ABCs of Immune Modifiers

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Relevant Disclosures

- Research Investigator Funds to University employer
  - Genentech
  - MedImmune/Astra Zeneca
- Legal opinion
  - Asthma death
  - Latex allergy
  - Corticosteroid allergy
  - Metal allergy
- Consultant
  - Novartis
  - Genentech
  - Astra Zeneca
  - Boehringer Ingelheim
- Speaker
  - Astra Zeneca
  - Genentech
  - Meda
  - Merck
  - TEVA

Objectives

- Review the therapeutic potential of biologics or monoclonal antibodies and immune modifiers in asthma and allergic disease
- Discuss strategies to optimize treatment with monoclonal antibodies and immune modifiers
- Discuss patient-specific features that can influence monoclonal antibodies efficacy
  - Biology and Biomarkers

The Mother of All Biologic Modifiers

The Mother of All Biologic Modifiers

CORTICOSTEROIDS

Small Molecule Biololgic Modifiers

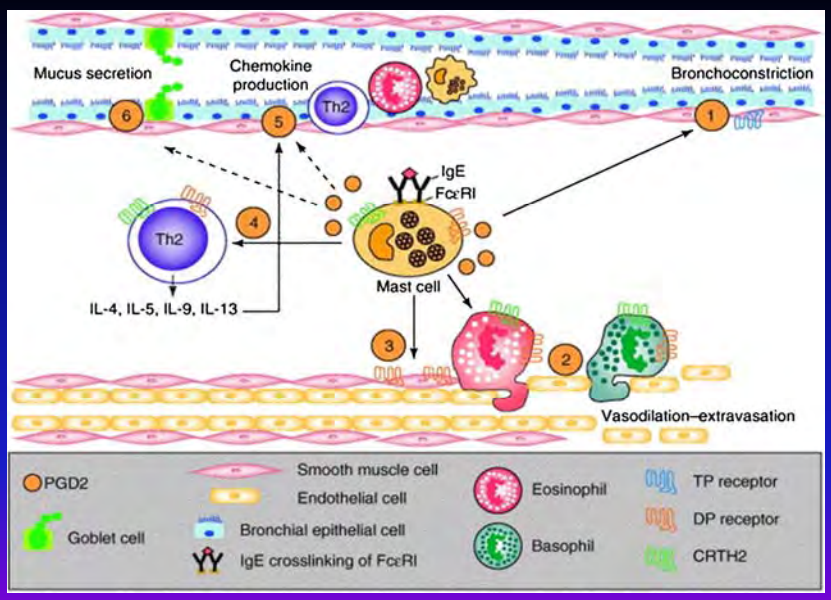
- Hydroxychloroquine
  - Toll receptor inhibitor (TLR9, TLR3,7)
- Dapsone
  - Neutrophil myeloperoxidase inhibitor
- Methotrexate
  - Antimetabolite
  - Adenosine inhibitor for neutrophils
- H1 or H2 inhibitors
  - High dose
  - Questionable effects

Small Molecule Biololgic Modifiers

- Phosphodiesterase inhibitors
  - Increased cyclic AMP
  - Possible adenosine inhibitors
  - Asthma and atopic dermatitis
- Mycophenalate mofetil
  - Interfers with inosine metabolism
  - Targets B and T cells
- Colchicine
  - Interfers with microtubules
  - PMN chemokinesis and phagocytosis

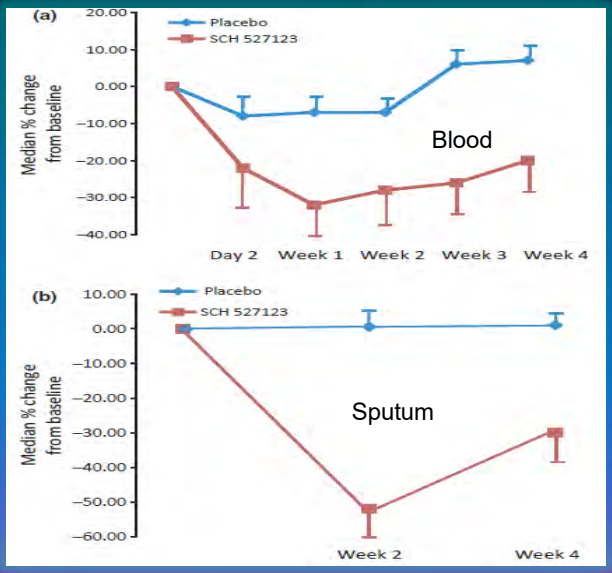
Small Molecule Biololgic Modifiers

- Antimetabolites
  - Inhibit cell division without long term toxicity
- Cytotoxic therapies
  - Inhibit cell division with potential of DNA modification and long term cancer risk
- CRTH2 inhibitors
  - Inhibits T cell and eosinophil migration
- Calcineurin inibitors
  - Select T cell inhibitors



Annals Allergy Asthma Immunol 2102;109:365

Efficacy Of A CXCR2 (IL-8R) Antagonist In Severe Asthma With Sputum Neutrophils

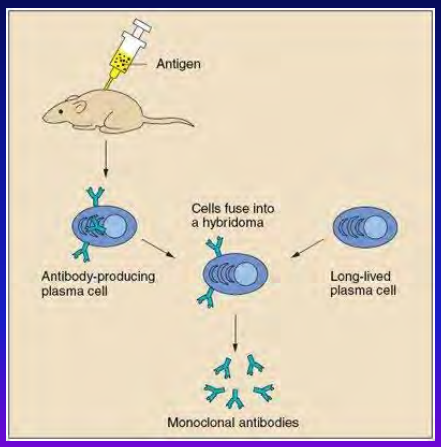


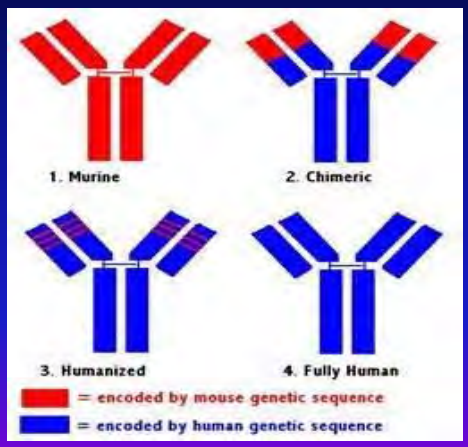
Nair P, et al. Clin Exp Allergy. 2012 Jul;42(7):1097-103.

Monoclonal Antibodies

- Engineered specificity
  - Typically animal antibody due to limited ability of human immune system to respond to human antigens
  - Targets usually molecules or receptors
- Humanized
  - Reduced animal determinants by grafting genetic segments into human

Monoclonal Antibodies





Monoclonal Antibodies

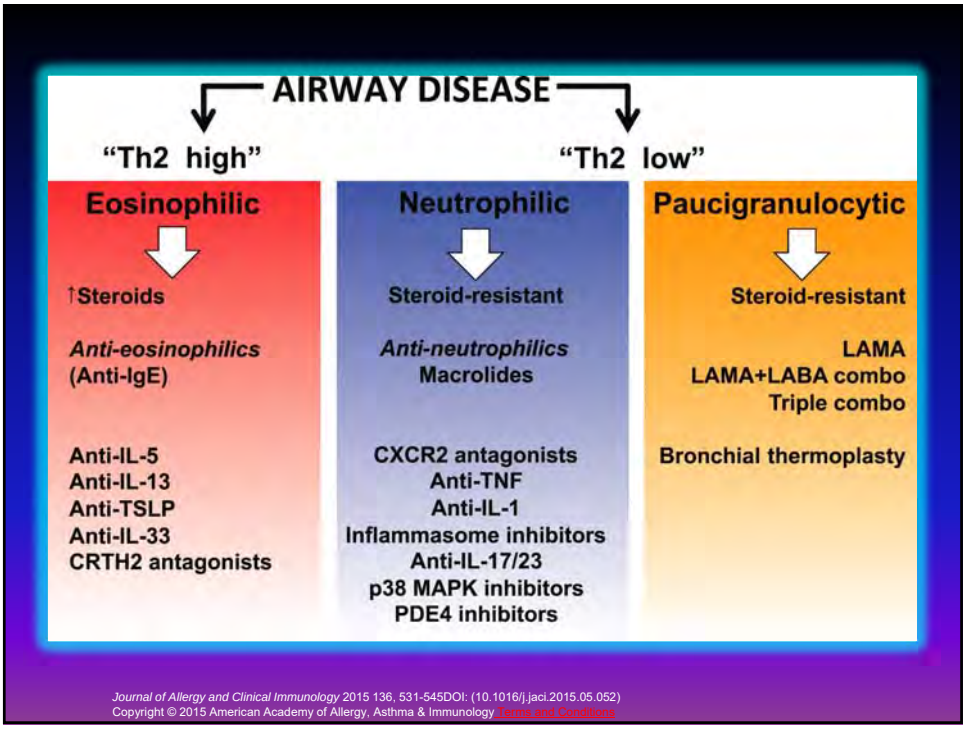
- Murine (-omab)
  - Short half-life with resistance
  - Side-effects
- Chimeric (-ximab)
  - Grafting of variable region or receptor
- Humanized (-zumab)
  - 95% human
  - Mouse hypervariable region
- Human (-umab)
  - Transgenic mice or phage libraries

Monoclonals To Be Discussed

- Anti-IgE
  - Omalizumab
  - Ligelizumab
- Anti-IL-5
  - Mepolizumab
  - Reslizumab
- Anti-IL-5Rα
  - Benralizumab
- Anti-IL4/13Rα
  - Dupilumab
- Anti-IL-13
  - Lebrikizumab
  - Tralokinumab
- Others
  - TNF-α inhibitors
  - Rituximab

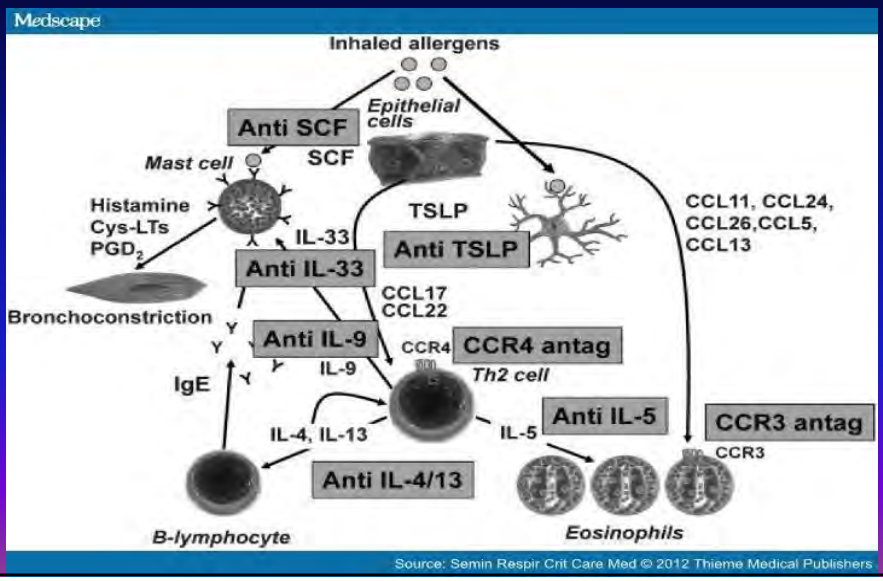
Therapeutic Response Variability

- Due to the heterogeneity of asthma, it is inevitable that distinct dominant pathogenic mechanisms exist (e.g. Th2/eosinophil dominant inflammation)
- Finding which pathogenic factor(s) are important in individual patients is a challenge in treating severe asthma
- Pathogenic pathways may vary with time
- A broad spectrum immunomodulator approach for all patients is problematic due to potential adverse consequences, cost and lack of efficacy in all patients

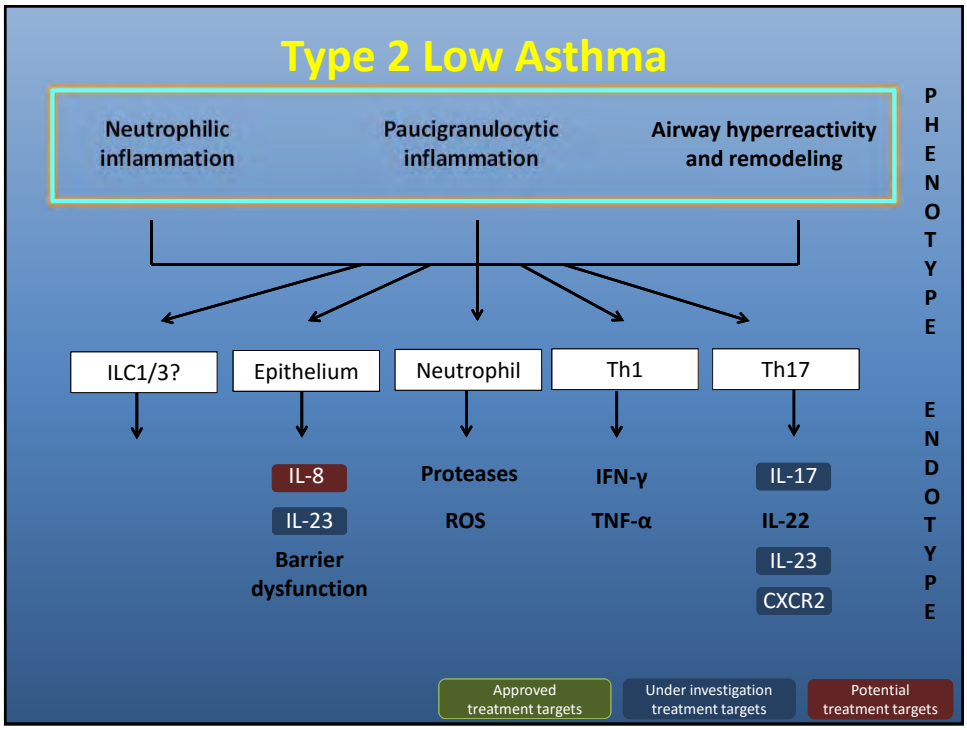


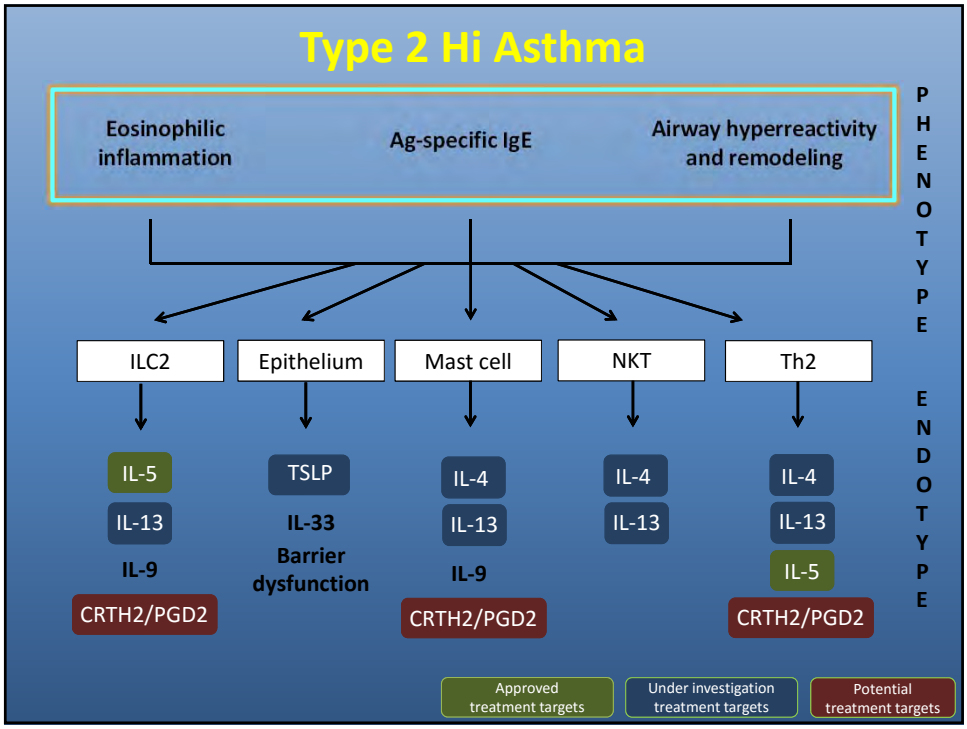
Journal of Allergy and Clinical Immunology 2015 136, 531-545DOI: (10.1016/j.jaci.2015.05.052)

Asthma Targets



Type 2 Low Asthma

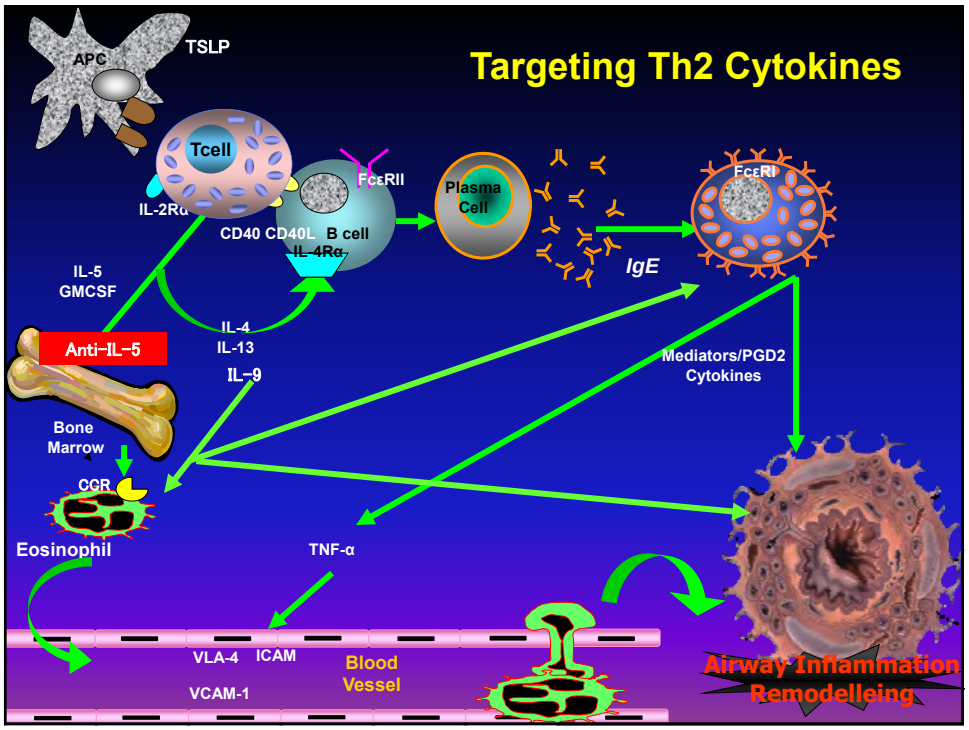




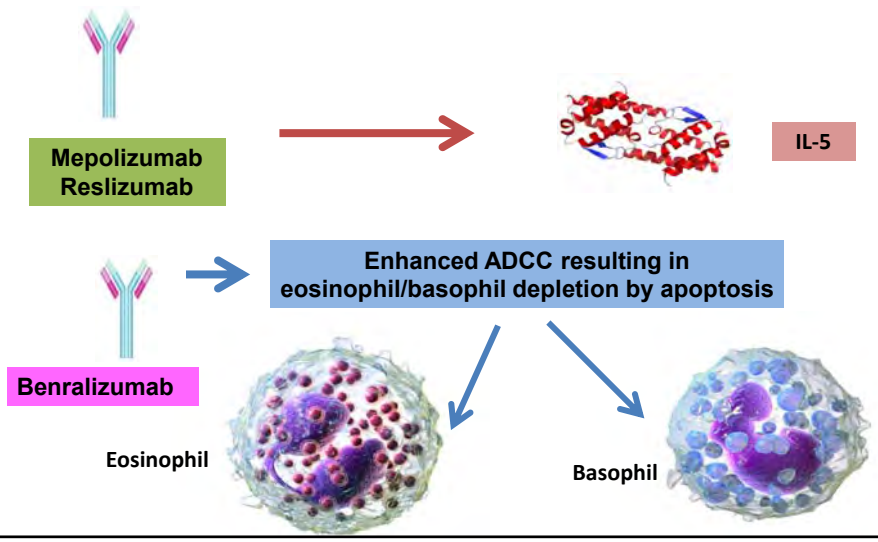
Biomarker	Treatment expected to produce a response	Associations	Comments (point of care, variability/fluctuation)
BLOOD			
Eosinophil	Anti-IL5 Anti -IgE Anti- IL-4/IL-13 Corticosteroids (CS) CRTH2 antagonists	Exacerbations LF decline Fixed airway obstruction	Easily available Significant fluctuation
Specific IgE	Anti-IgE AIT	Exacerbations AHR (AIT)	
Periostin Dipeptidyl peptidase-4 (DPP-4)	Anti-IL13	LF decline Exacerbations	Research type Assay dependent[ref]
INDUCED SPUTUM			
Eosinophils	Anti IL-5 ICS	Exacerbations	Research type Significant fluctuation[ref]
IL-13	Anti IL-13	?	Research type
EXHALED BREATH			
FeNO	Anti IL-5 Anti IgE Anti IL-13 ICS	Exacerbations, LF decline	Easily available Point of care Significant fluctuation[ref]
Metabolomics (VOC)	ICS	?	Research type

Monoclonals To Be Discussed

- Anti-IgE
  - Omalizumab
  - Ligelizumab
- Anti-IL-5
  - Mepolizumab
  - Reslizumab
- Anti-IL-5Rα
  - Benralizumab
- Anti-IL4/13Rα
  - Dupliumab
- Anti-IL-13
  - Lebrikizumab
  - Tralokinumab
- Anti-IL-33



The Targets: IL-5 or Eosinophils/Basophils (IL-5Rα)

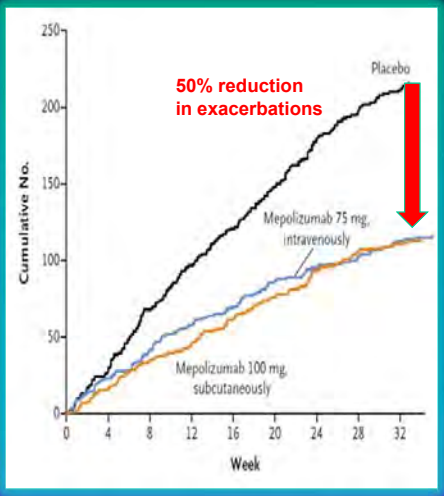


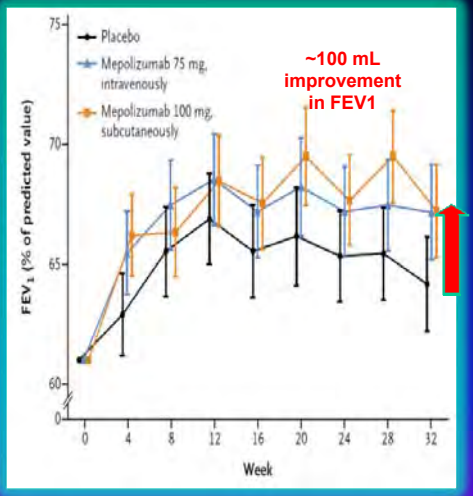
Mepolizumab Phase III Studies

Phase (trial name(s))	Phase III (SIRIUS, MENSA), PhIIb/III (DREAM), plus extensions (MEA115666, MEA115661)
Target Patient Population	• 12 years and older • HD ICS/LABA (>880 µg/day fluticasone or equivalent) +/- chronic OCS (5-35mg/d) • Blood eosinophil count ≥150 cells/µL at screening OR ≥300 cells/µL in the past 12 months • H/O Exacerbations
Admin and Frequency	100 mg SC or 75 mg IV Q4W

Ortega et al . N Engl J Med 2014; 371:1198-1207; Bel et al . N Engl J Med 2014; 371:1189-1197

The MENSA Study

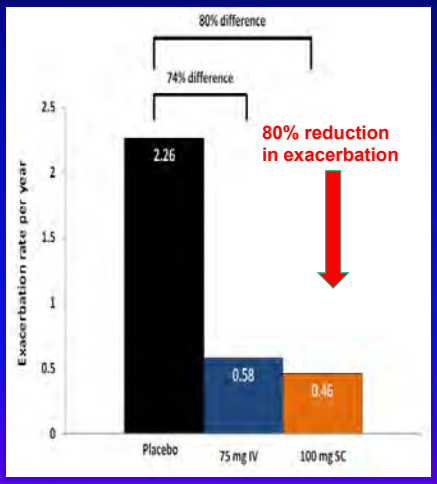


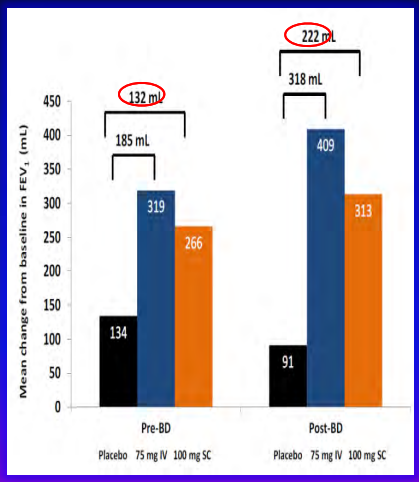


- **Significant improvements in ACQ-5 (4.2-4.4) and SGRQ (6.4-7.0)**

Ortega et al . N Engl J Med 2014; 371:1198-1207

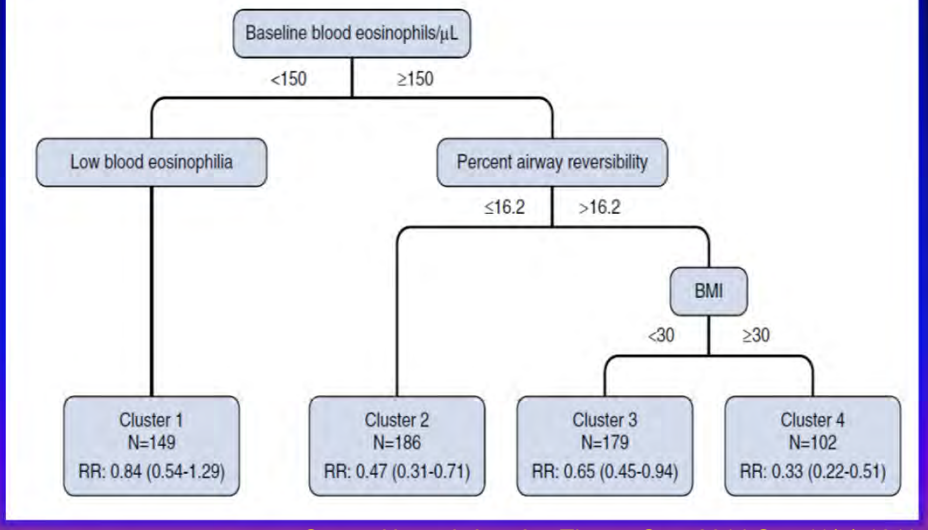
Subgroup analysis of 177 patients with blood eosinophils ≥500 cells/µL from MENSA population



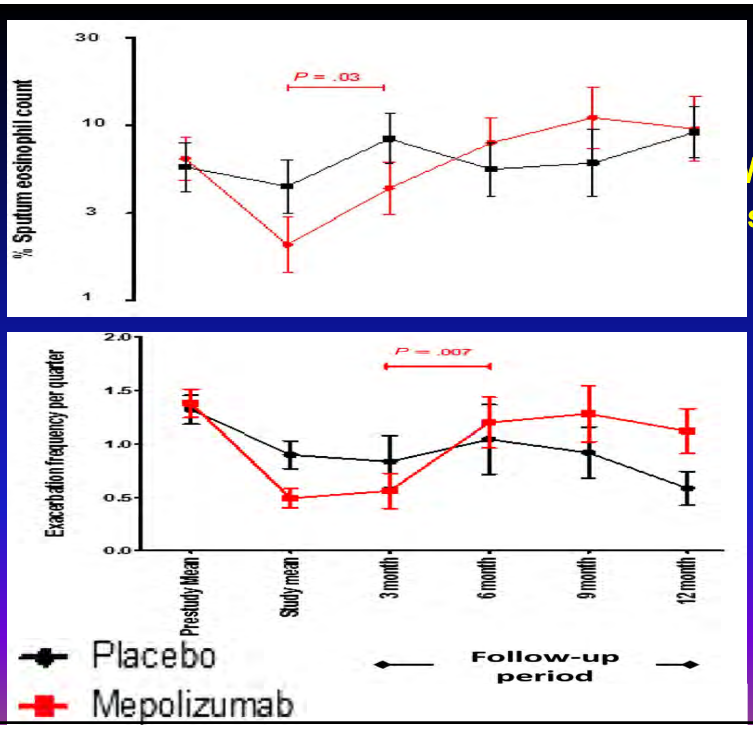


Source: Ortega et al . N Engl J Med 2014; 371:1198-1207

Cluster and Response Analyses of DREAM Study



Ortega H, et al. Ann Am Thorac Soc. 2014 Sep;11(7):1011.



What Happens When Mepo s Stopped?

Haldar et al, JACI, 3/2014

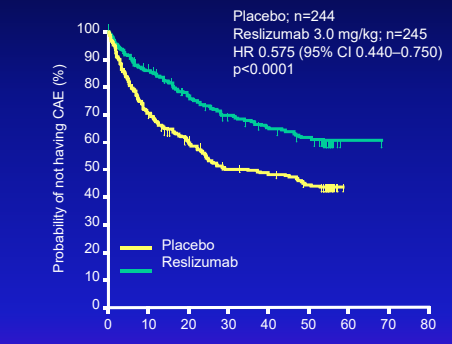
Reslizumab IV Program Overview

Blood eosinophils ≥400 cells/μL

Two 52-week studies (n = 489)	Two 16-week studies (n = 315)
Primary endpoint: exacerbations	Primary endpoint: lung function

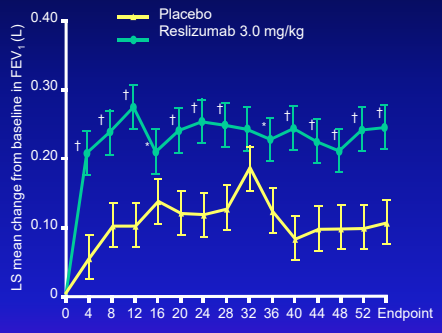
- Ages 12–75
- ≥ Medium doses of ICS ± other controller
- Inadequately controlled (ACQ ≥1.5)
- Reversible to SABA (12%) during screening
- Exacerbation studies:
  - Required ≥1 asthma exacerbation in prior year
  - OCS-dependent asthma allowed

Reslizumab Effects on Exacerbations and Lung Function



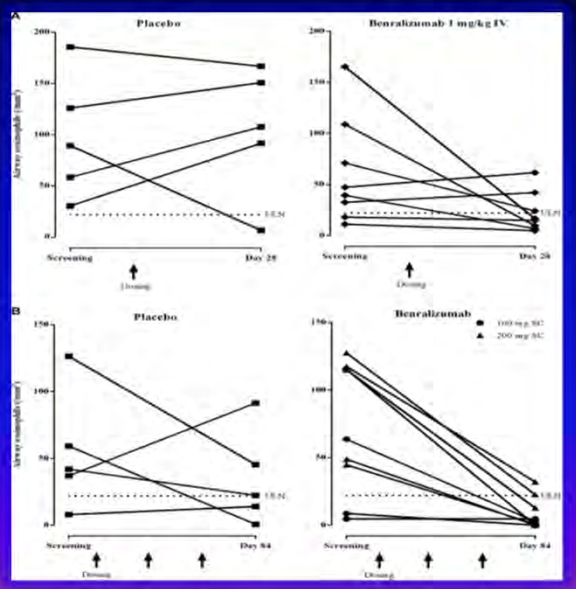
Number at risk

Placebo	244	169	138	112	107	97	0	0	0
Reslizumab	245	207	177	158	146	136	1	0	0



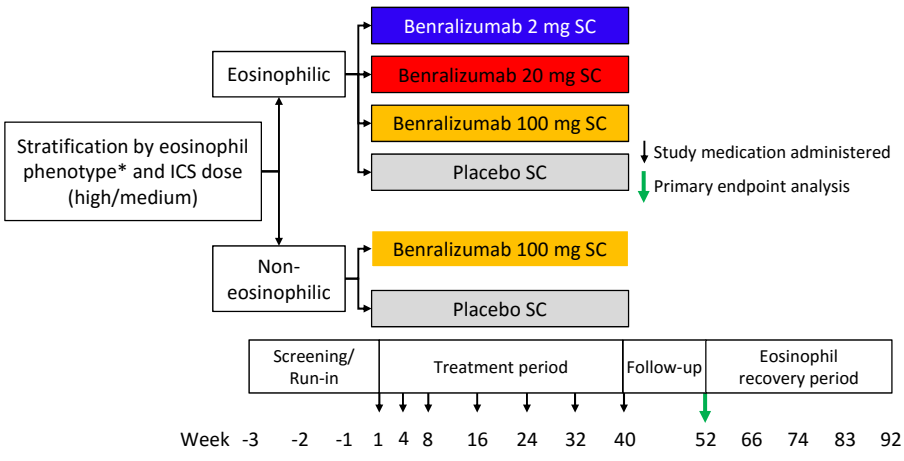
Castro et al. Lancet Respir Med , May 2015

Benralizumab and Airway Eosinophils



J Allergy Clin Immunol 2013;132:1086

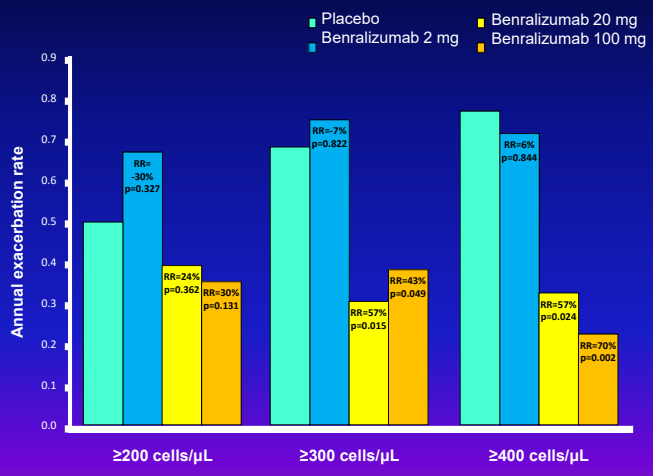
Benralizumab: Phase IIb Study In Patients With Uncontrolled Eosinophilic Asthma



*ELEN Index positive and/or FE_{NO} ≥50 ppb.
ICS, inhaled corticosteroid; SC, subcutaneous

Castro M et al. Lancet Resp Med 2014; S2213-26

Benralizumab's Effects on Annual Exacerbation Rate By Eosinophil Level



RR, rate ratio
Castro et al. Lancet Resp Med 2014; 2: 879–90

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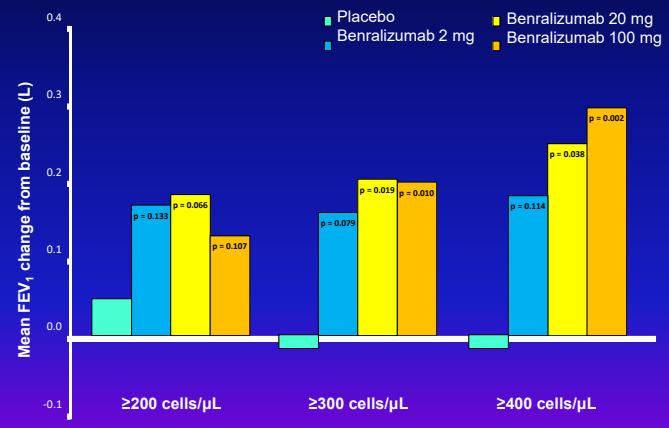
Benralizumab's Effects on Change in FEV_1 By Baseline Eosinophil Level



FEV_1, forced expiratory volume in 1 second
Castro et al. Lancet Resp Med 2014; 2: 879–90

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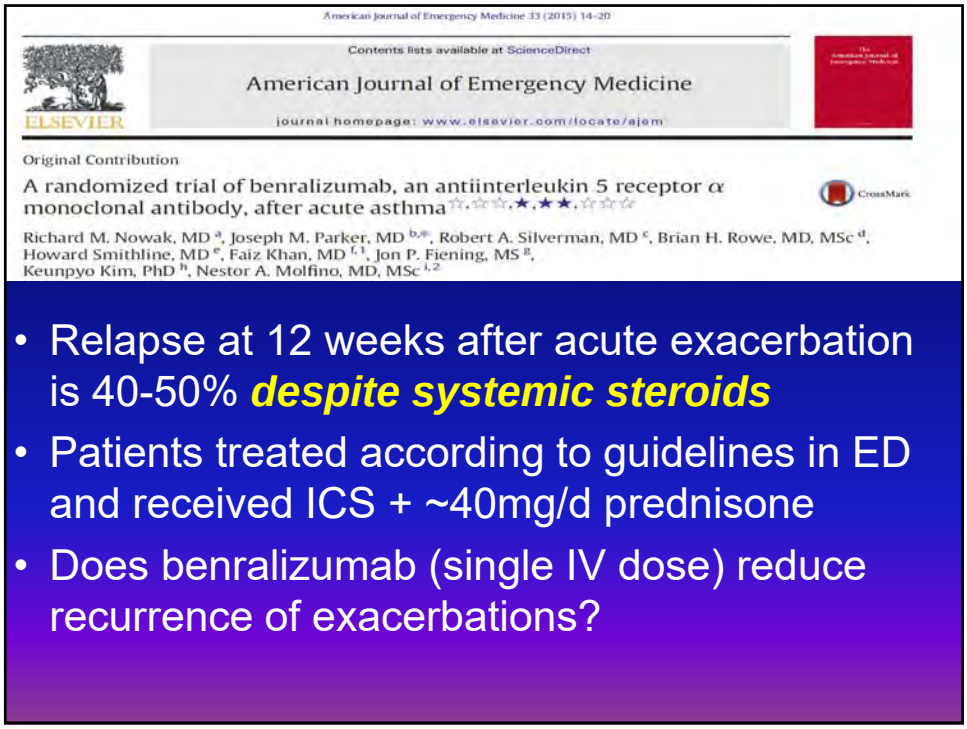

American Journal of Emergency Medicine 33 (2015) 14–20

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journal homepage: www.elsevier.com/locate/ajem

Original Contribution

A randomized trial of benralizumab, an antiinterleukin 5 receptor α monoclonal antibody, after acute asthma☆,☆☆,★,★★,☆☆☆

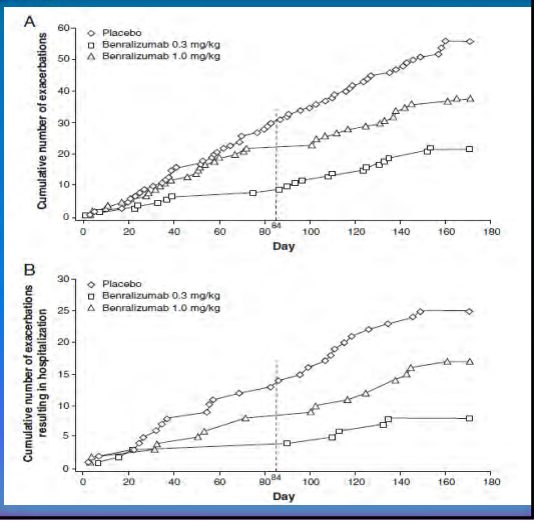
Richard M. Nowak, MD [a], Joseph M. Parker, MD [b,*], Robert A. Silverman, MD [c], Brian H. Rowe, MD, MSc [d], Howard Smithline, MD [e], Faiz Khan, MD [f,1], Jon P. Fiening, MS [g], Keunpyo Kim, PhD [h], Nestor A. Molfino, MD, MSc [i,2]

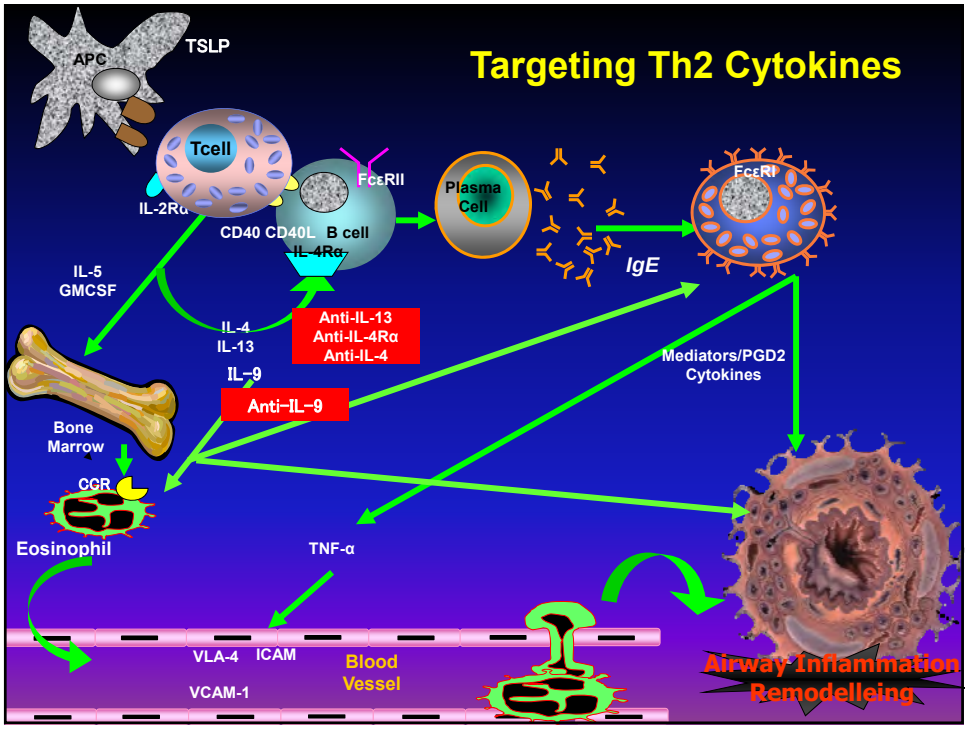
- Relapse at 12 weeks after acute exacerbation is 40-50% ***despite systemic steroids***
- Patients treated according to guidelines in ED and received ICS + ~40mg/d prednisone
- Does benralizumab (single IV dose) reduce recurrence of exacerbations?

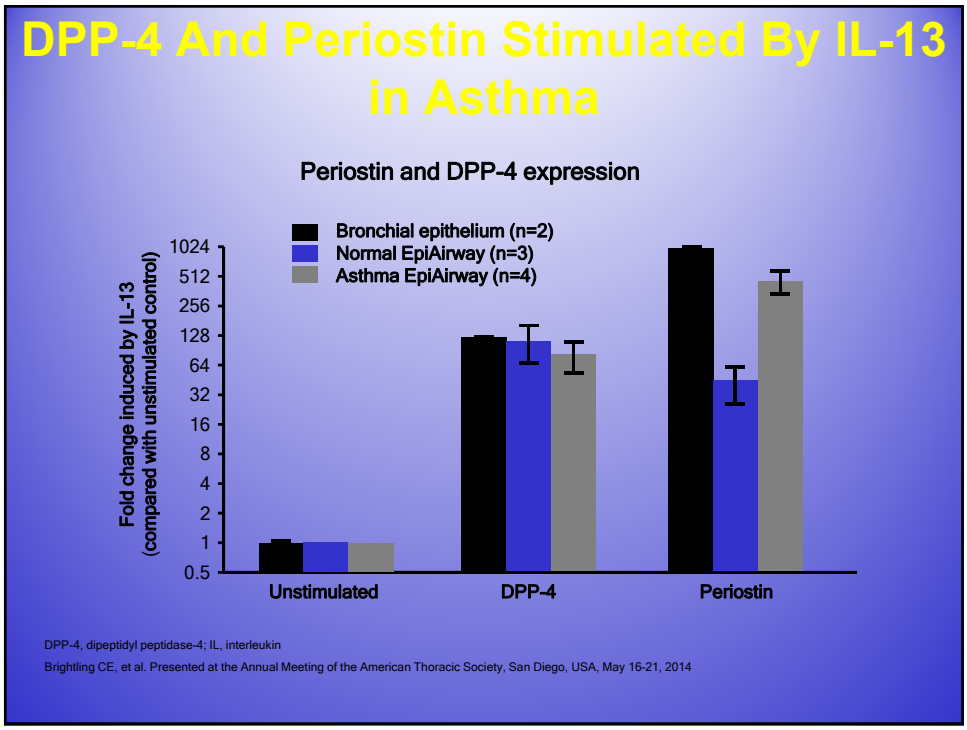
Benralizumab Primary Outcomes

Proportion of subjects with ≥ 1 exacerbation at 12 weeks was not different between placebo and combined benralizumab groups (38.9% vs 33.3%; P=.67).

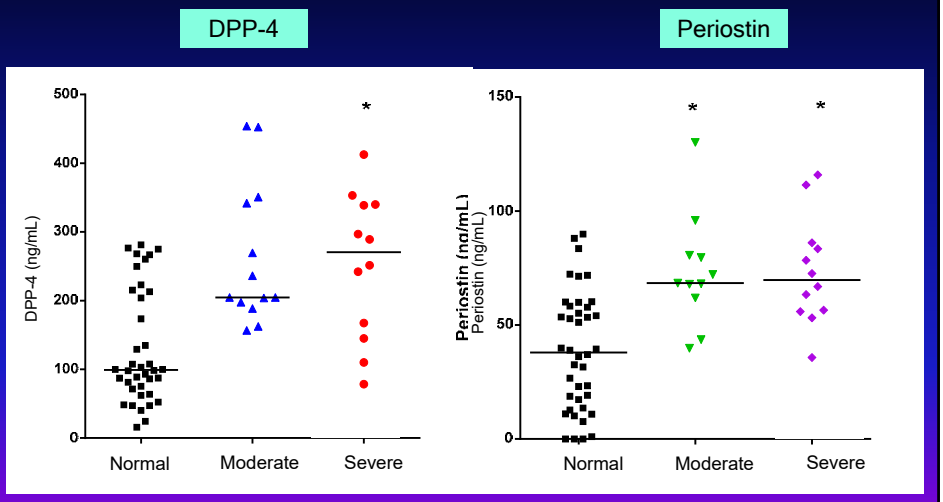
Compared with placebo, exacerbation rates reduced by 49% (3.59 vs 1.82; P=.01) and exacerbations resulting in hospitalization by 60% (1.62 vs 0.65; P=.02) in the combined groups



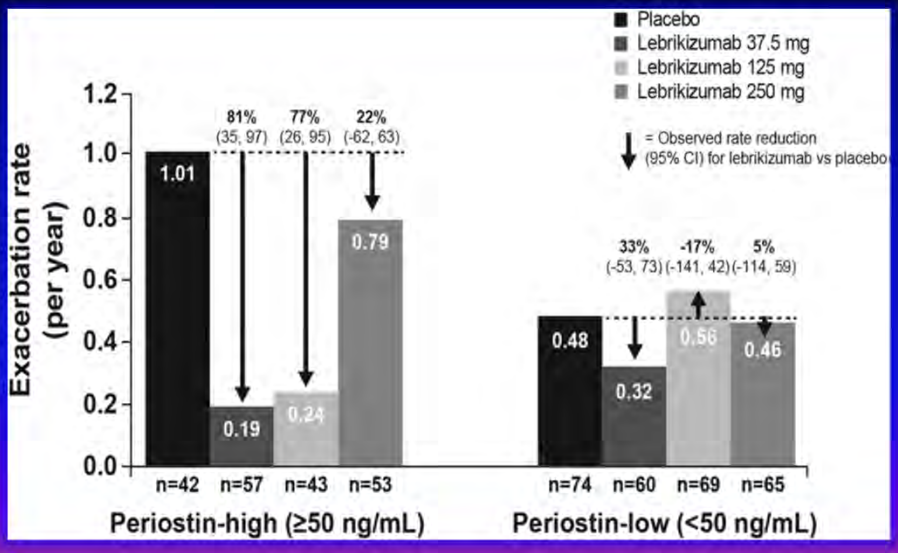

Targeting Th2 Cytokines
APC
TSLP
Tcell
IL-2Rα
CD40 CD40L
B cell
IL-4Rα
FcεRII
Plasma Cell
IgE
FcεRI
IL-5
GMCSF
IL-4
IL-13
IL-9
Anti-IL-13
Anti-IL-4Rα
Anti-IL-4
Anti-IL-9
Mediators/PGD2
Cytokines
Bone Marrow
CCR
Eosinophil
TNF-α
VLA-4
ICAM
VCAM-1
Blood Vessel
Airway Inflammation
Remodelleing


DPP-4 And Periostin Stimulated By IL-13 in Asthma
Periostin and DPP-4 expression
Bronchial epithelium (n=2)
Normal EpiAirway (n=3)
Asthma EpiAirway (n=4)
Fold change induced by IL-13 (compared with unstimulated control)
1024
512
256
128
64
32
16
8
4
2
1
0.5
Unstimulated
DPP-4
Periostin
DPP-4, dipeptidyl peptidase-4; IL, interleukin
Brightling CE, et al. Presented at the Annual Meeting of the American Thoracic Society, San Diego, USA, May 16-21, 2014

Serum DPP-4 And Periostin Elevated In A Subset Of Patients With Asthma

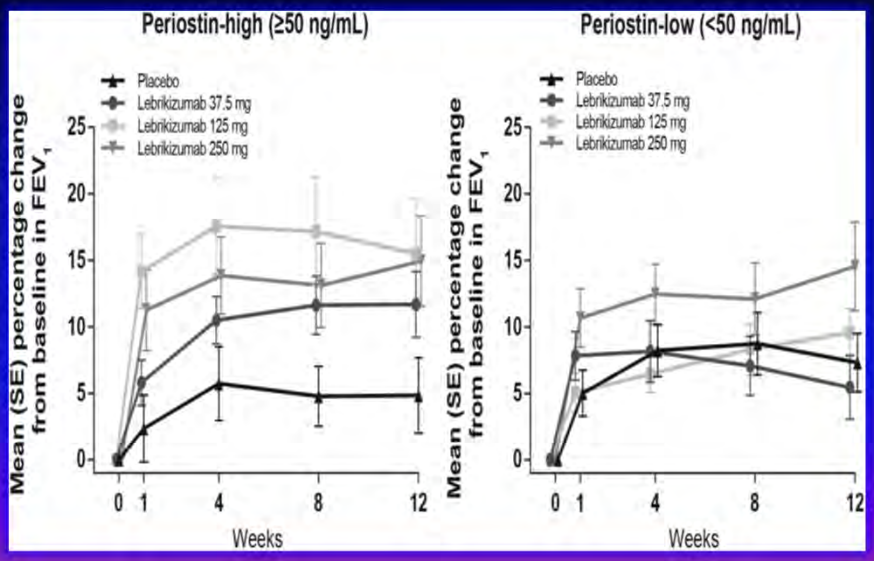


52-Week Replicate Lebrikizumab Trials in Adults with Asthma



Hanania NA, et al. Th.orax. 2015 Aug;70(8):748

52-Week Replicate Lebrikizumab Trials in Adults with Asthma



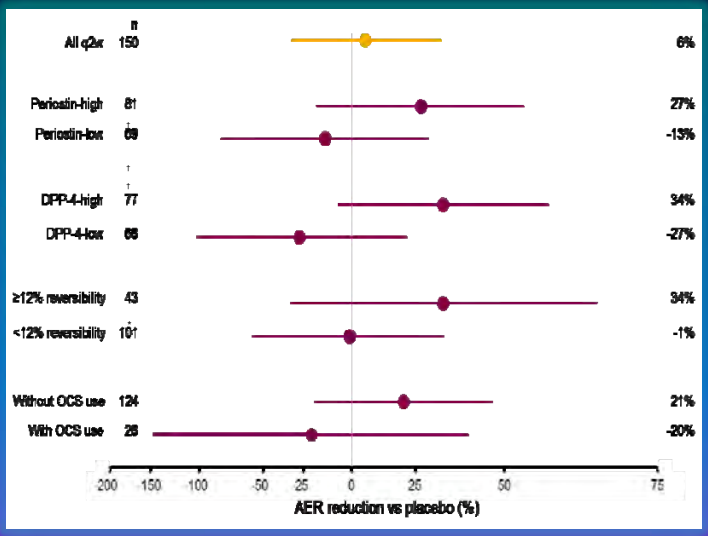
Hanania NA, et al. Thorax. 2015 Aug;70(8):748.

Lavolta I and II

- Two phase 3 multicenter trials with more than 2100 subjects in 28 countries
- Endpoint: asthma exacerbations over 52 wk
- Lavolta I: reductions in exacerbations in subjects with increased eosinophils and periostin with minimal increase in FEV1
- Lavolta II: NO statistical reduction in exacerbations

American Thoracic Society, 2016. A1318-A1318.

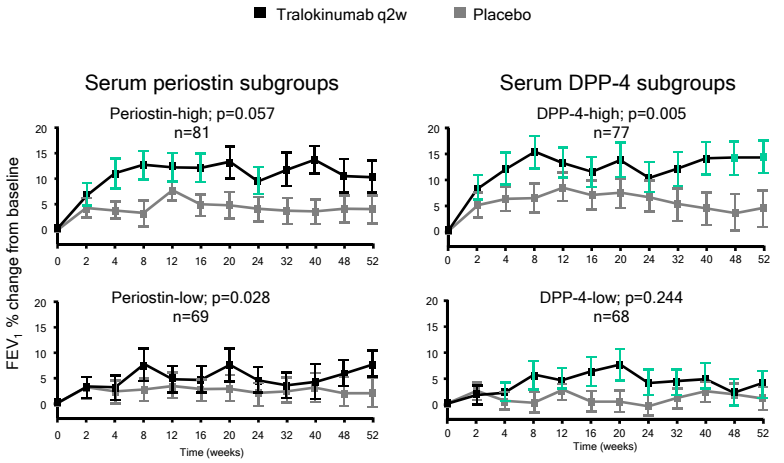
Asthma Exacerbation Rates in Subgroups Treated with Tralokinumab for 52 Weeks



†High and low biomarker levels defined by median values

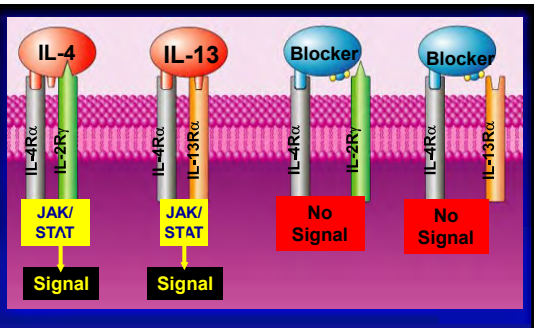
Plot created from data presented in: Brightling CE, et al. Lancet Respir Med 2015;DOI:10.1016/S2213-2600(15)00197-6

Changes In FEV_1 In Subgroups Treated With Tralokinumab for 52 Weeks



Brightling CE, et al. Lancet Respir Med 2015;DOI:10.1016/S2213-2600(15)00197-6

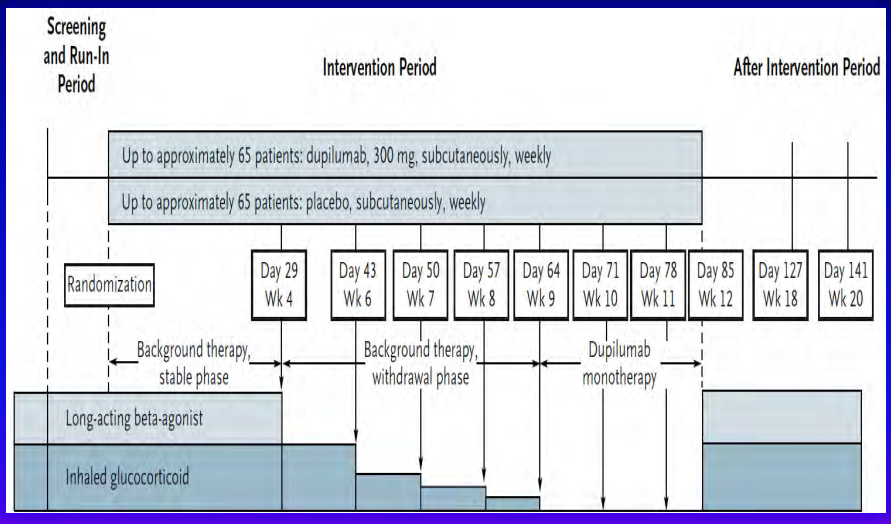
Dupilumab:
Fully human mAb to IL-4Rα



- Phase II study: assess efficacy in *adults* with persistent, *moderate-to-severe asthma* and *symptoms* not well controlled with medium- to high-dose ICS + LABA and elevated *eosinophil* levels:
  - blood eos ≥300 or sputum eos level ≥3%

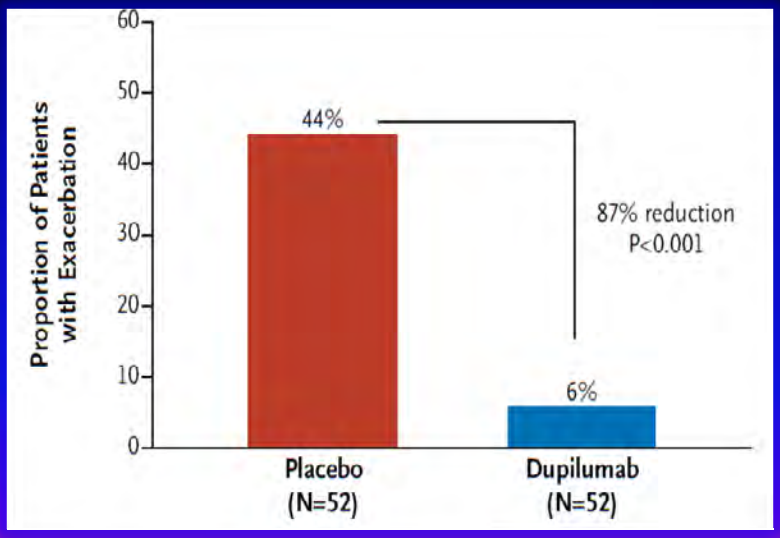
Wenzel et al. NEJM: 05/2013

Dupilumab Study Design



Wenzel et al. NEJM: 05/2013

Dupilumab's Effects On Exacerbations



Wenzel etl al NEJM 05/2013

Dupilumab Improved Secondary Endpoints

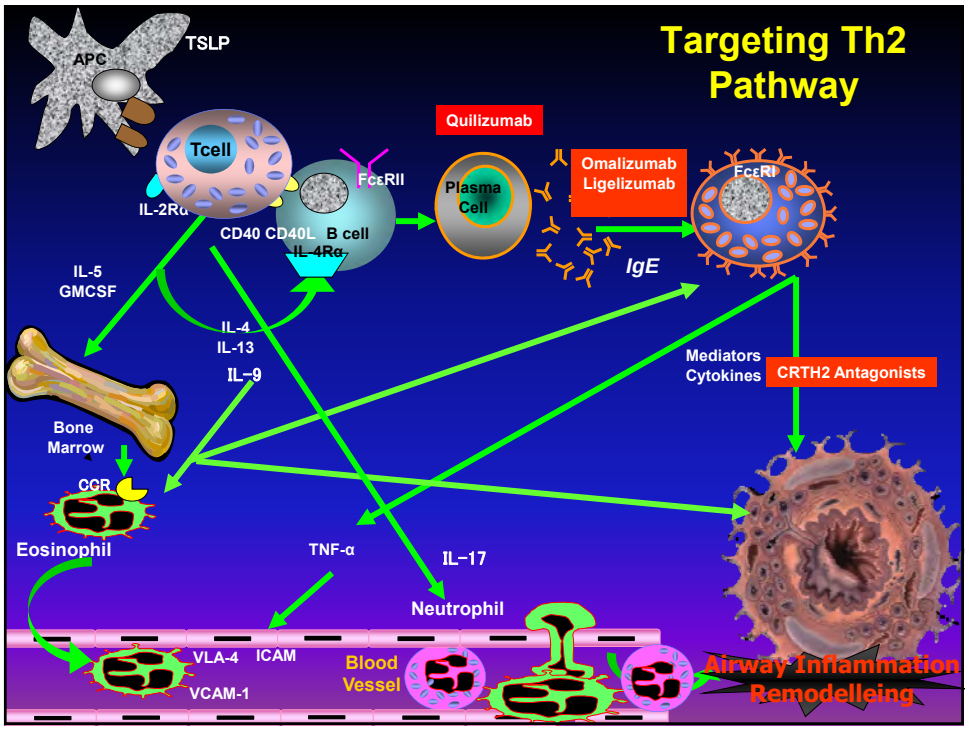
- FEV1 and PEF
- ACQ
- Sx Scores
- SABA use
- Nocturnal awakenings
- SNOT-22 score

Wenzel et al. NEJM: 05/2013

Phase 2B Study Results

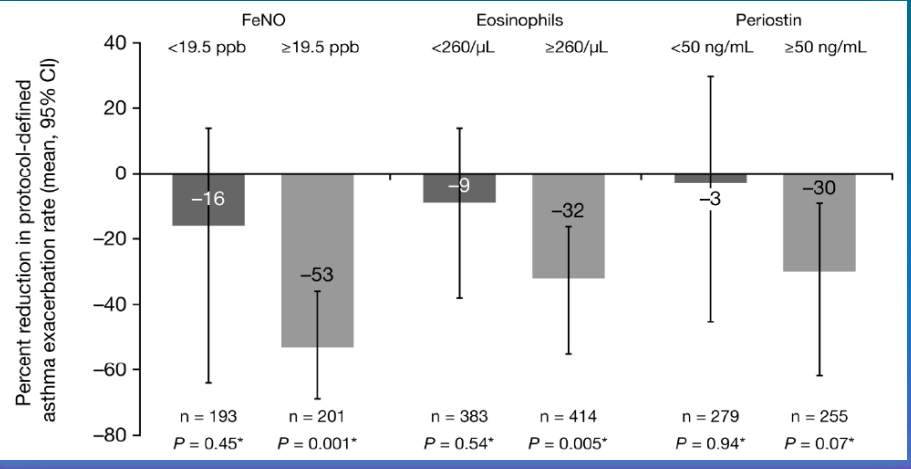
- Every 2 weeks works well
- If Eos >300:
  - Decreased exacerbations
  - Improved FEV1
- Causes an initial increase in blood Eos which declines towards baseline with further treatment.
- Well tolerated

Presented at ERS 2015



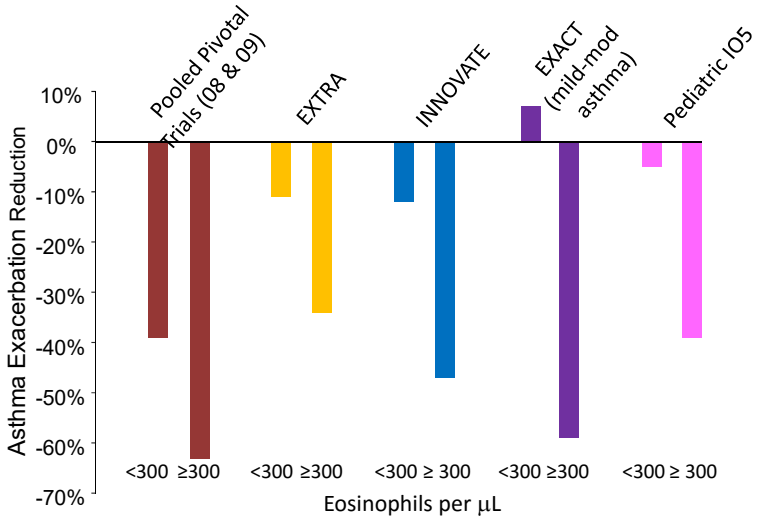
How Does Omalizumab Compare to New Biologics In Similar Patients?

Omalizumab's Effects Based on Th2 Biomarkers



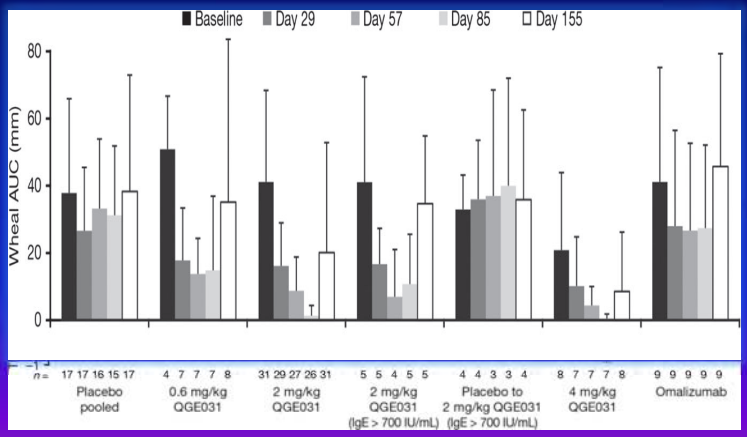
Hanania et al, AJRCCM, 2013

Asthma Exacerbation Reductions in Omalizumab Clinical Trials by Eosinophil Strata

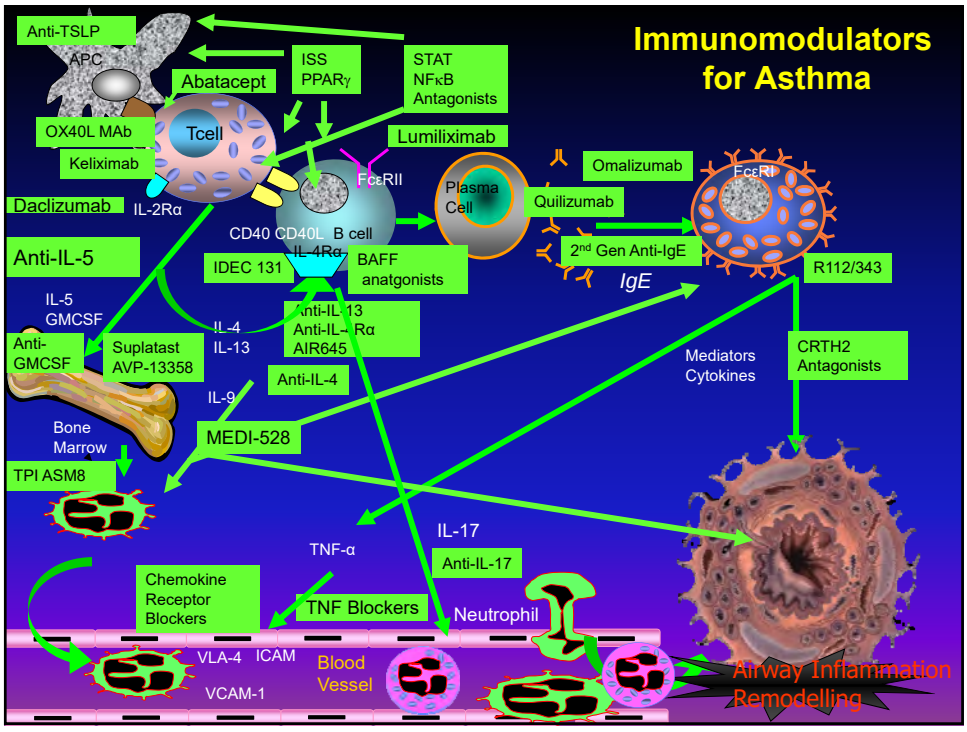


Sources: Hanania et al. *AJRCCM* 2013; Busse et al. *JACI* 2013; Genentech and Novartis Data on File

Effects of QGE031 (Ligelizumab) on Ag-Induced Wheal



Arm JP, et al. Clin Exp Allergy. 2014 Nov;44(11):1371.



Critical Issues /Questions for Th2 Blockers

- Many options for similar patient populations.
  - Phenotype/Endotype (Biomarker) driven choices overlap: *No specific biomarkers*
- Optimal treatment goals have not yet been met:
  - True Immunomodulation: prevent/alter disease course
- Th2 blockers likely have favorable risk/benefit ratio

Non-Th2 High Asthma

- Heterogeneous group
- Primary targets not well defined
- Likely treatment population size smaller, incentive for development is reduced
- May be our most challenging patient population

Other Potential Applications

- Asthma
  - TNF-α inhibitors
  - Rituximab
- Atopic dermatitis
  - Calcineurin inhibitors
  - Antimetabolites including mycophenalate mofetil
  - Omalizumab, dupilumab, rituximab
  - Phosphodiesterase 4 inhibitor (apremilast)

Other Potential Applications

- Nasal polyps
  - Omalizumab, dupilumab, mepolizumab
- Urticaria
  - Omalizumab
  - Antimetabolites
  - Dapsone
  - Hydroxychloroquine
  - Rituximab
  - Colchicine

Conclusions

- Immune mechanism modification offers the possibility of treating asthma and allergic disease at a basic and not symptomatic level
- Understanding of the immune mechanism of the disease is critical to intentional application of biologic modifiers
- Targets that are limited to one disease or organ system are unusual resulting in side effects, Th2 mechanisms tend to be less risky
- Small molecules cannot be easily designed but offer oral therapy
- Monoclonal therapies offer designed target development but will be SQ or IV