

## Treatment of Severe Asthma: Biologics to Bronchial Thermoplasty

Monica Kraft, M.D.

Robert and Irene Flinn Professor of Medicine  
Chair, Department of Medicine  
Deputy Director, Asthma and Airway Disease  
Research Center  
University of Arizona Health Sciences Center  
Tucson, Arizona

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## Disclosures

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NIH, Roche, Sanofi, Chiesi

Consulting: TEVA, Astra-Zeneca,  
Regeneron (all < \$5000)

Royalties: Elsevier

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HPI: 38 year old female with severe persistent asthma on chronic oral steroid therapy p/w increasing SOB and worsening wheezing.

### Asthma history

Diagnosed with asthma at age 13

30-40 hospitalizations for asthma throughout her life

Endotracheal intubation X 1 for status asthmaticus

Chronic steroid dependence since 2003

Has been treated for contributing diseases

- GERD, Allergic rhinitis (h/o nasal polyps)

### Current status:

- Daily symptoms of shortness and wheezing, limited activity
- Use of rescue inhalers 6-8x/day
- Adherent with her medical regimen

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**Past Medical History:**

1. Severe Persistent Asthma
2. Allergic rhinitis
3. GERD
4. Fibromyalgia
5. Major Depressive Disorder

**Allergies:**

ASA- causes rash and wheezing

**Medications:**

1. Methylprednisolone 32 mg daily
2. Fluticasone/Salmeterol 500/50 mcg inhalation b.i.d.
3. Montelukast 10 mg daily
4. DuoNeb as needed
5. Albuterol INH 3-4 times daily
6. Omeprazole 20 mg twice daily
7. Loratadine 10 mg daily
8. Fluticasone Nasal 1 puff twice daily
9. Calcium/Vitamin D
10. Alendronate 70 mg weekly
11. Omalizumab 300 mg q 2 weeks

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**Social History:** Married with 3 children and husband, 2 dogs, outside cats, office work with no exposures, non-smoker.

**Family History:**

mother with asthma and atopic dermatitis

**Physical Exam:**

Pulmonary- prolonged expiration with moderate air movement and diffuse expiratory wheezing.

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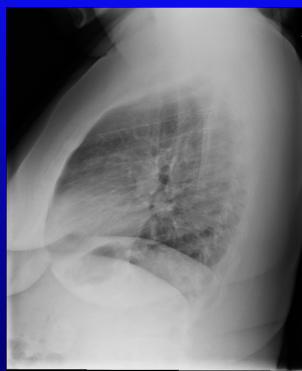
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Pulmonary Function Testing:

	Ref	Best	% Pred
FVC	3.05	2.40	78%
FEV1	2.65	1.27	48%
FEV1/FVC	86	53	
FEF 25-75%	3.28	0.58	18%
PEF	5.78	2.89	50%
MVV	109	45	41%

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Additional biomarkers

FeNO: 25 ppb  
Peripheral eosinophils: 250

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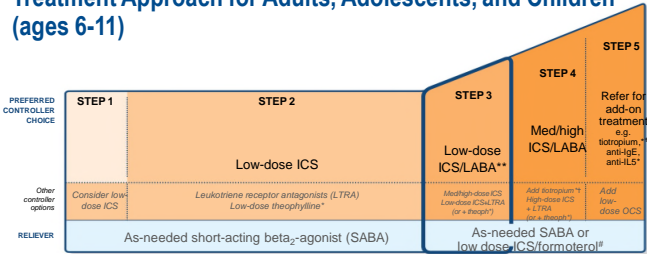
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The GINA Report Has A More Updated Treatment Approach for Adults, Adolescents, and Children (ages 6-11)



\*Not for children <12 years  
\*\*For children 6-11 years, the preferred Step 3 treatment is medium dose ICS  
††For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy  
† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

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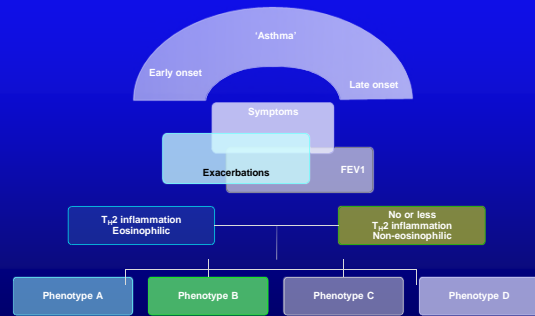
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## What is Asthma?



Wenzel S. Nature Medicine 18, 716-725 (2012)

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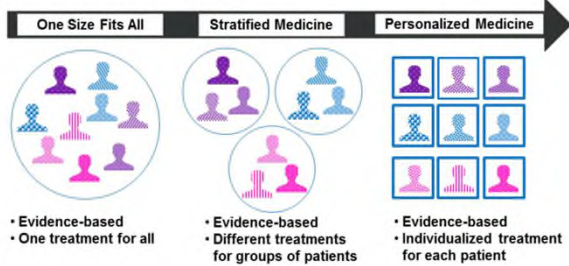
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## Understanding Disease Mechanisms May Guide Therapy to a More Personalized Approach



Willis JC, Lord GM. Nat Rev Immunol 2015;15(5):323-329.

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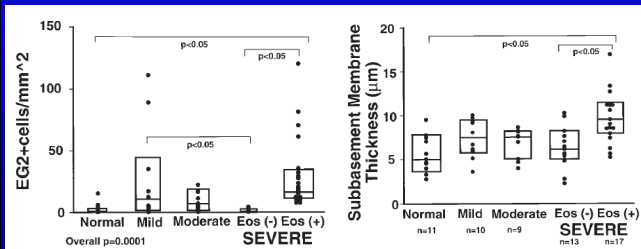
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## Asthma Inflammatory Phenotypes: Early Investigation



Wenzel et al. AJRCCM 1999; 160:1001

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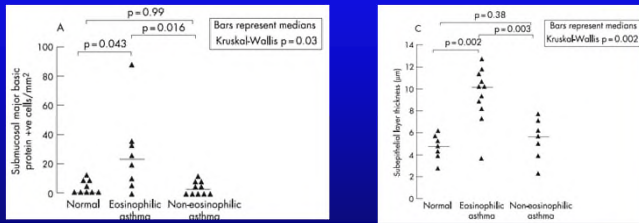
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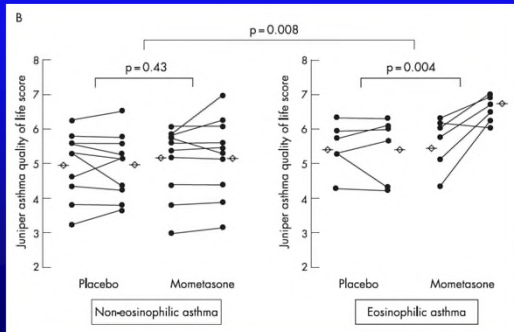
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## A pathologic comparison of eosinophilic and non-eosinophilic asthma



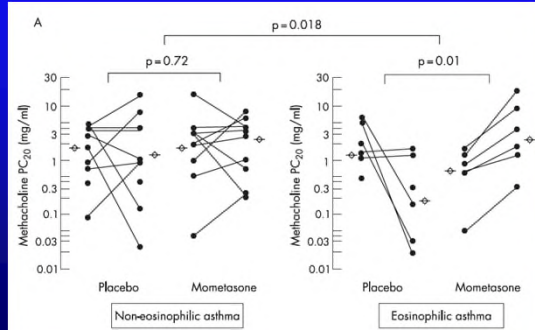
Berry et al. Thorax 2007;62:1043

## Quality of Life after Inhaled Corticosteroids (Berry et al.)



Berry et al. Thorax 2007;62:1043

## Airways Hyperresponsiveness After Inhaled Corticosteroids (Berry et al.)



Berry et al. Thorax 2007;62:1043

## Asthma Phenotypes

- **Phenotype:** observable properties of an organism that are produced by the interactions of the genotype and the environment
- Asthma phenotypes are based on clinical characteristics, triggers or general inflammatory processes have been proposed and do not always suggest an underlying mechanism
- **Endotype:** a specific biological pathway is identified that explains the observable properties of a phenotype

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## Th2/T2 asthma

- **T2/Th2-associated asthma linked to:**
  - atopy and allergy
    - type I hypersensitivity reactions
    - eosinophilic inflammation and response to corticosteroids
- **Early-onset (preadolescence) mostly atopic and allergic asthma phenotype**
  - Strong family history of atopic disease
  - Overlap with other co-morbid atopic conditions: allergic rhinitis and atopic dermatitis
  - Early-onset allergic asthma can present with mild to severe disease; unclear whether mild allergic asthma progresses to severe disease or whether severe allergic asthma arises in childhood and remains severe
  - Can be exacerbated by obesity

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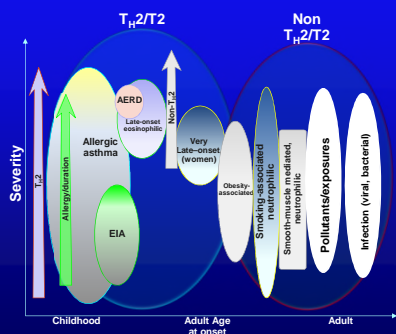
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## Overview of Asthma Phenotypes



Adapted from Wenzel S. Nature Medicine 18, 716–725 (2012)

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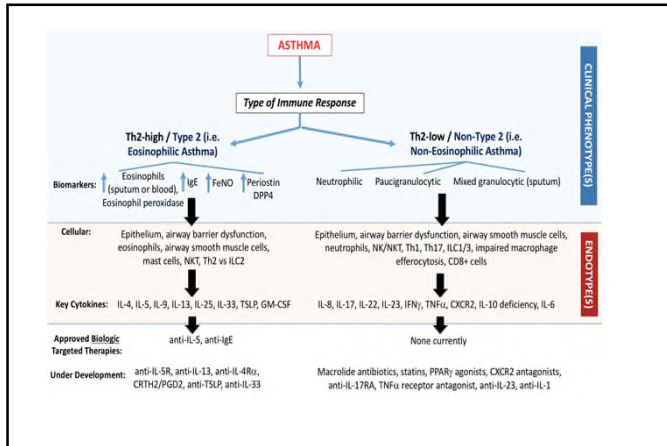
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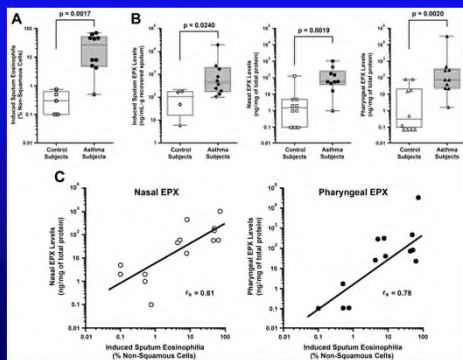
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## Biomarkers to identify the Th2 phenotype

- Sputum eosinophils
- Exhaled nitric oxide
- Circulating eosinophils
- Periostin - ? Future
- DPP4
- IgE
- Allergen skin testing
- Eosinophil Peroxidase?

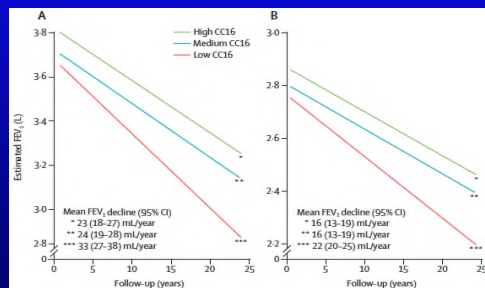
## EPX is increased in eosinophilic asthma and correlates with sputum eosinophils



## CC16

- Club (formerly Clara) cell secretory protein
- Pneumoprotein: produced mainly by non-ciliated airway epithelial cells (including club cells)
- Possible protective effects from noxious exposures and against obstructive lung diseases (asthma and COPD)
- Serum levels substantially reduced in smokers
- Cross-sectional associations with asthma and COPD
- Currently being investigated in longitudinal studies

## CC16 levels in childhood and lung function decline



Guerra et al. Lancet Resp Med 2015

## Airway epithelial CC16 gene expression and asthma outcomes

Table 1	
Association Test (BEC CC16 mRNA levels)	P-value (n=107)
Healthy Control vs Asthma	0.0388
Mild vs Moderate vs Severe Asthma	0.0263
Healthy Control vs Mild vs Moderate vs Severe Asthma	0.0060

Table 2	
Association Test (BEC CC16 mRNA levels)	P-value (n=107)
Baseline FEV <sub>1</sub> (% predicted)	0.0097
Baseline FVC (% predicted)	0.196
Baseline FEV <sub>1</sub> /FVC	0.0006
Maximal FEV <sub>1</sub> (% predicted)	0.0361
Maximal change in FEV <sub>1</sub> (reversibility)	0.0228

Table 3	
Association Test (BEC CC16 mRNA levels)	P-value (n=107)
ER/urgent care visit for asthma in last year	no (n=61) yes (n=43) 0.0499
Oral or injected corticosteroid use	no (n=82) yes (n=22) 0.0042

Kraft, Ledford, Li  
Bleeker & SARP  
ATS 2018



## What Are Treatment Options for the T2/Eosinophilic Phenotype Beyond Combination Therapy?

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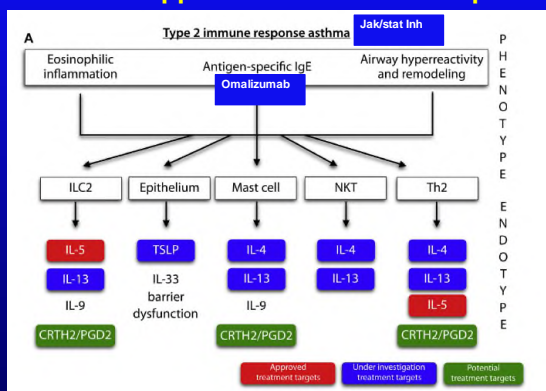
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### Treatments approved or under development



Muraro et al. JACI 2016 137, 1347-1358

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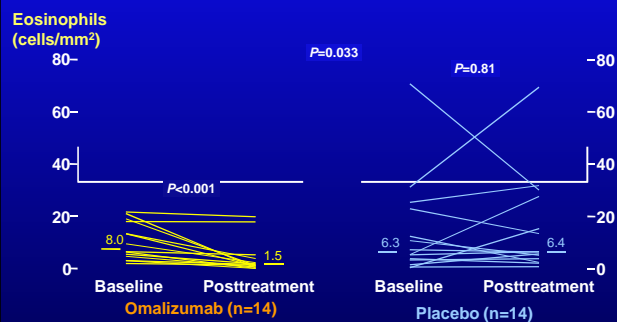
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## Omalizumab Significantly Reduces Submucosal Eosinophils



Djukanovic et al. AJRCCM 2004

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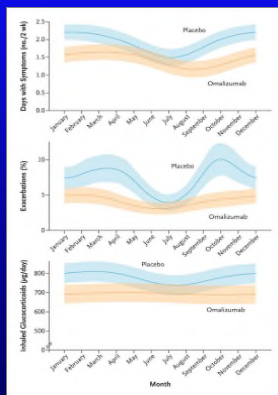
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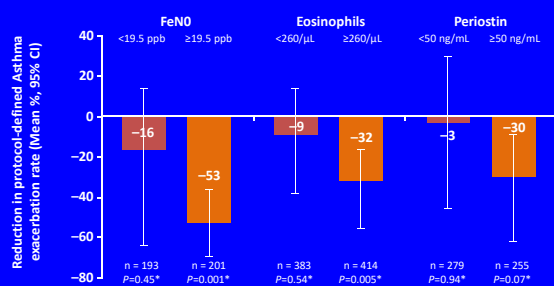
### Seasonal Variation in Days with Symptoms, Frequency of Exacerbations, and Dose of Inhaled Glucocorticoids.



Jussie WW et al. N Engl J Med 2011; 364:1005-1015

### How Does Omalizumab Compare With New Biologics In Similar Patients?

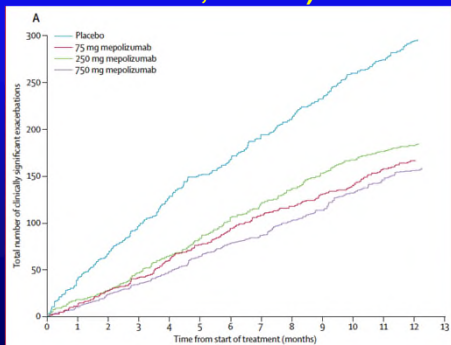
#### Effect of omalizumab based on Th2 biomarkers



\*Exacerbation reduction P-values; omalizumab versus placebo in each biomarker subgroup.  
Hanania NA et al. Am J Respir Crit Care Med. 2013;187:804-811.

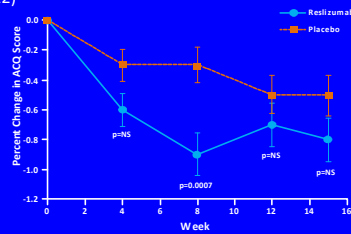
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### Mepolizumab (anti-IL-5) in Severe, Eosinophilic Asthma (Pavord et al. Lancet 2012;380:651)



## Reslizumab for Poorly Controlled Eosinophilic Asthma

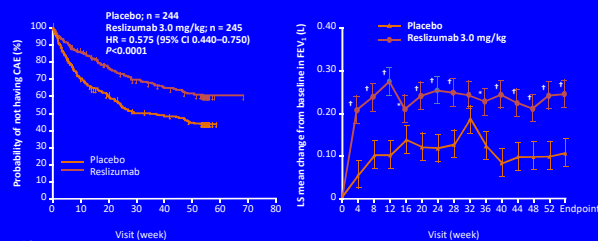
- 106 patients randomized to reslizumab 3 mg/kg vs. placebo (IV dosing at weeks 0, 4, 8, and 12)
- Sputum eosinophil count reduced by 95.4% in reslizumab group vs. 38.7% in placebo group ( $P=0.0068$ )
- Mean change in FEV1 was  $-0.08$  in the placebo group versus  $+0.18$  in reslizumab group ( $P=0.0023$ )
- Exacerbations reduced ( $P=0.08$ )
- Greater change from baseline in patients with nasal polyps  $-1.0$  vs.  $-0.1$  with placebo ( $P=0.012$ )



Castro M et al. *Am J Respir Crit Care Med*. 2011;184:1125-1132.

81

## Reslizumab—Effects on Exacerbations and Lung Function



No. at risk  
 Placebo 244 169 138 112 107 97 0 0 0  
 Reslizumab 245 207 177 158 146 136 1 0 0

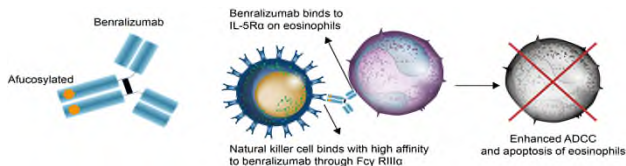
HR = hazard ratio; CI = confidence interval; LS = least square (mean).

Castro M et al. *Lancet Respir Med*. 2015;3:355-366.

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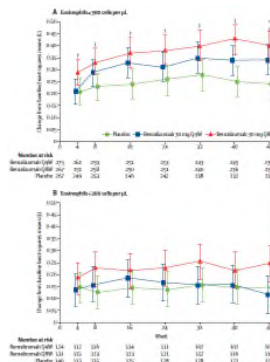
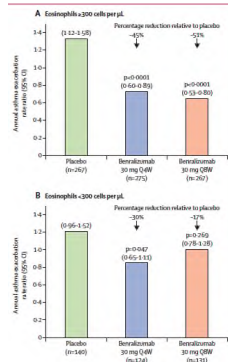
## Benralizumab (anti-IL-5R $\alpha$ )

Benralizumab is a humanised, afucosylated monoclonal antibody (IgG1k) that binds with high affinity to IL-5R $\alpha$  and efficiently depletes eosinophils by inducing apoptosis through ADCC



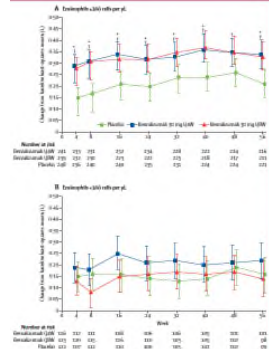
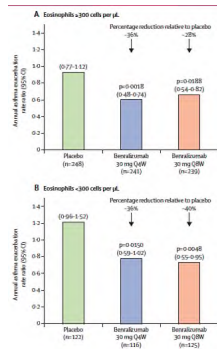
## Benralizumab Phase III (Sirocco)

Bleecker et al. Lancet 2016;388:2115-2127

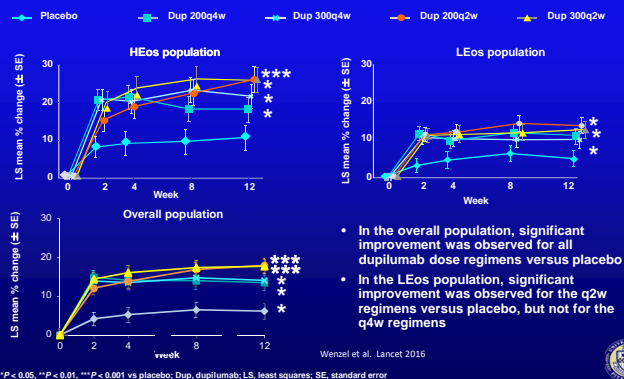


## Benralizumab Phase III (CALIMA)

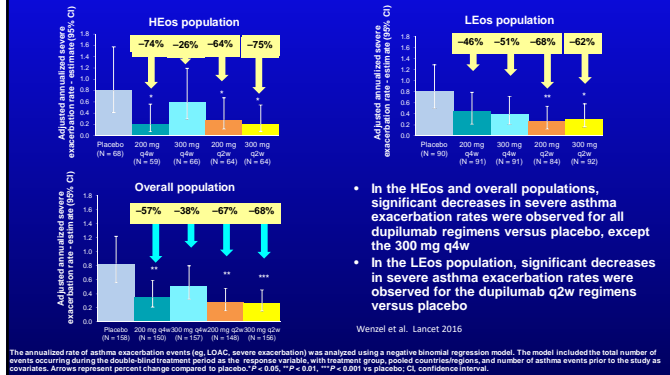
Fitzgerald et al. Lancet 2016;388:2128-2141



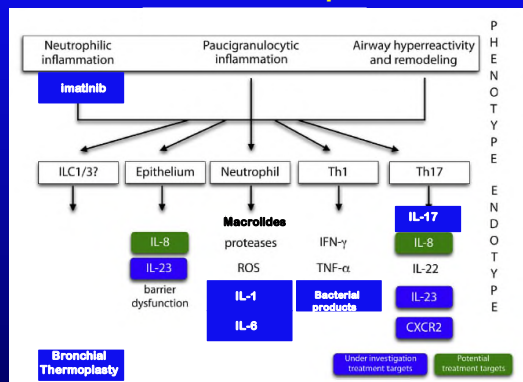
## Lung Function: % Change in FEV<sub>1</sub>



## Adjusted Annual Severe Exacerbation Event Rate



## Treatments under development – Non T2

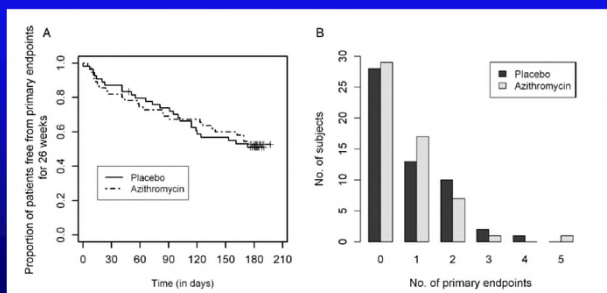


Adapted from Muraro et al. JACI 2016 137, 1347-1358

## Asthma Phenotypes and Macrolides

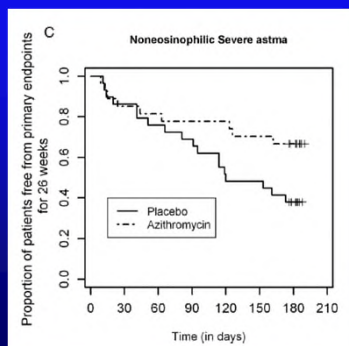
- Brusselle et al. recruited 109 subjects with asthma, on combination therapy (Thorax 2013;177:148)
- Subjects were “exacerbation prone” as they were required to have had two exacerbations requiring oral corticosteroids or LRTI requiring antibiotics in the previous 12 months
- Azithromycin vs. placebo added to combination therapy for 6 months in a double-blind fashion
- Primary outcome was the rate of exacerbations and LRTI requiring antibiotics

## Asthma Phenotypes and Macrolides- Results in the Entire Cohort



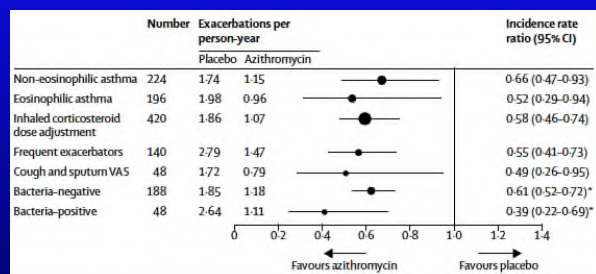
Brusselle et al. Thorax 2013;177:148

## Results in Nonoesinophilic Asthma Only (defined as blood eos < 200/ $\mu$ l)



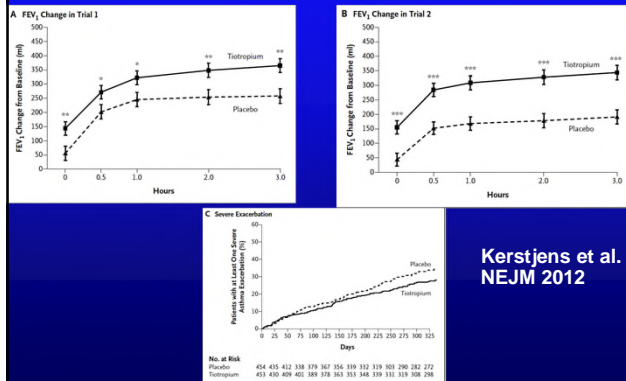
Brusselle et al. Thorax 2013;177:148

## Phenotype agonistic: Macrolides?



Gibson PG et al. Lancet 2017; 390:659-668

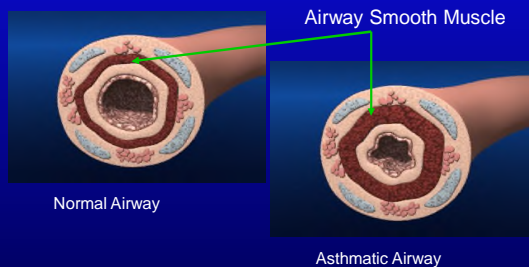
## Tiotropium in Severe Asthma



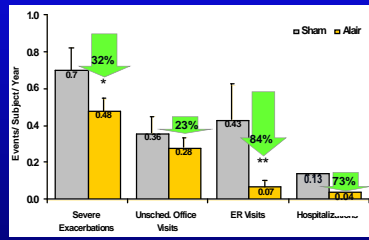
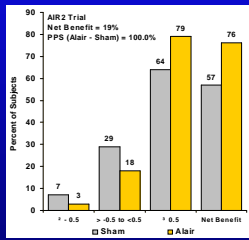
## Predictors of Response to Tiotropium (JACI 2013;132:1068 )

- Bronchodilator response to albuterol
- Reduced FEV<sub>1</sub>/FVC ratio
- Higher cholinergic tone (lower resting HR)
- **What did not predict response:**
- Ethnicity, gender, atopy, IgE, sputum eos, FeNO, BMI, asthma duration

## Airway Smooth Muscle

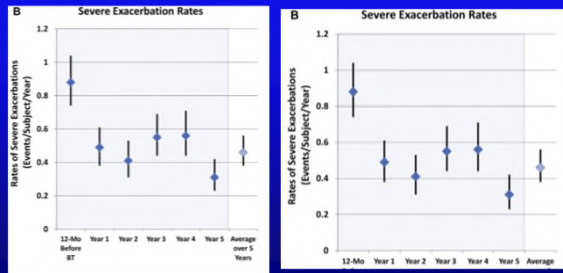


# Bronchial Thermoplasty



Castro M et al. Am J Respir Crit Care Med. 2010;181(2):116-24

## Five Year Safety Data – AIR2 Study



Wechsler M et al. J All Clin Immunol 2013;132:1295

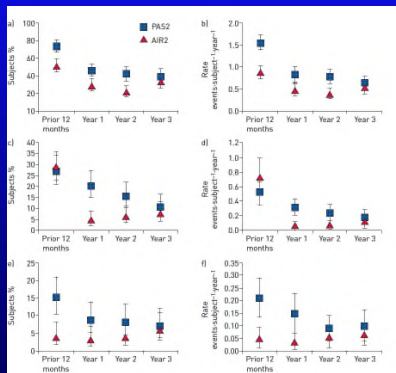
## Comparison of two BT trials – AIR2 and PAS2

Exacerbations  
# subj & rate

Emergency Dept  
# subjects & rate

Hospitalizations  
# subjects & rate

Chupp et al ERJ 2017;  
50: 1700017





## New Concept: How Can Early Immune Development Lead to Protection from Asthma?

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## Bacterial Extracts

- Bacterial extracts (OM-85BV) are extracts of bacteria such as *H. influenzae*, *D. pneumoniae*, *K. ozaenae*, *K. pneumoniae*, *S. aureus*, *S. pyogenes*, *S. viridans*, and *N. catarrhalis*
- It is a mixture of acidic proteins, peptides and amino acids, with minor components of detoxified LPS and lipoteichoic acids

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## Clinical Use of Bacterial Extracts

- Bacterial extracts have been widely used in Europe for the last 2-3 decades in children and adults as oral medicines to reduce the frequency and duration of upper respiratory infections.
- They have also been used in the prevention of acute symptoms in cystic fibrosis and chronic obstructive pulmonary disease (COPD).

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## Studies with OM85-BV in Asthma

- OM85-BV reduced the frequency and duration of wheezing episodes in children with asthma. (Razi et al. J Allergy and Clinical Immunology 2010)
- The overall incidence of adverse effects in clinical trials was between 3 and 4%. Gastrointestinal troubles and respiratory disorders were the most frequent complaints reported.
- OM85-BV was also studied in an animal model of asthma and found to be protective through the development of an important type of cell in the lungs that stops inflammation, the T regulatory cell.

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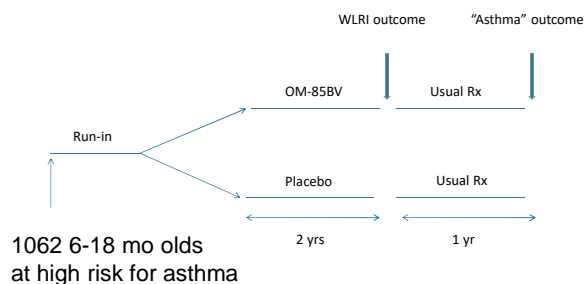
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## ORBEX Trial Schemata



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## Our Approach to Asthma is Changing

- Our understanding of the biology of asthma heterogeneity has improved dramatically.
- The use of clinical characteristics, biomarkers and response to treatment will further hone our ability to deliver personalized/precision therapy.
- We need readily available point-of-care biomarkers to make real time decisions regarding therapies for our patients.

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