

Novel and Emerging Therapies in Severe Asthma

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BWH Severe Asthma Program



I disclose the following relationships in the past year:

- Asthma Education Prevention Program (NAEPP) Coordinating Committee 2017-
 - AB Science Consultant
 - Amgen Consultant
 - AstraZeneca Consultant & Clinical Research Support
 - Avillion Consultant & Clinical Research Support
 - Circassia Pharmaceuticals Clinical Research Support
 - Cowen Consultant
 - GlaxoSmithKline Consultant
 - Gossamer Bio Clinical Research Support
 - Merck Consultant
 - Novartis Consultant
 - Pneuma Respiratory Consultant
 - PPS Health Consultant
 - Regeneron Pharmaceuticals Consultant
 - Sanofi Consultant
 - TEVA Consultant & Clinical Research

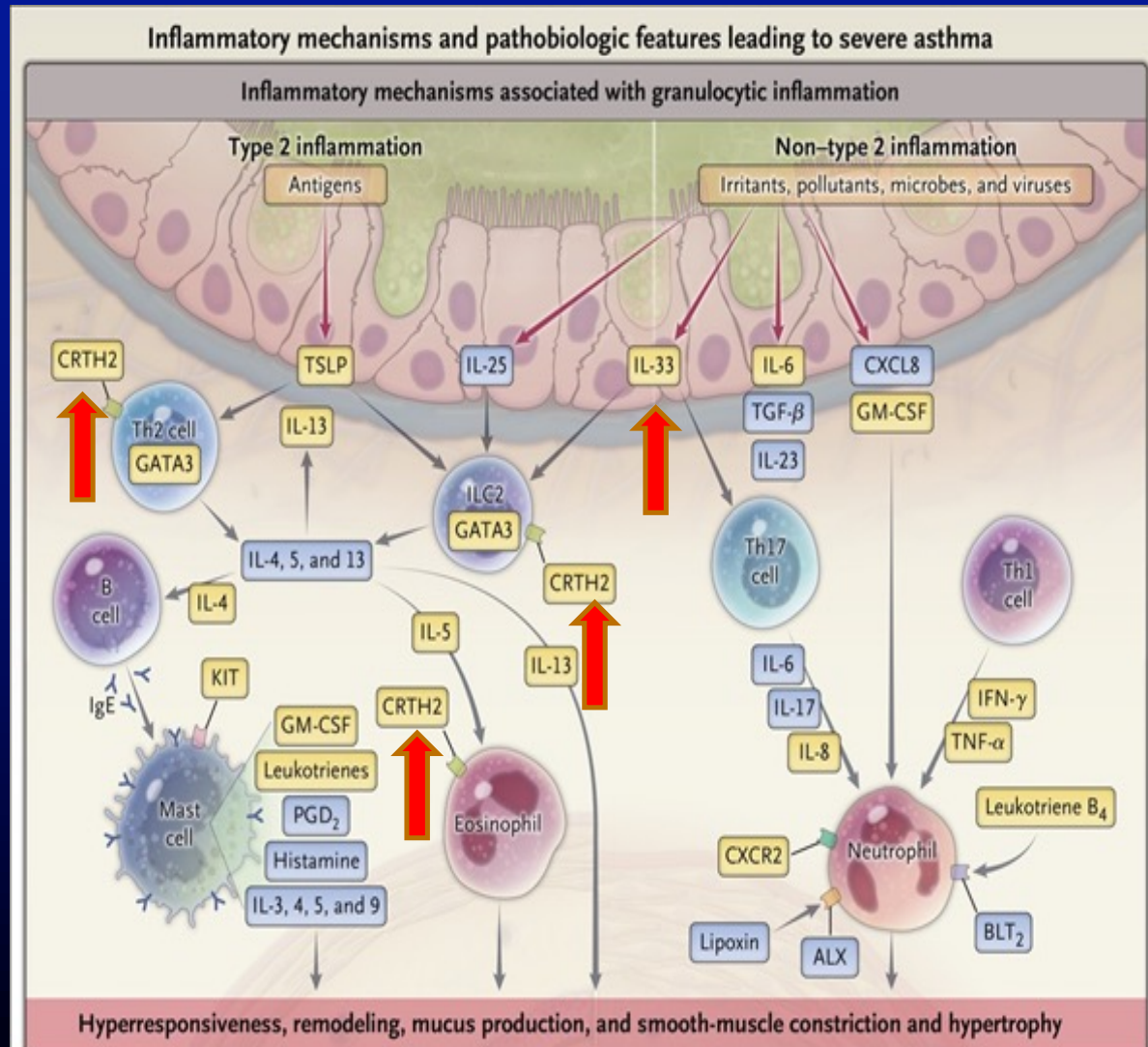


Novel Approaches in Development that Are Being Tested in Humans

- Anti CRTH2
- Mast cell inhibitors
- GATA3 Inhibitors
- Anti-IL33
- Other approaches



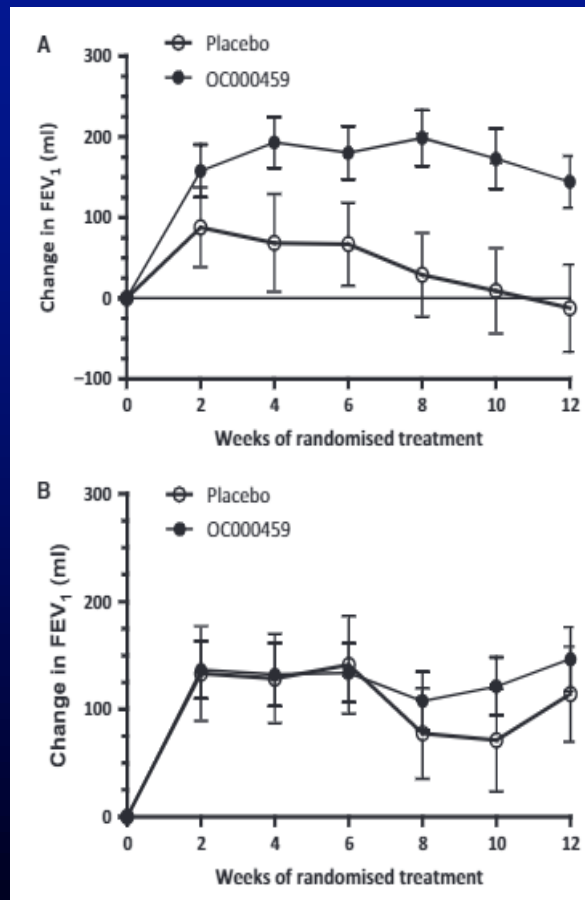
Pathways Involved in Severe Asthma



Israel & Reddel, NEJM,

FEV1 Improvement to CRTh2 Antagonist (OC) Greater in those with Higher Eosinophils

Eos ≥ 250 /ul

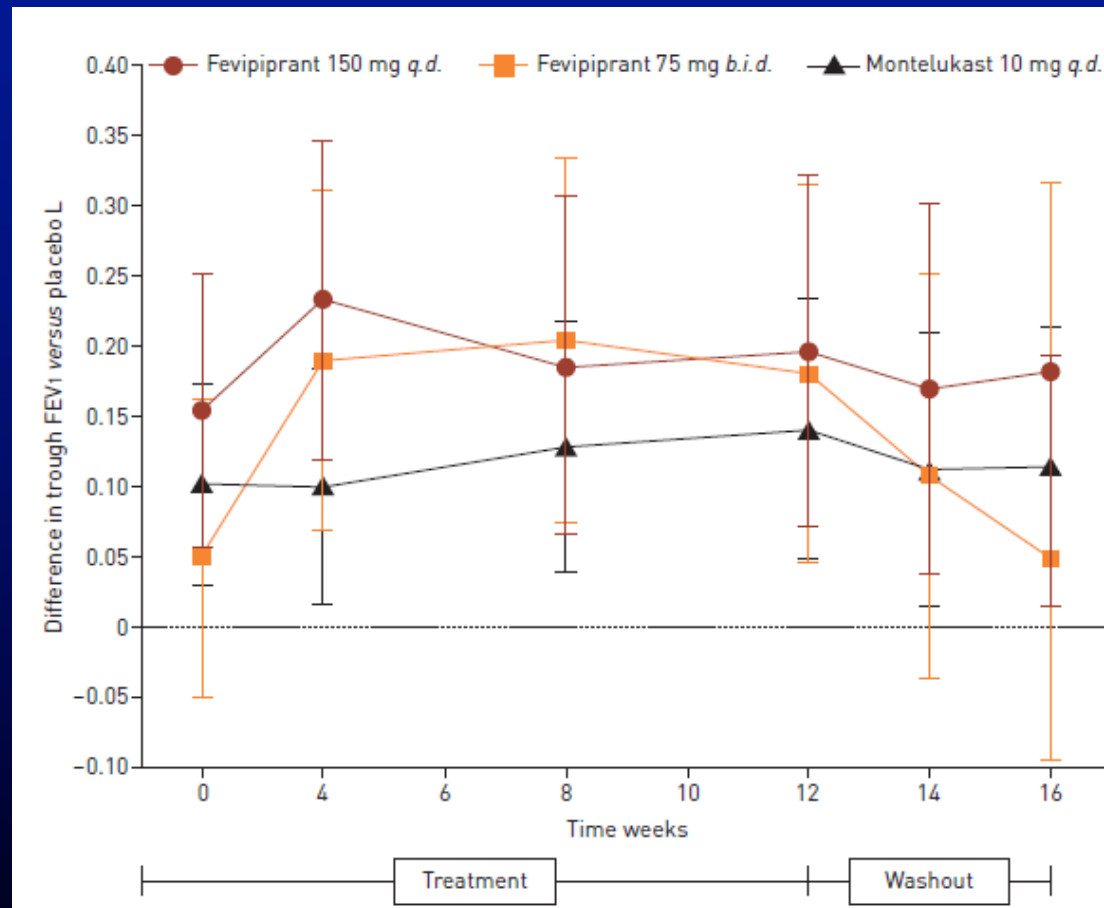


Eos < 250/uL



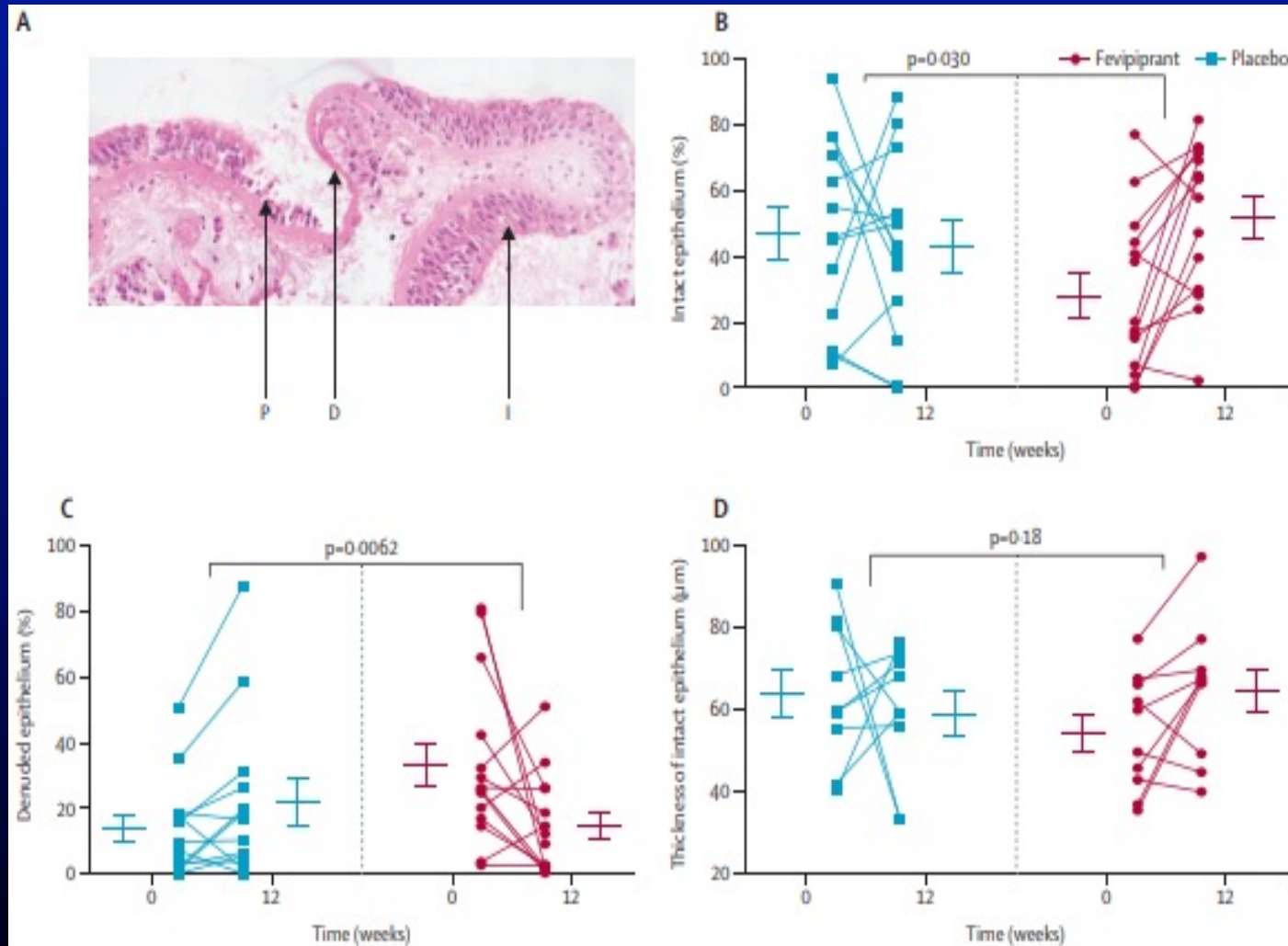
Pettipher, Allergy, 2014

Fevipiprant Increased FEV1 in Allergic Patients on Low Dose ICS



Bateman, ERJ, 2017

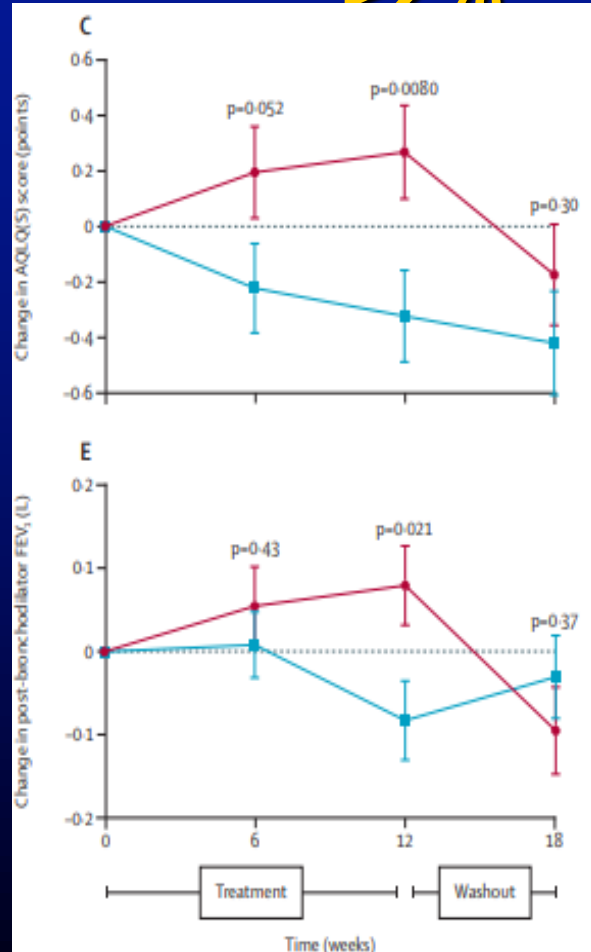
Fevipiprant Increased Intact Epithelium and Decreased Denuded Epithelium



Fevipiprant Improved ACQ5 and Post-BD- FEV1 in Patients on ICS w/ Sputum Eos >2%

ACQ5

Post-BD
FEV1

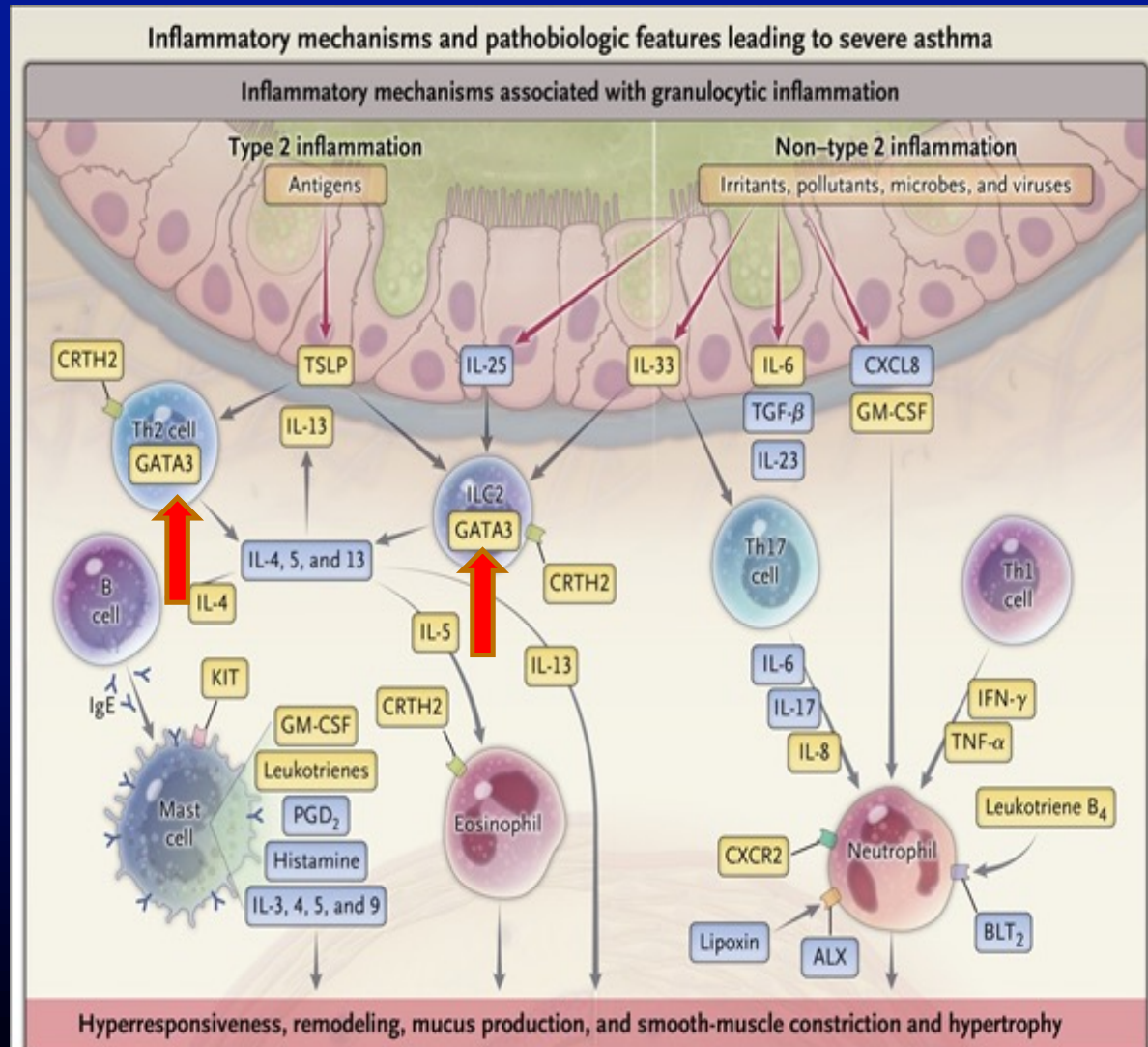


CRT_h2 Antagonists

- Was being studied in moderate to severe patients
- Oral tablets
- Novartis announced that fevipiprant failed to improve FEV₁ in 2 phase 3 trials
- Novartis announced that the 1 year exacerbation trials failed to meet their endpoint
- GB001 an oral DP₂ antagonist
 - Failed in asthma but perhaps a 1/3 reduction in exacerbations
 - Failed in chronic rhinosinusitis



Pathways Involved in Severe Asthma

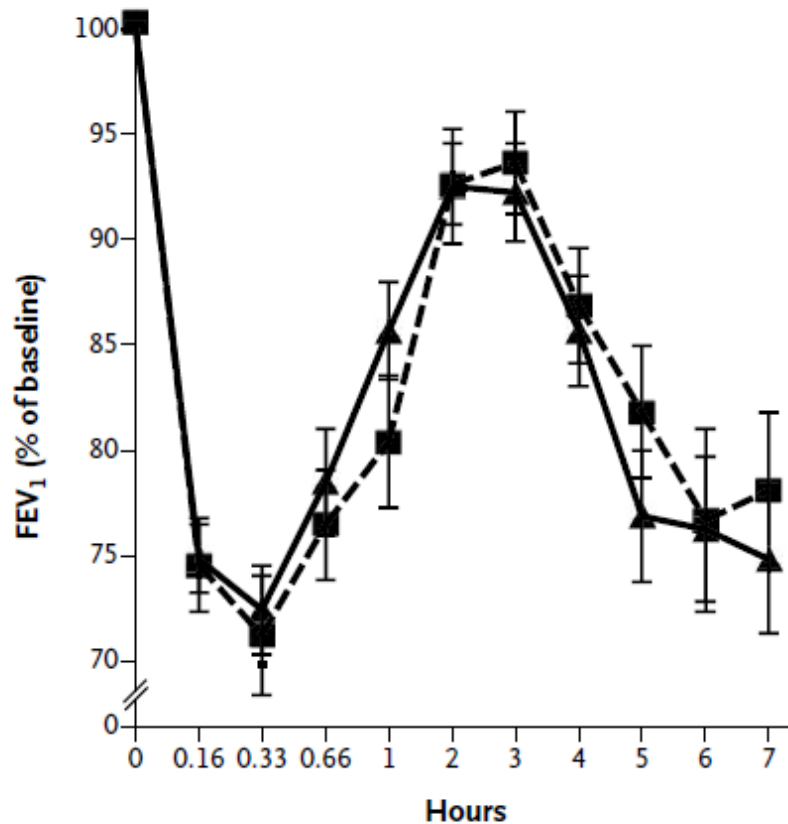


Israel & Reddel, NEJM, 2017

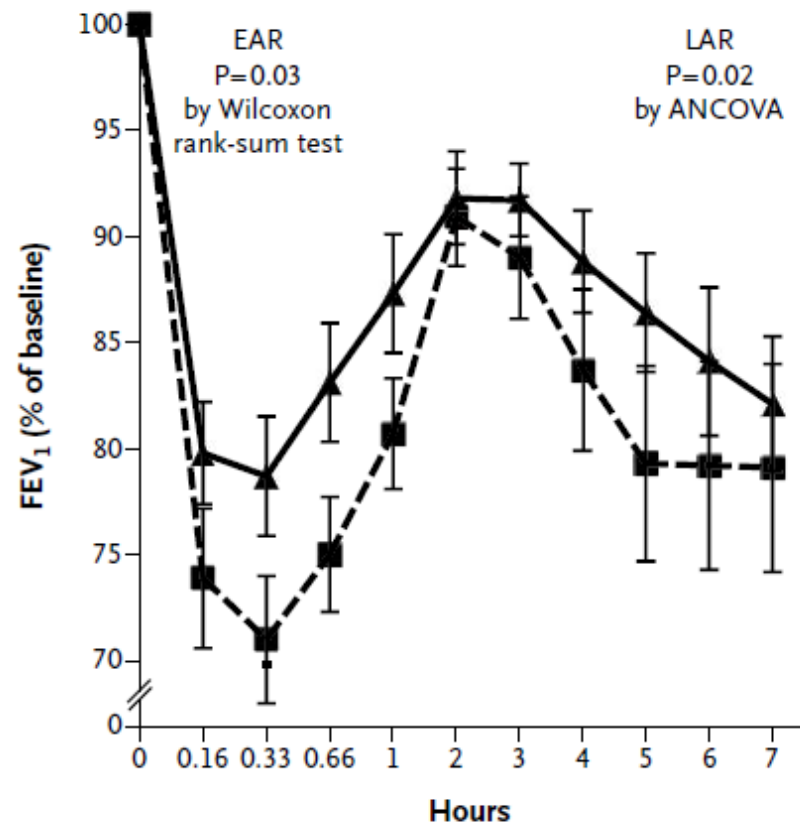
DNAzyme Against GATA3 mRNA decreases the FEV1 Response to Allergen Challenge

(Post-challenge sputum eosinophils and tryptase and serum IL5 decreased, but not FeNO or Mch PC₂₀)

A Before Initiation of Study Drug



B After 4 Wk of Study Drug



PARTNER
ASTHMA CENTER

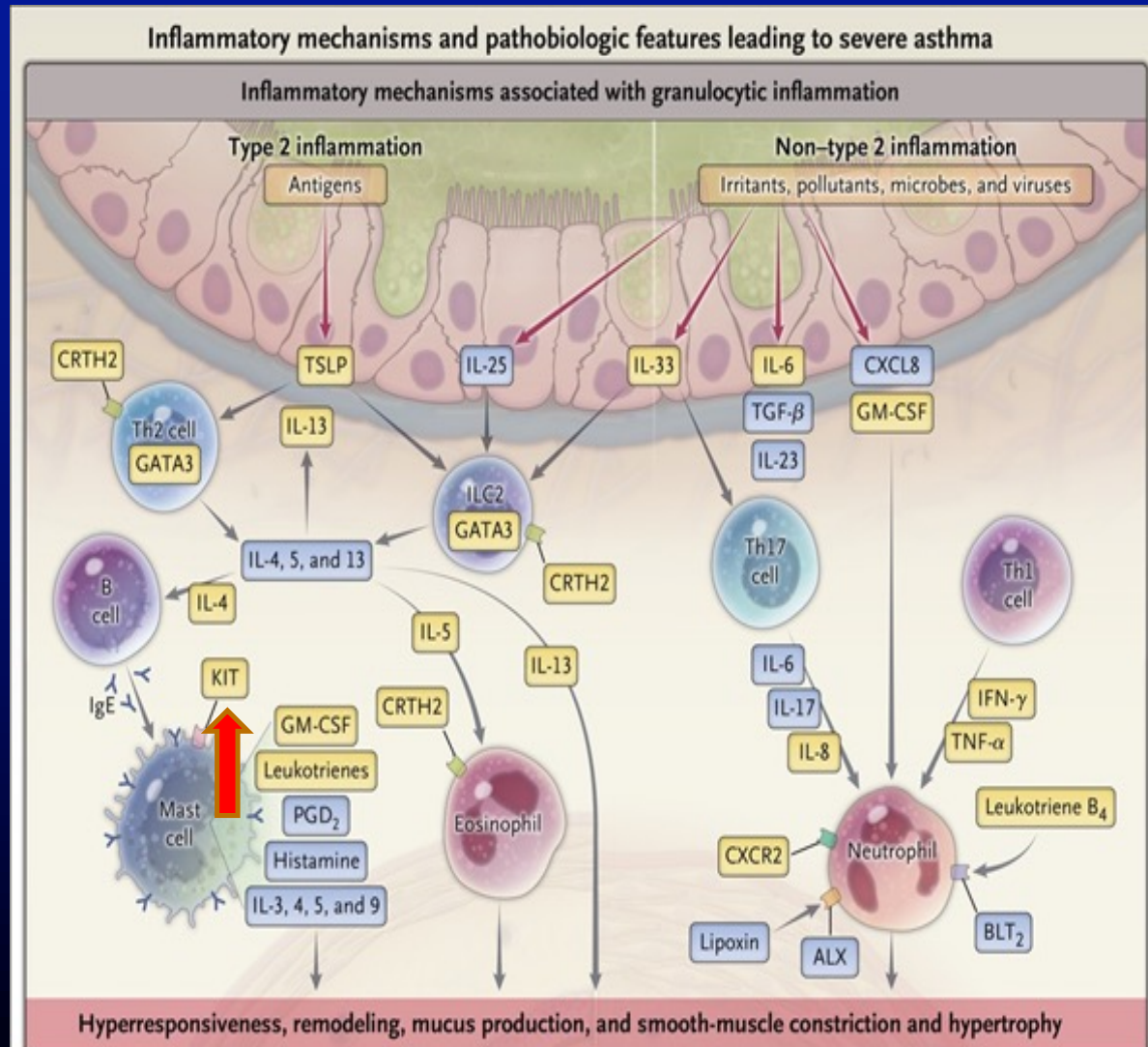
Krug, NEJM, 2015

DNAzyme

- Phase 2b Studies in Asthma are being prepared
- Phase 2a study in COPD with elevated sputum eosinophils showed reduction in sputum eosinophils with inhaled DNAzyme

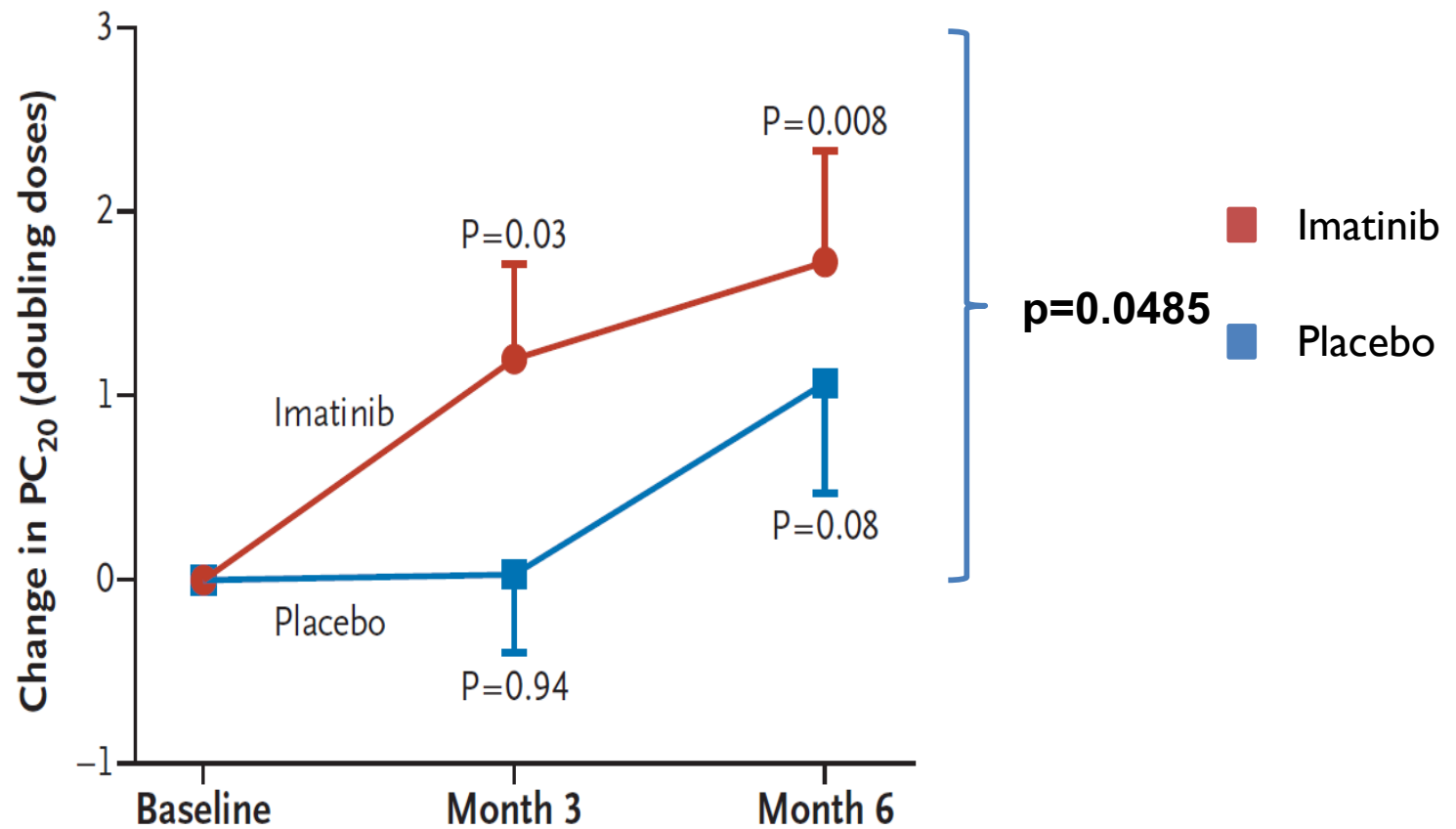


Pathways Involved in Severe Asthma

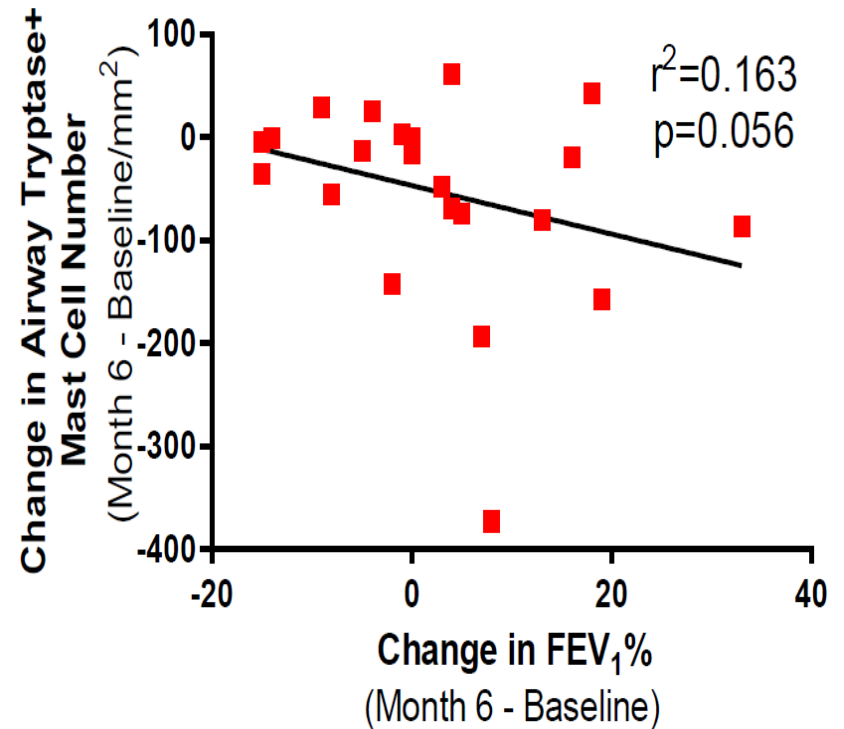
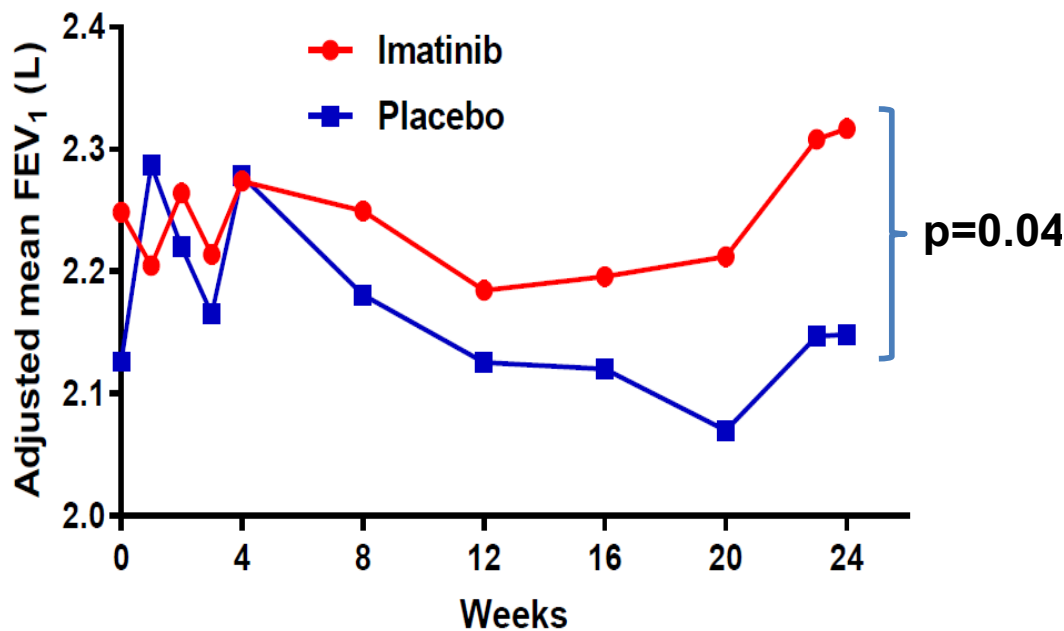


Israel & Reddel, NEJM, 2017

Imatinib Improved Airway Hyperresponsiveness in Patients with Severe Asthma

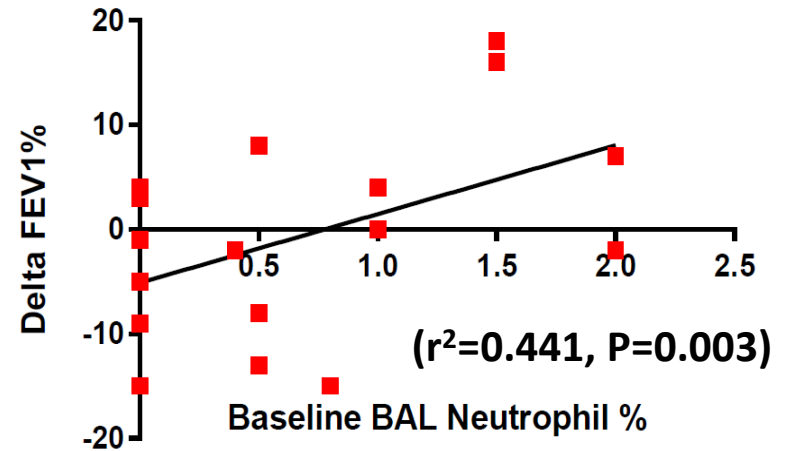
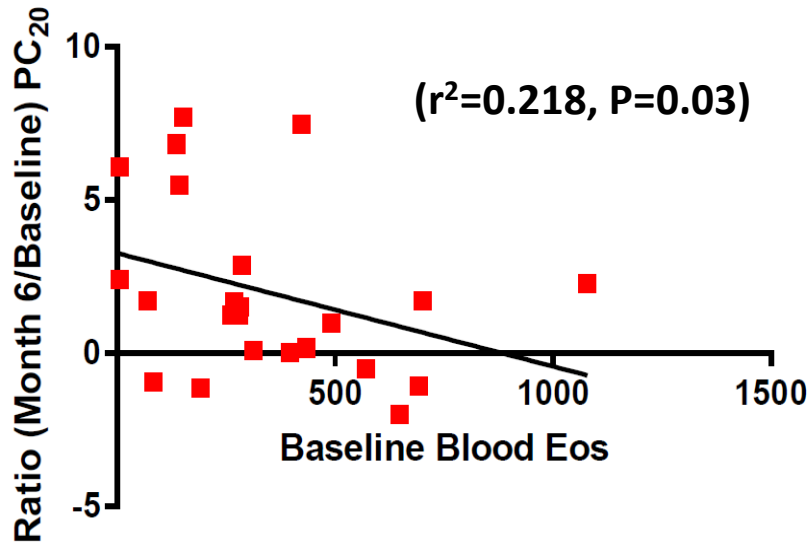


Imatinib Improved FEV₁ and Correlated with Decline in Airway Mast Cells



**Difference between groups:
46 mL (CI 36-56 mL)**

Imatinib was Most Effective in those with Reduced Evidence of T2 Inflammation



Imatinib

- Being studied in NIH Precision Medicine in Severe Asthma (PreclSE) network

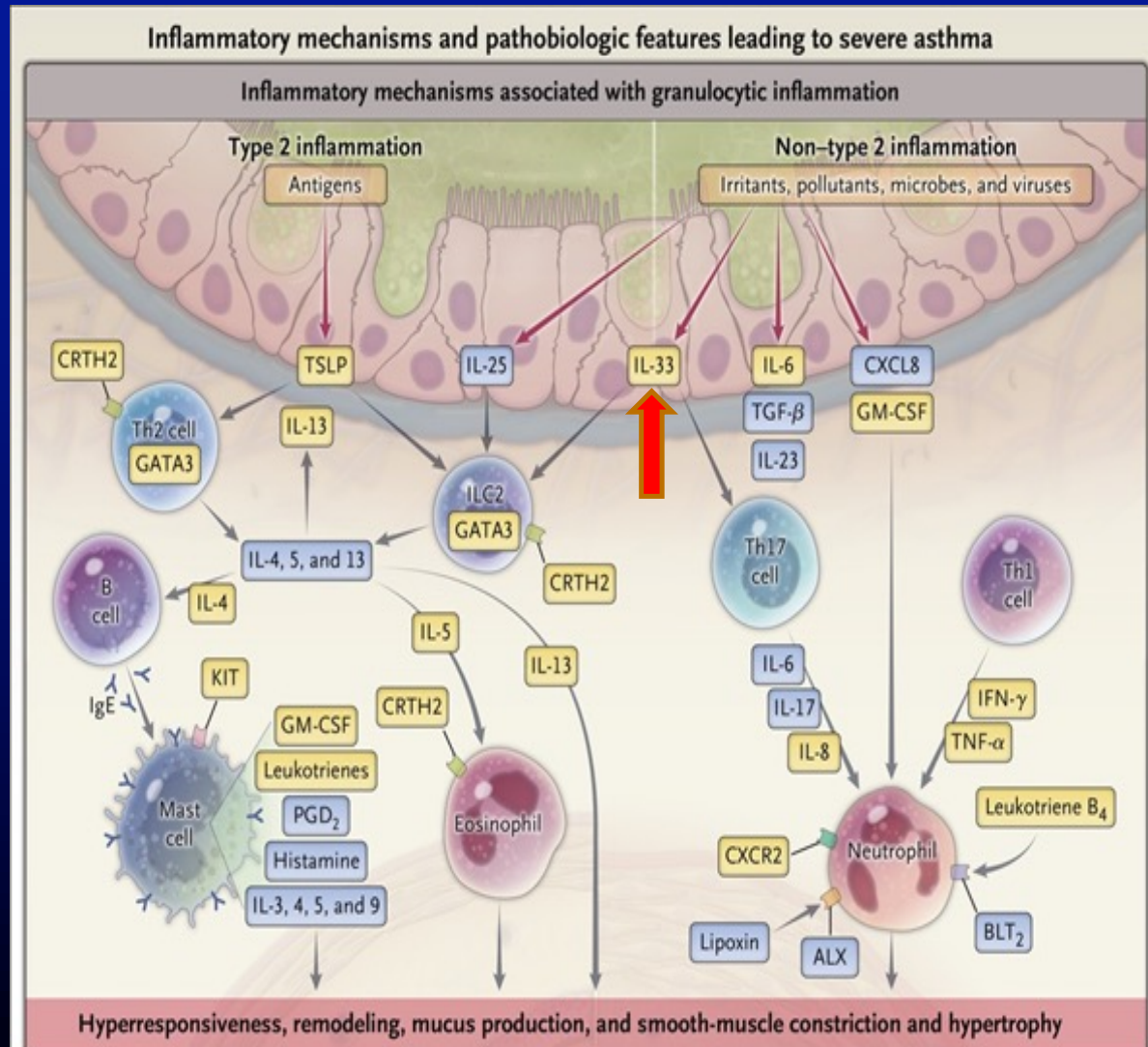


Masitinib

- Second generation tyrosine kinase inhibitor
- Company released results showing a decrease in exacerbations in patients with severe asthma on oral corticosteroids

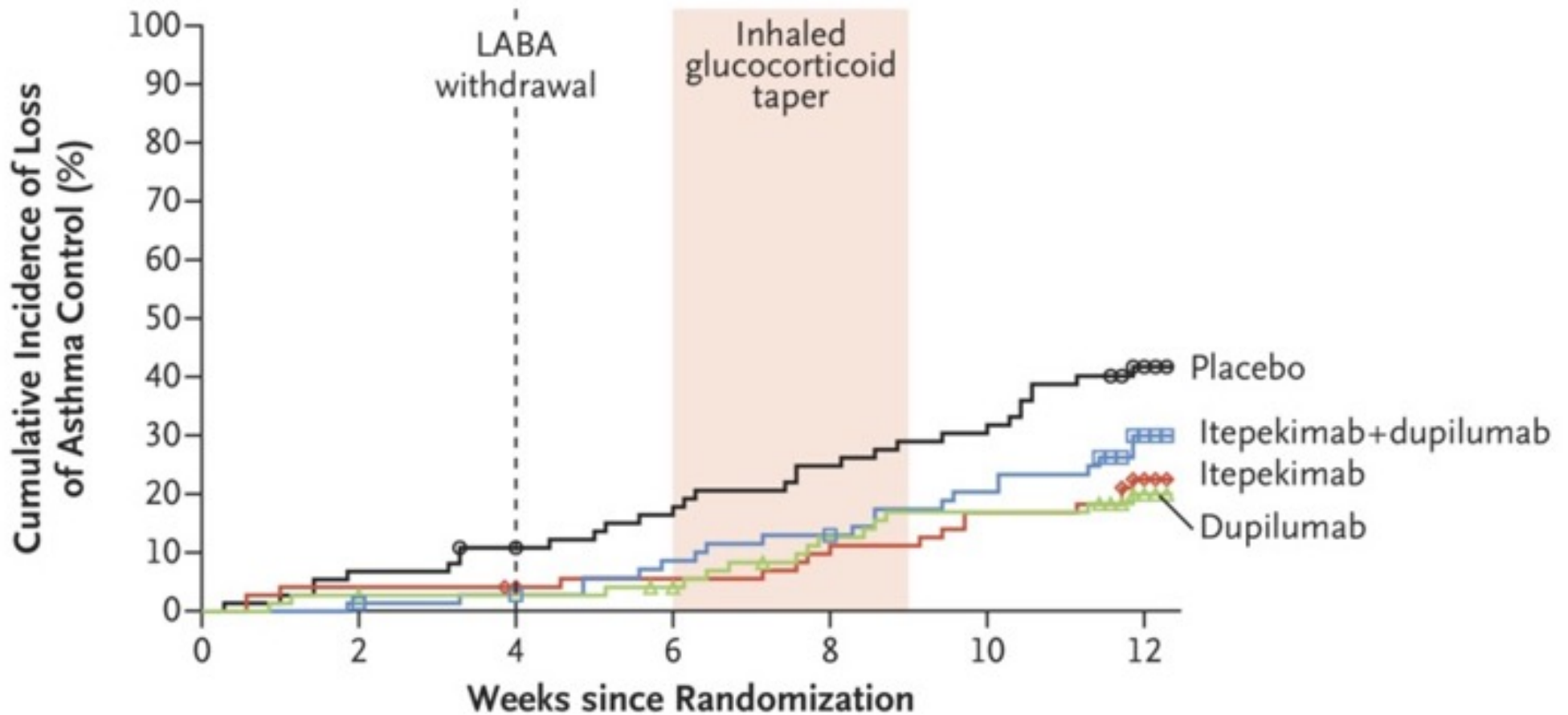


Pathways Involved in Severe Asthma



Israel & Reddel, NEJM, 2017

Anti-IL33 Reduced Time to Loss of Asthma Control to the Same Extent as Dupilumab & Was Not Additive



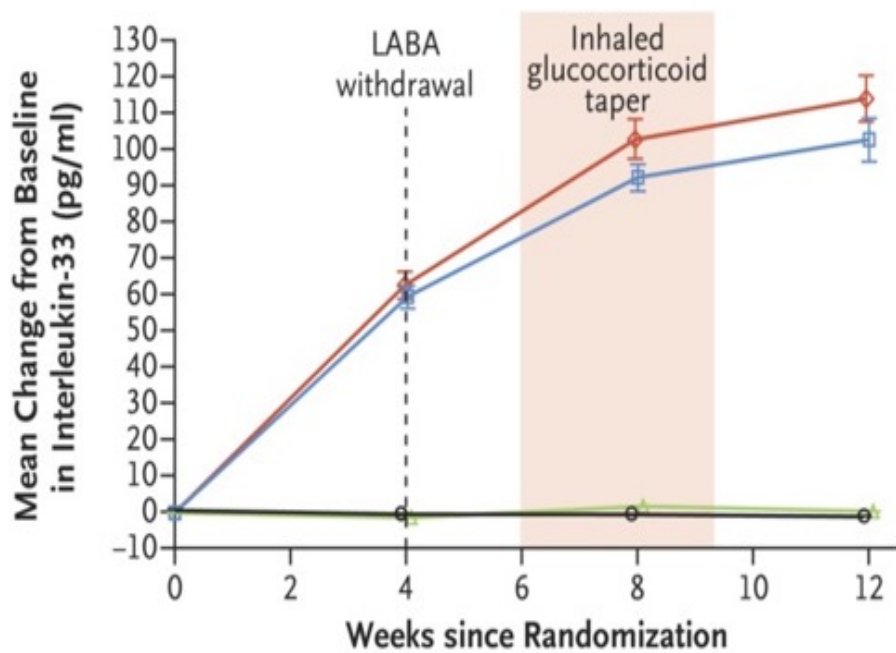
—●— Placebo —◇— Itepekimab —□— Itepekimab+dupilumab —△— Dupilumab



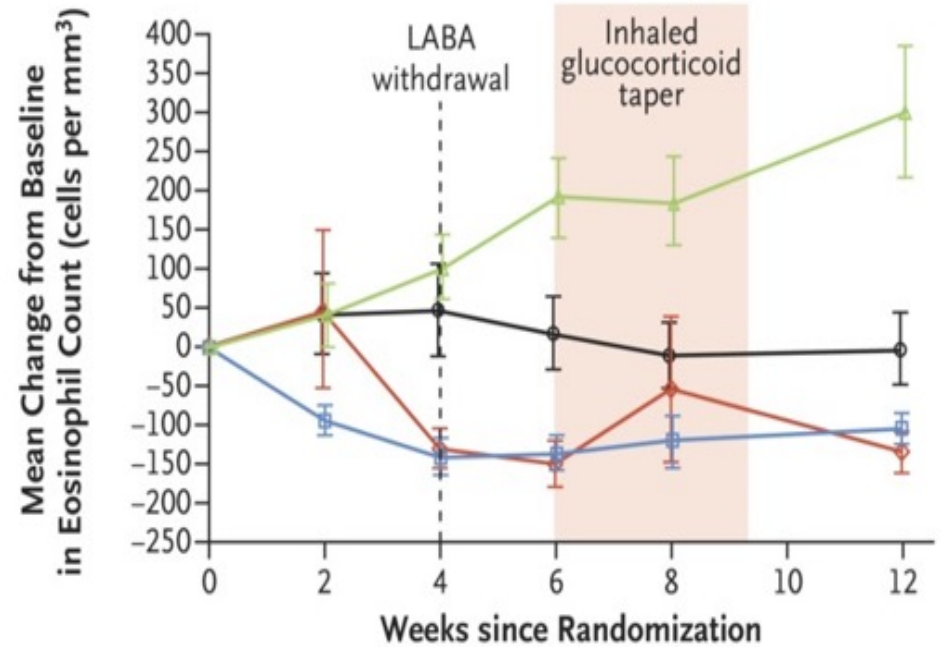
Wechsler ME et al. N Engl J Med 2021;385:1656-1668

Anti-IL33 Reduced Eosinophils

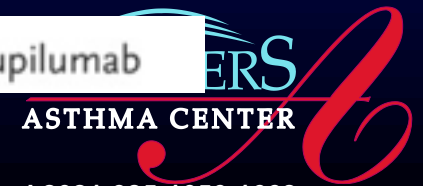
B Change in Total Interleukin-33 Level



C Change in Blood Eosinophil Count

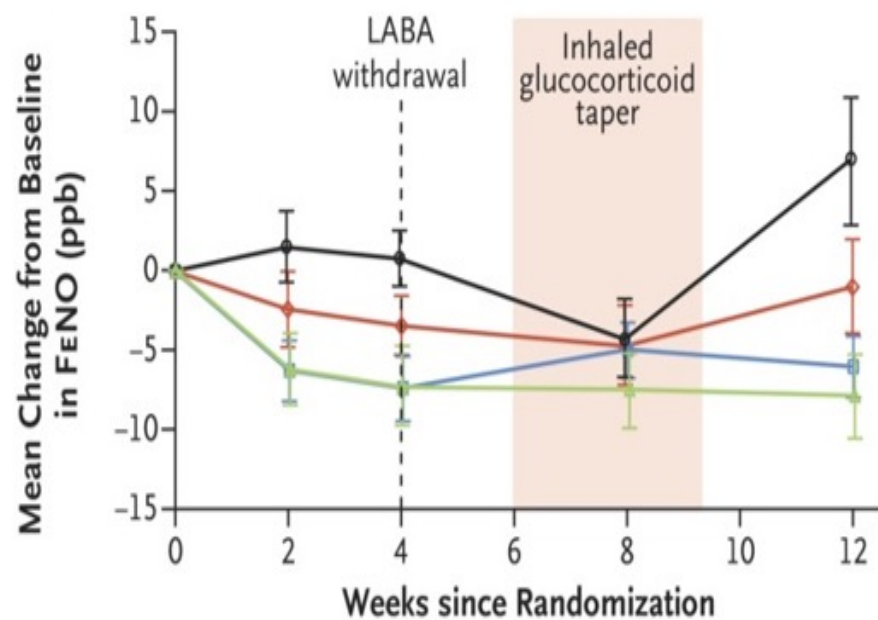


—○— Placebo —◇— Itepekimab —□— Itepekimab+dupilumab —△— Dupilumab

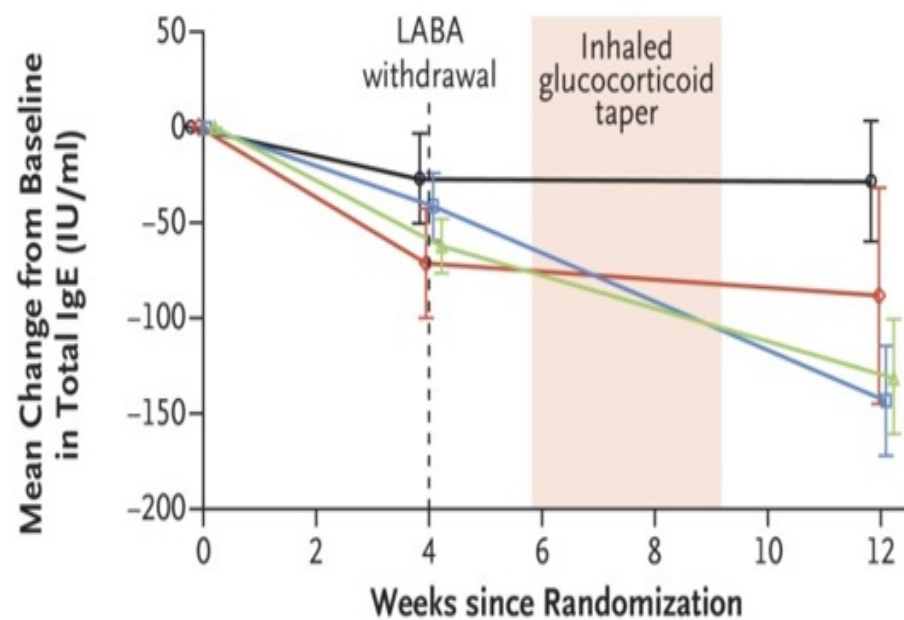


Anti-IL33 Appears to Have a Possible Effect on FeNO and IgE

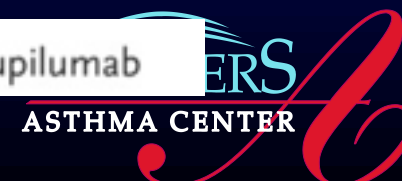
D Change in FeNO level



E Change in Total IgE Level



—●— Placebo —◇— Itepekimab —□— Itepekimab+dupilumab —△— Dupilumab

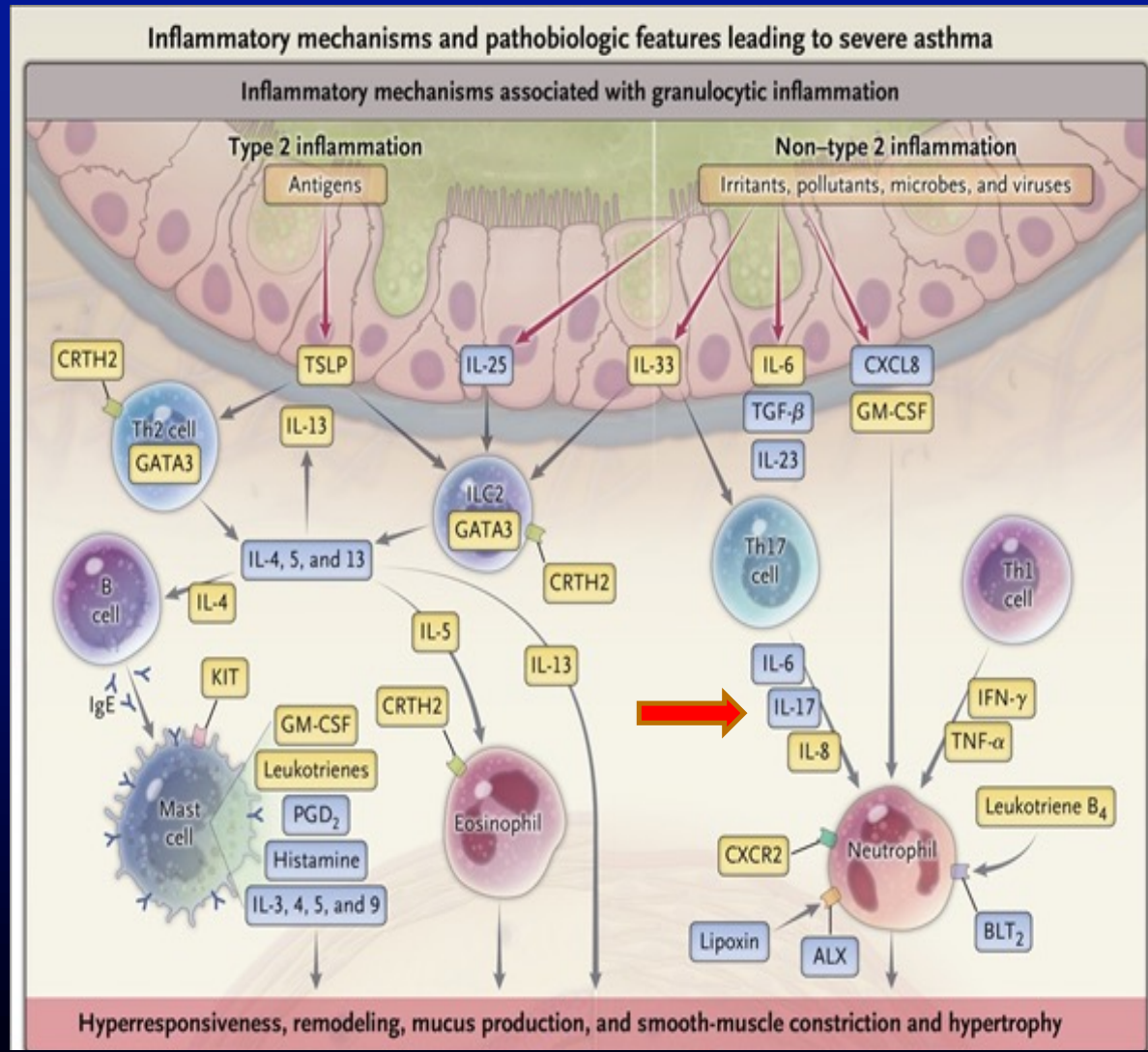


IL33

- The greatest improvement was seen in patients with eosinophils $\geq 300/\mu\text{l}$



Pathways Involved in Severe Asthma



Israel & Reddel, NEJM,

Anti-IL17RA

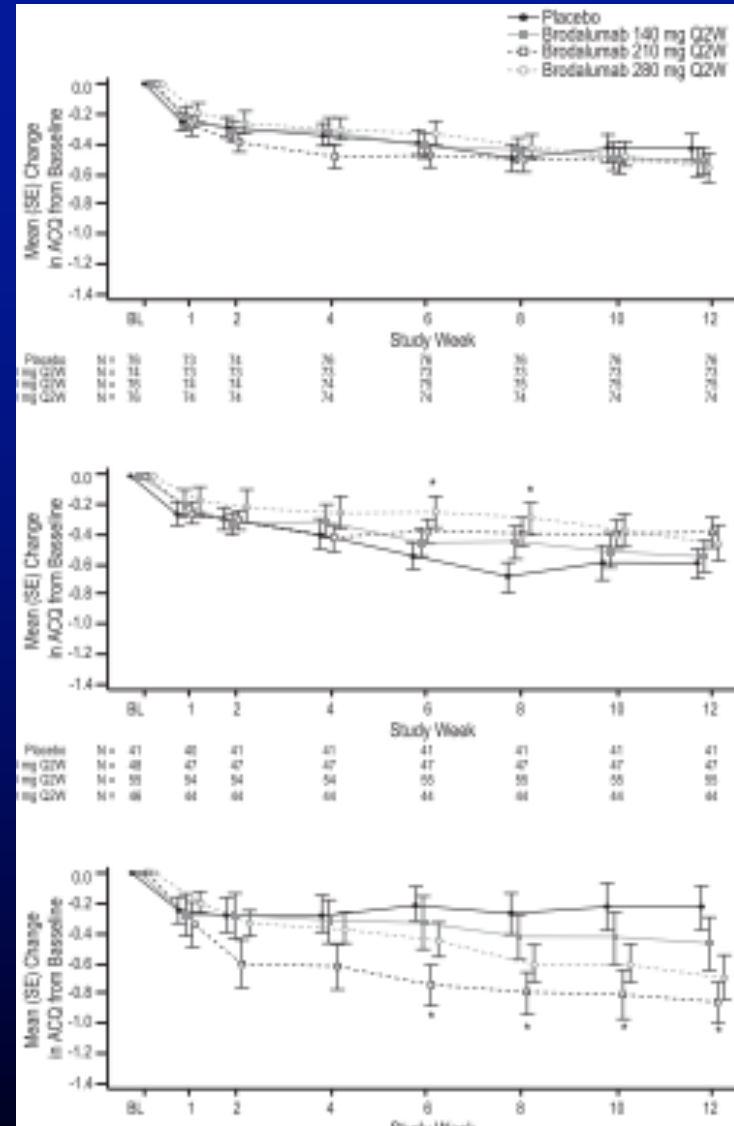
NO ACQ Response in Overall Population (Acq>1.5 on >200 ICS w/ >12% BDR and no required exacerbations)

Inconsistent Dose Trend in ACQ Response to Anti 17RA in Patient with >20% BDR

ALL

<20% BDR

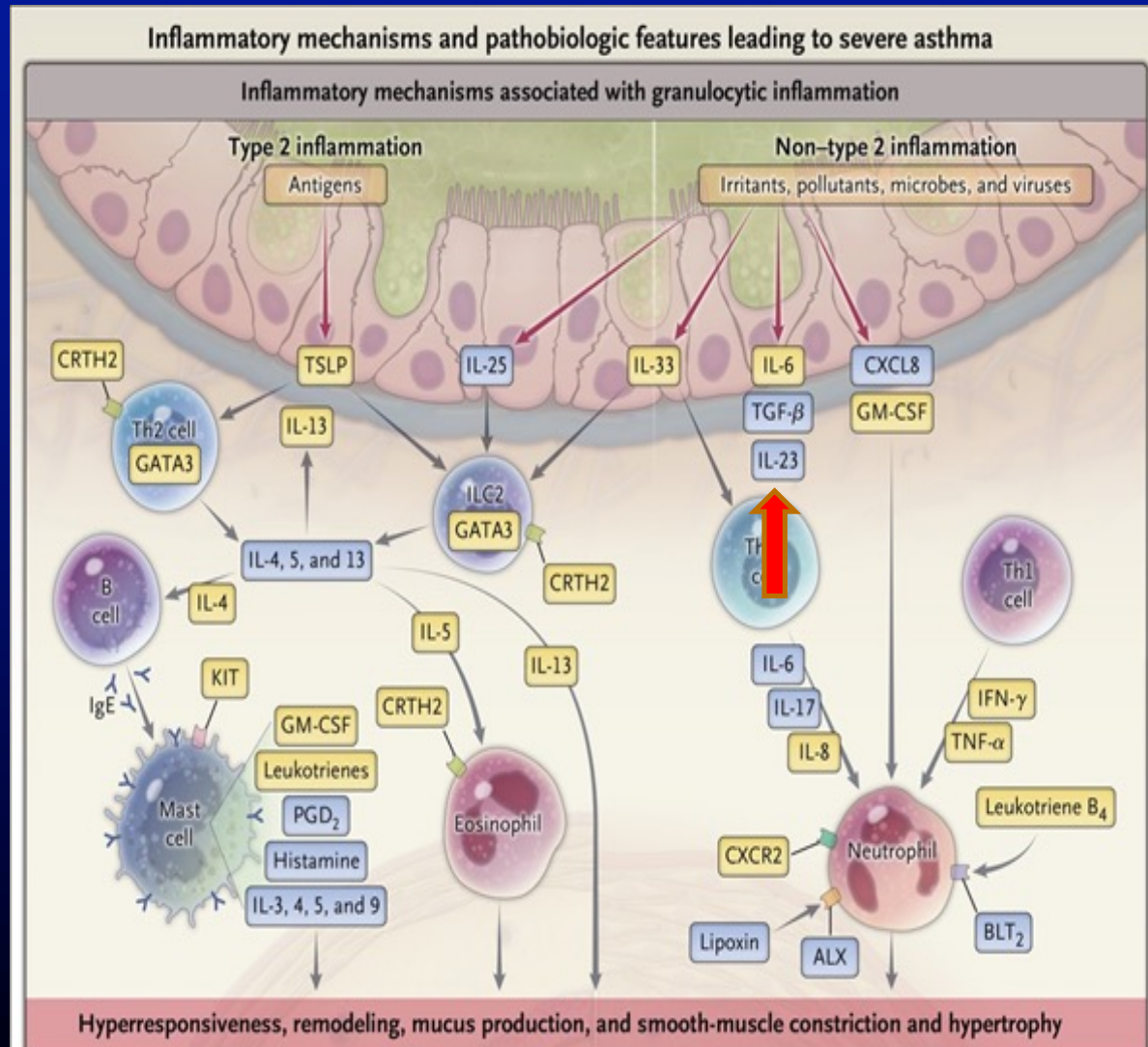
>20% BDR



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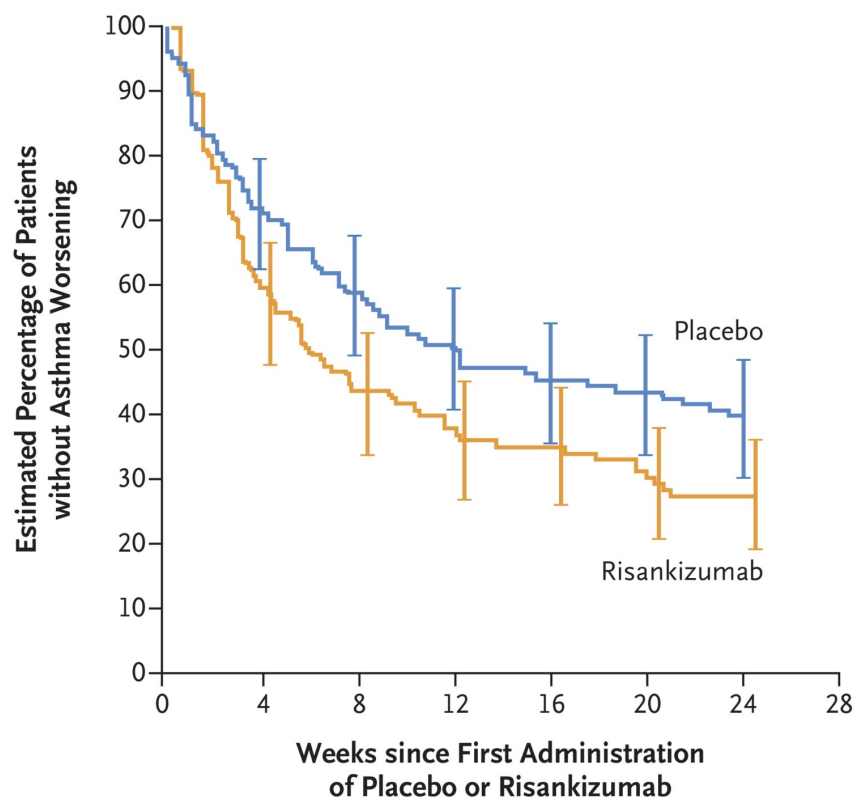
Busse, AJRCCM, 2013

Pathways Involved in Severe Asthma



Israel & Reddel, NEJM,

Annual Rate of Asthma Worsening was Increased by Anti-IL23

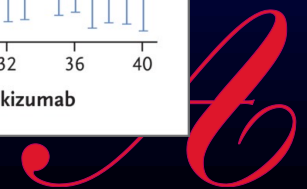
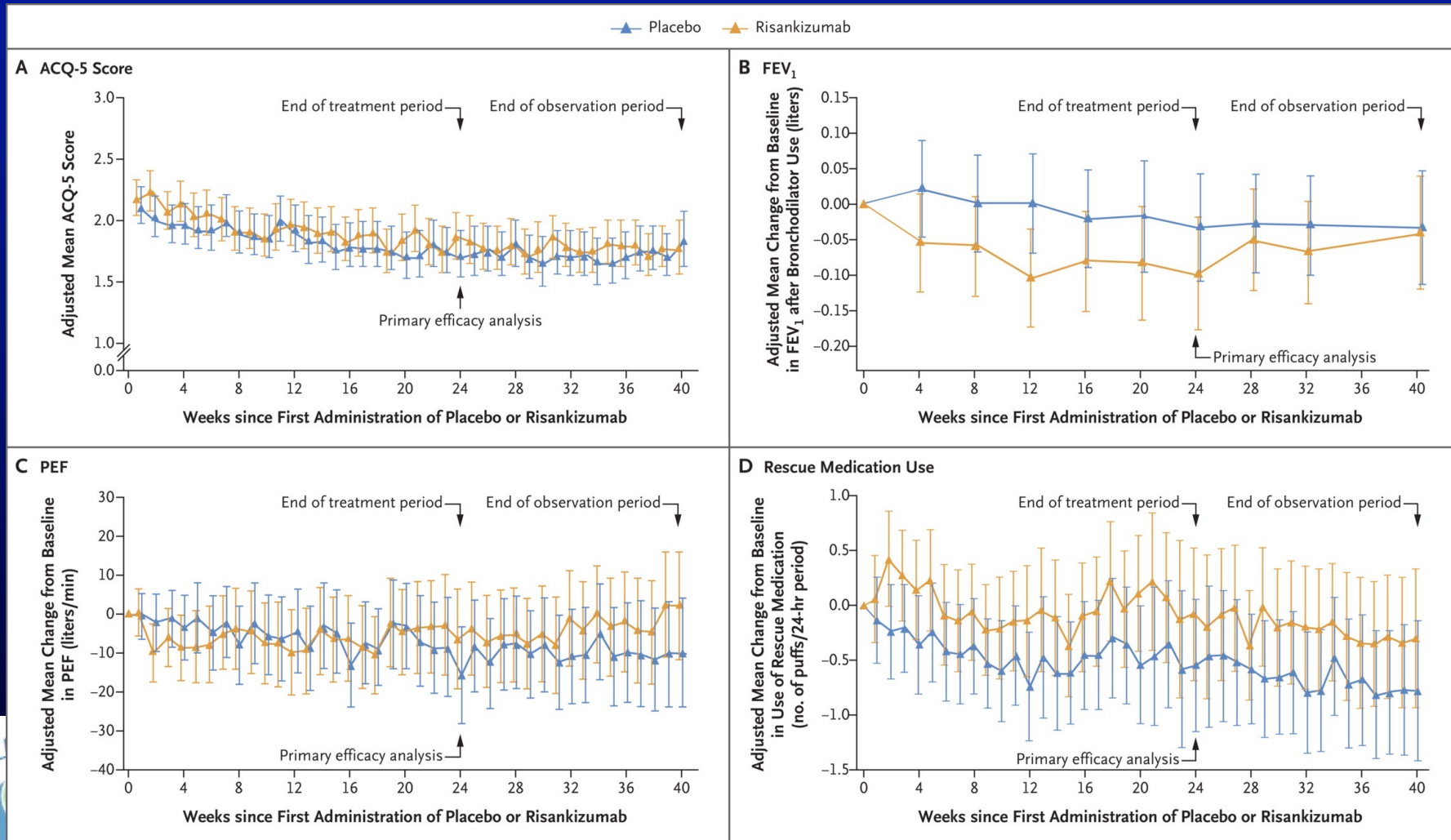


No. at Risk

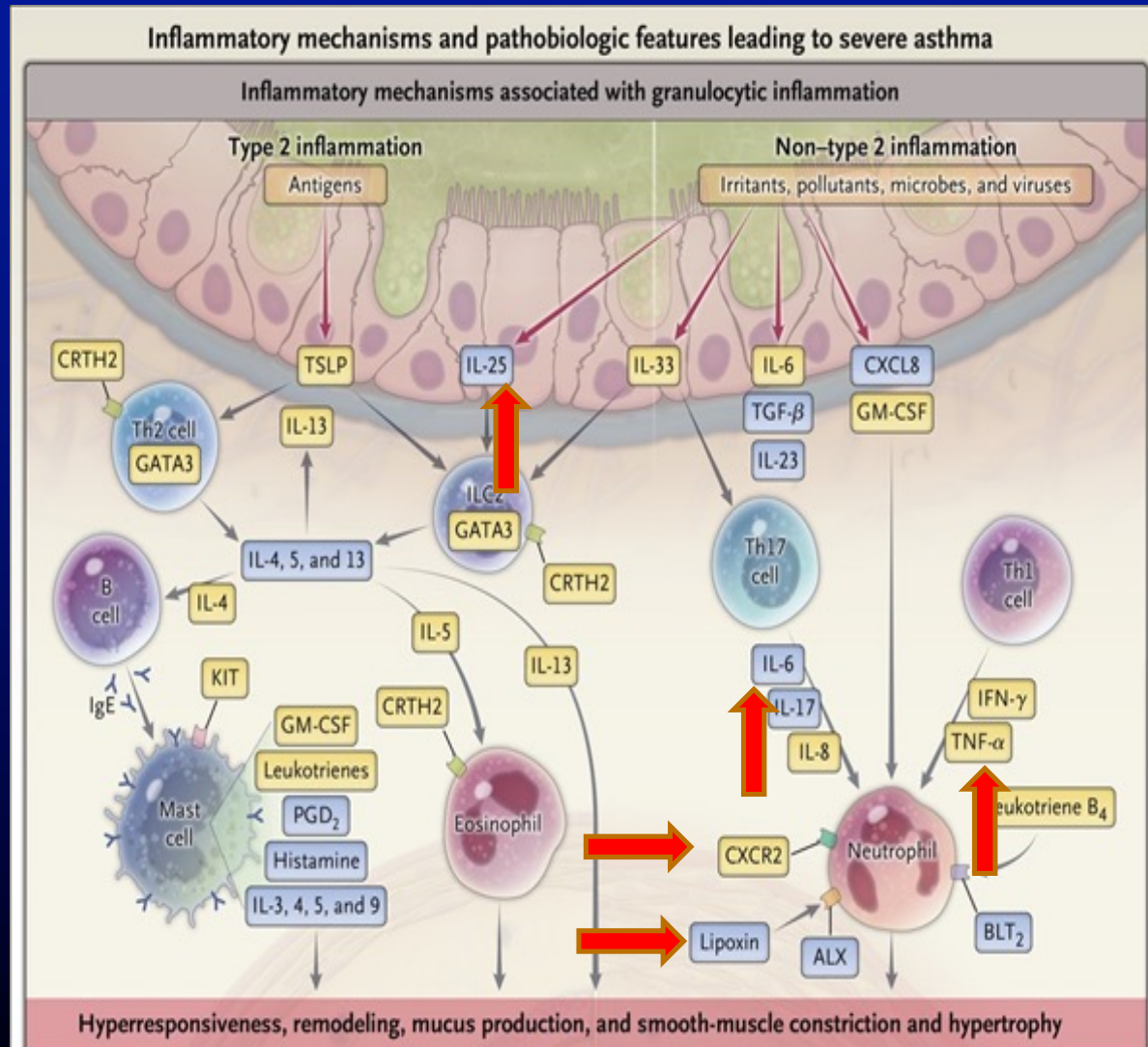
Placebo	109	78	64	55	49	47	43	0
Risankizumab	105	62	46	38	37	31	29	0



ACQ5, FEV₁, PEF, and Rescue Use were worse or no better with Anti-IL23



Pathways Involved in Severe Asthma



Israel & Reddel, NEJM,

Additional Phase 1 and Phase 2 Agents and Targets

- Azithromycin
- Targeting MUC5AC
- Targeting the JAK Kinases
- Targeting MMP 12 – macrophage elastase
- Administration of bacteria that downregulate T2 responses
- CGRP antagonists
- Anti-IL6
- Targeting)X40 Ligand expressed on memory T2 cells
- 8 expressed on eosinophils and mast cells



Additional Phase 1 and Phase 2 Agents and Targets

- FLAP antagonists
- GLP1 receptor antagonists in obesity-related asthma
- LIGHT (Lymphotoxin-like, exhibits Inducible expression, and competes with Herpes Virus Glycoprotein D for Herpesvirus Entry Mediator (HVEM), a receptor expressed by T lymphocytes). –
- Rilzabrutinib, an oral, reversible covalent inhibitor of Bruton's tyrosine kinase,
- Targeting β_c , CD131- receptor β common for -signaling cytokines interleukin (IL)-3, granulocyte-macrophage colony stimulating factor (GM-CSF) and IL-5 (
- CXA10 - an endogenous nitro-fatty acid (NFA) modulator of Nrf2 and NF- κ B in obesity associated asthma
- SM17 - monoclonal antibodies targeting IL17BR blocking IL17B and E
- -Anti-Siglec



Summary

- Additional therapies targeting Type 2 pathway are being developed
- The greatest unmet need persists in non-Type 2 disease

