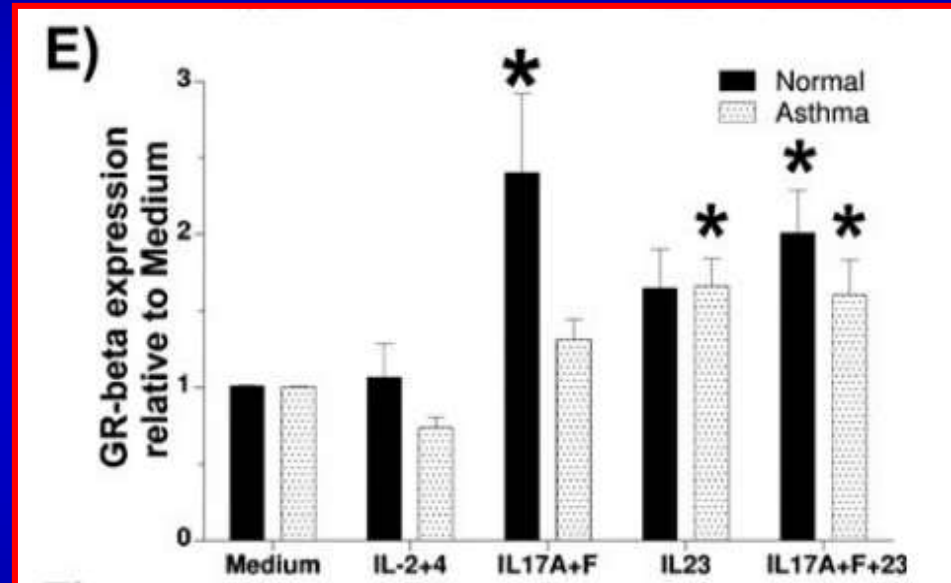


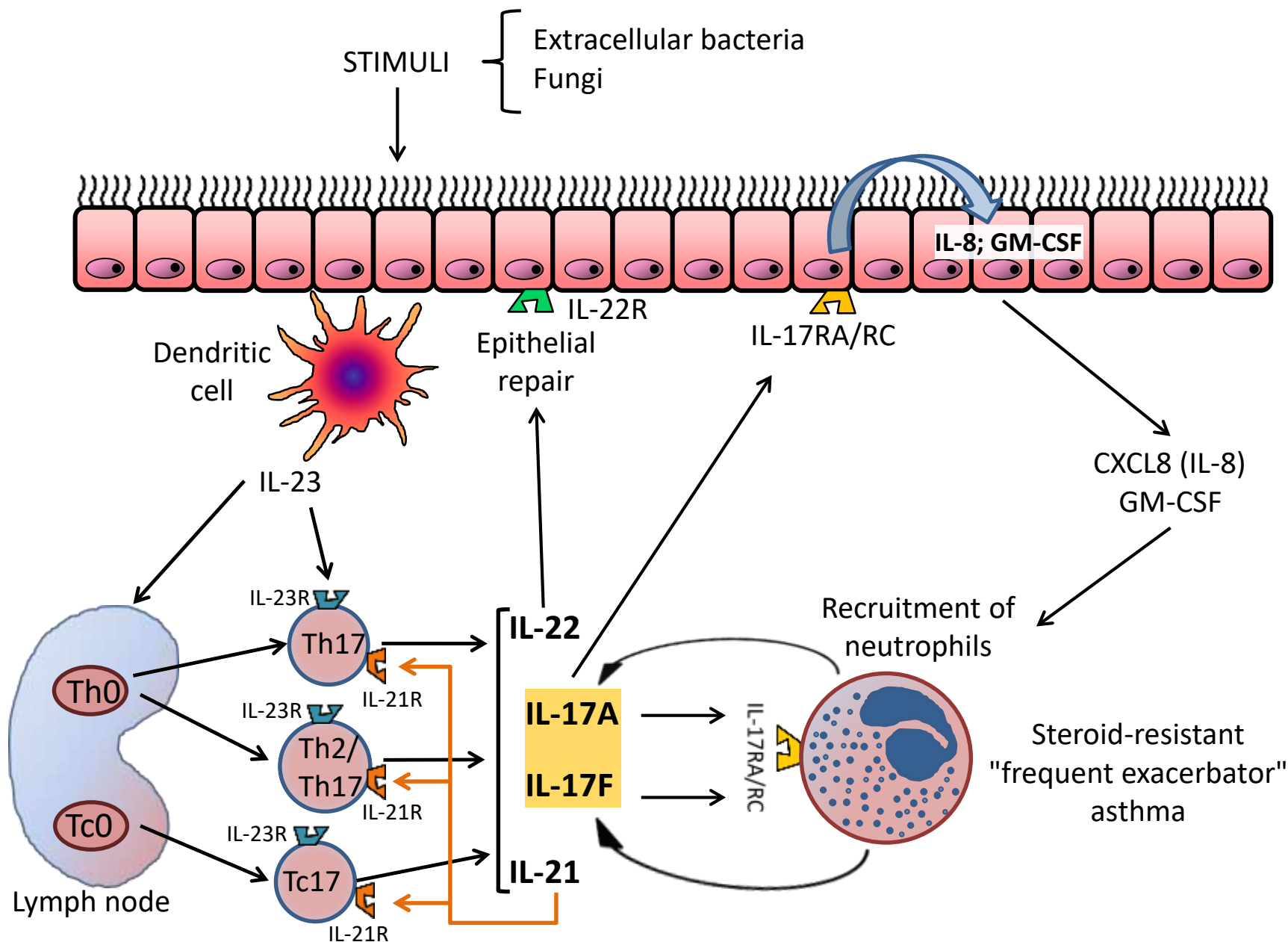
GR-beta up-regulation and steroid resistance induction by IL-17 and IL-23 in PBMC

mRNA



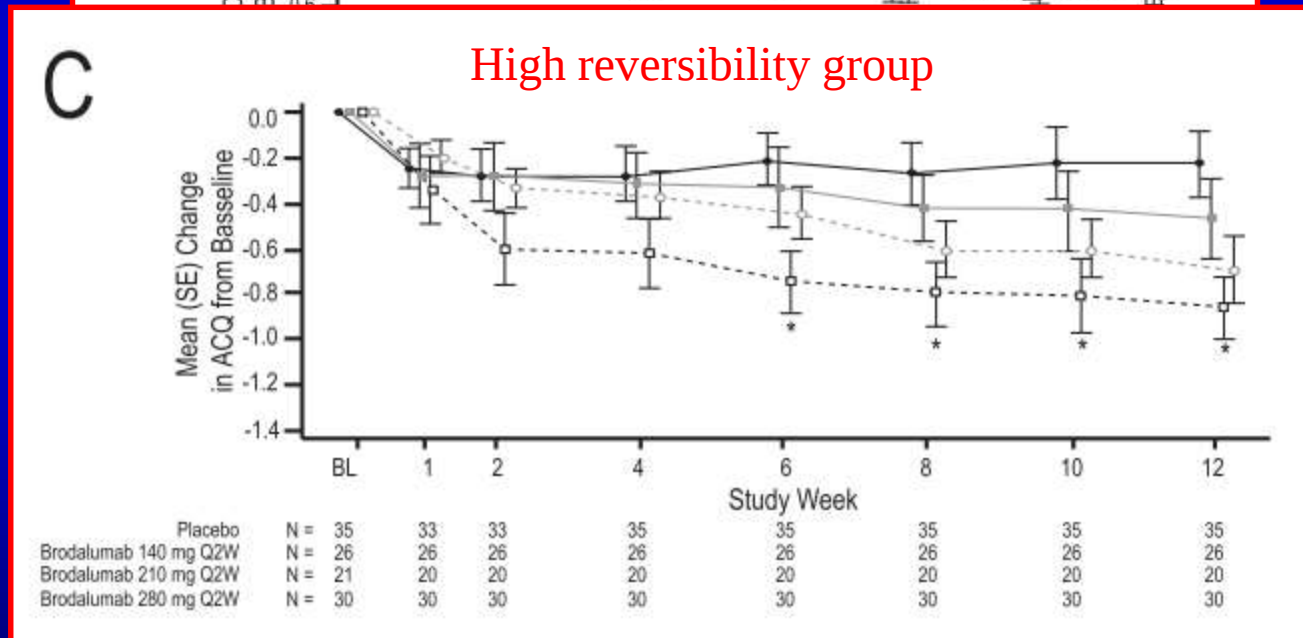
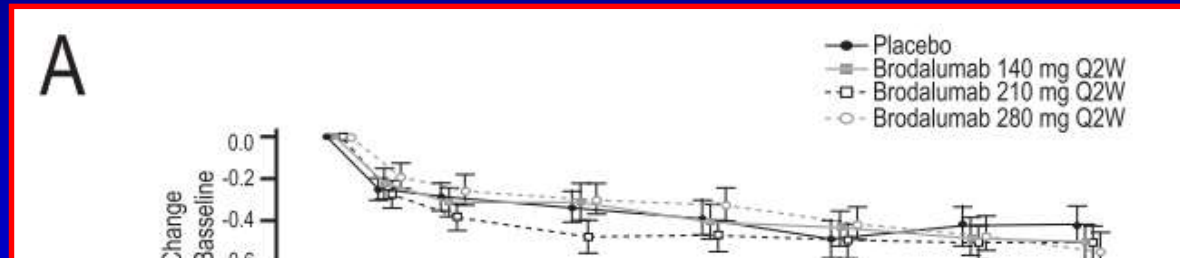
protein





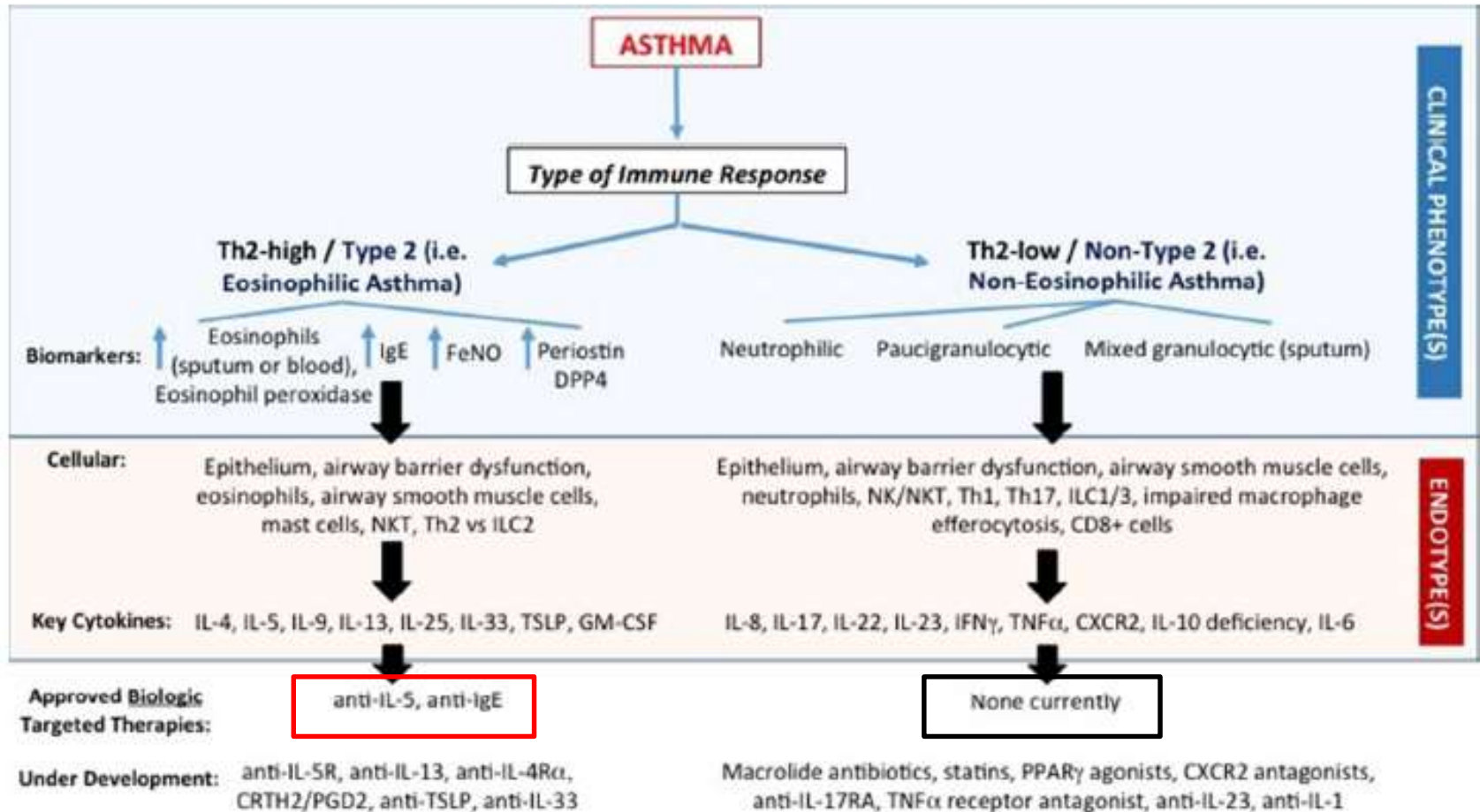
Brodalumab (hAb IL-17RA) in Severe Asthma

Patients=302

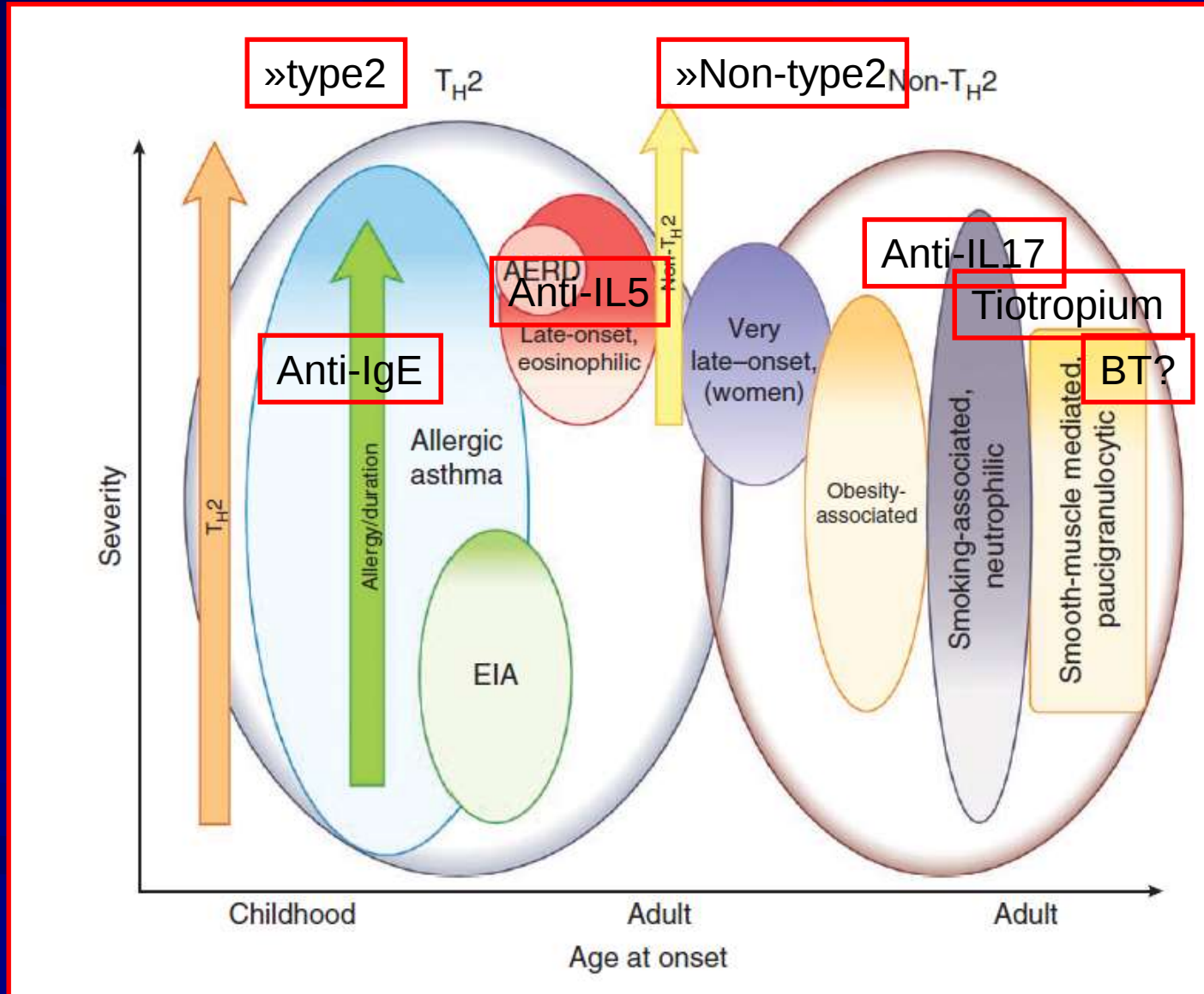


Primary endpoint was ACQ score

Phenotypes/Endotypes and personalized therapy in asthma



Add-on therapy in severe asthma



Anti-eosinophil drugs for asthma

