New/emerging Therapies for Refractory Severe Asthma

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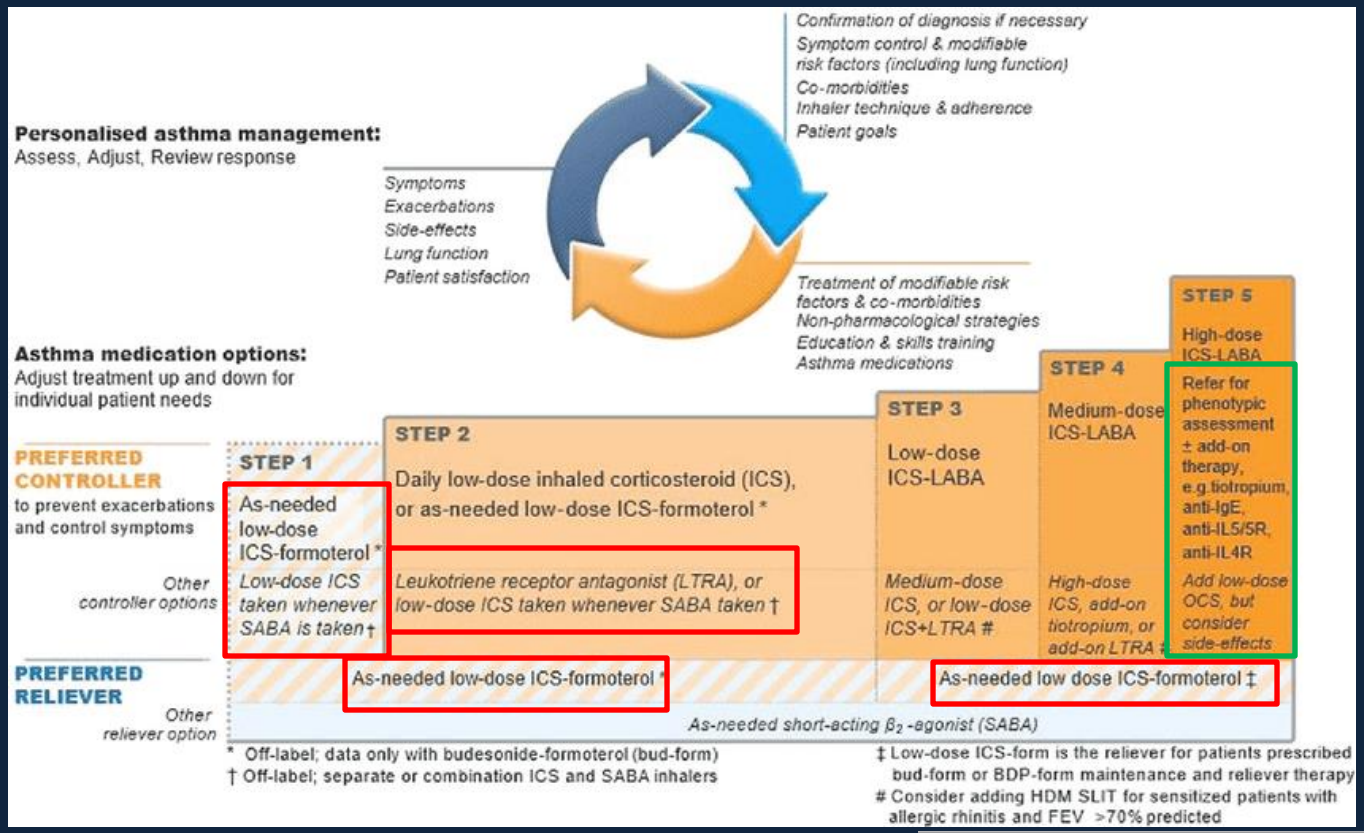
Today's talk will discuss numerous medications used to treat severe asthma.

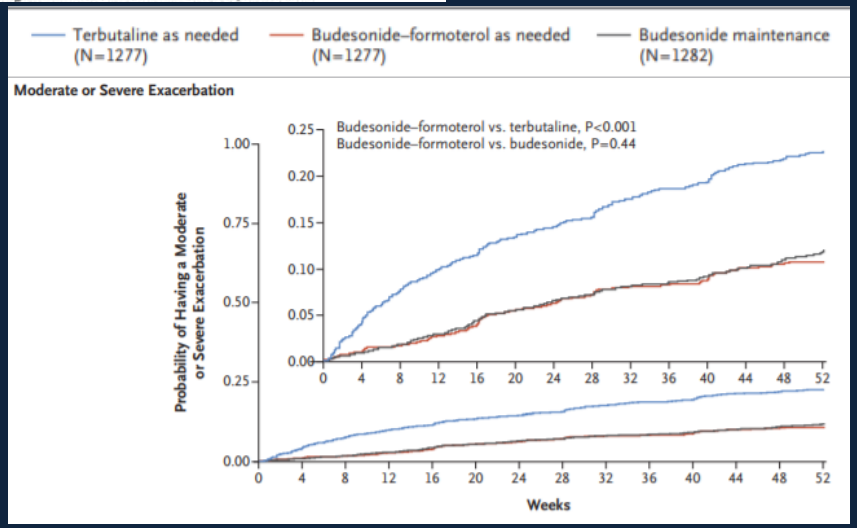
I have no financial conflicts or interests in any of the companies making these drugs.

Today's update in asthma therapies will:

1. Touch on major changes in recent asthma guidelines regarding rescue medications
2. Discuss asthma phenotypes
3. Discuss add-on therapies/biologics for severe type 2 asthma
4. Discuss progress and future directions in non-type 2 asthma

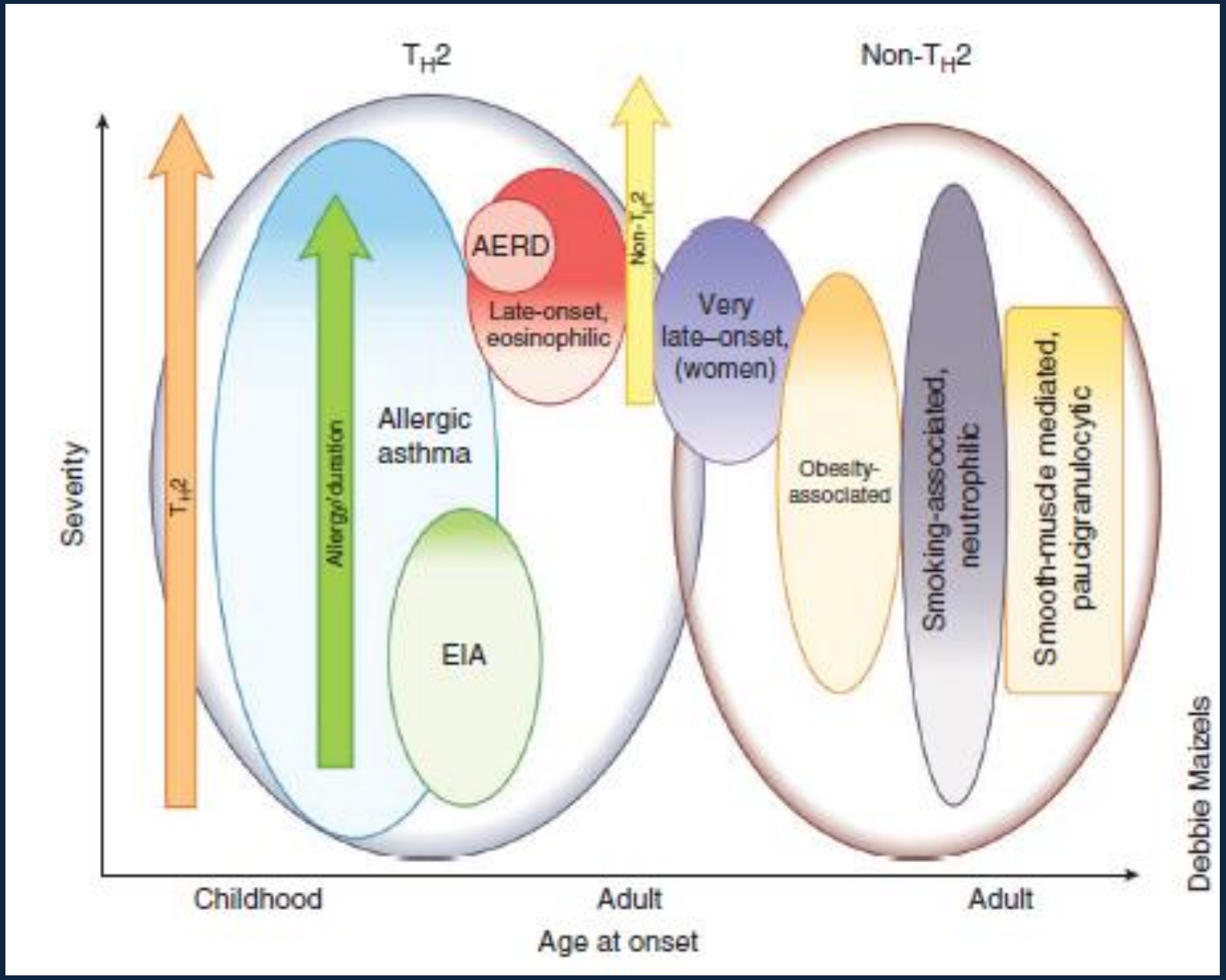


Global Initiative for Asthma (GINA) 2019



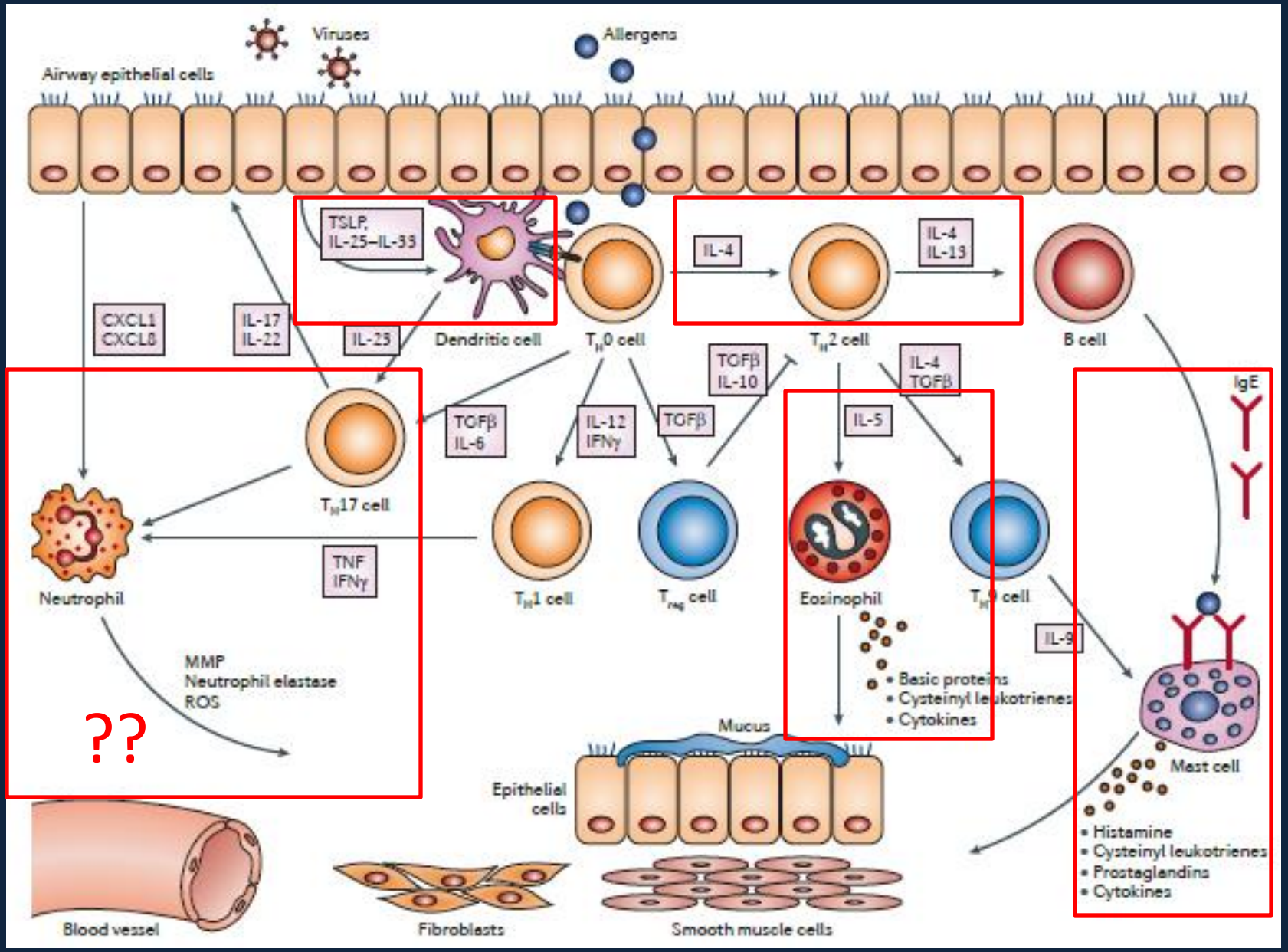
O'Byrne PM et al 2018 NEJM

Asthma Phenotypes



Wenzel, SE 2012 Nature Medicine

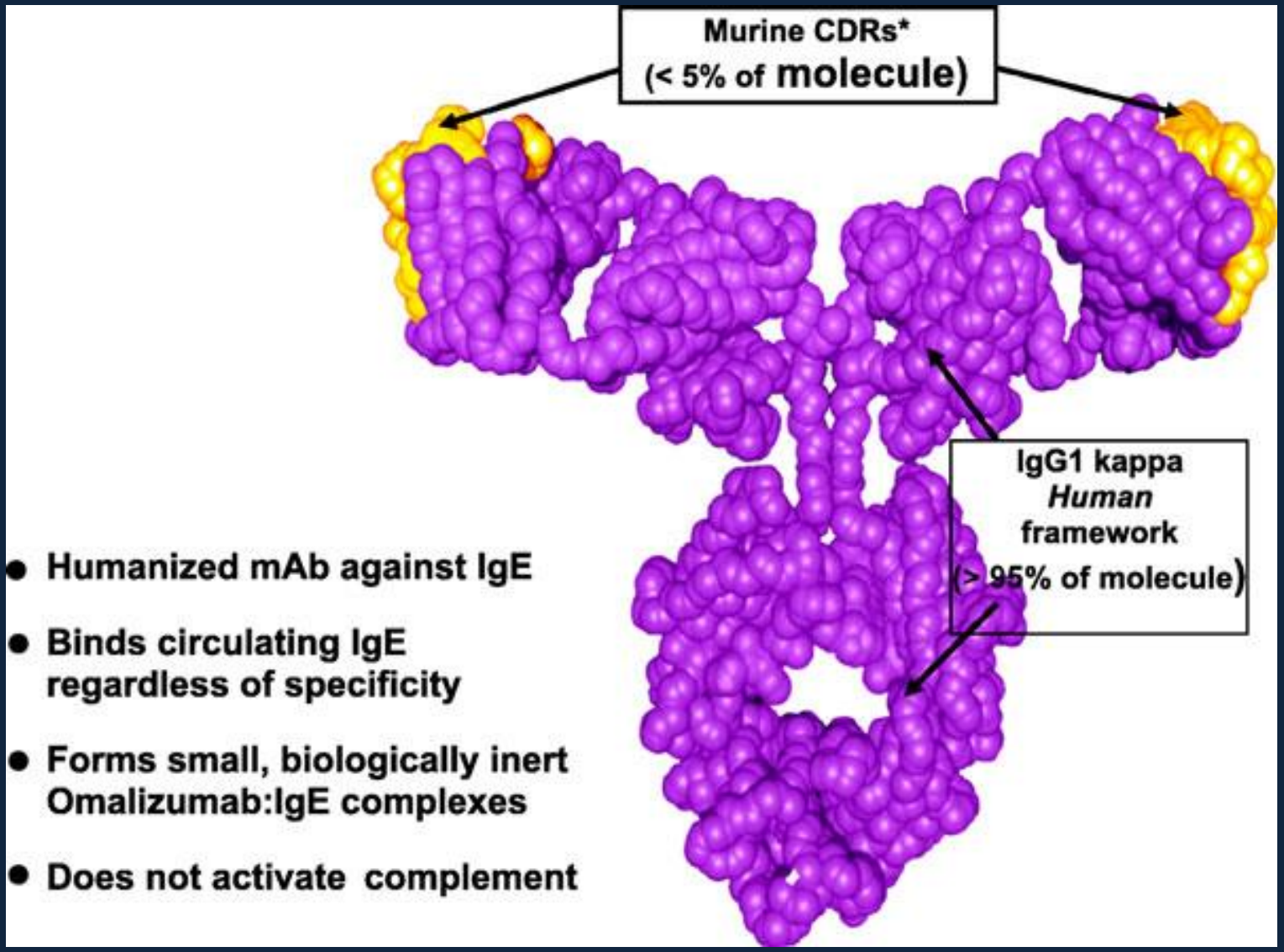
Asthma Immunobiology and Therapeutic Targets



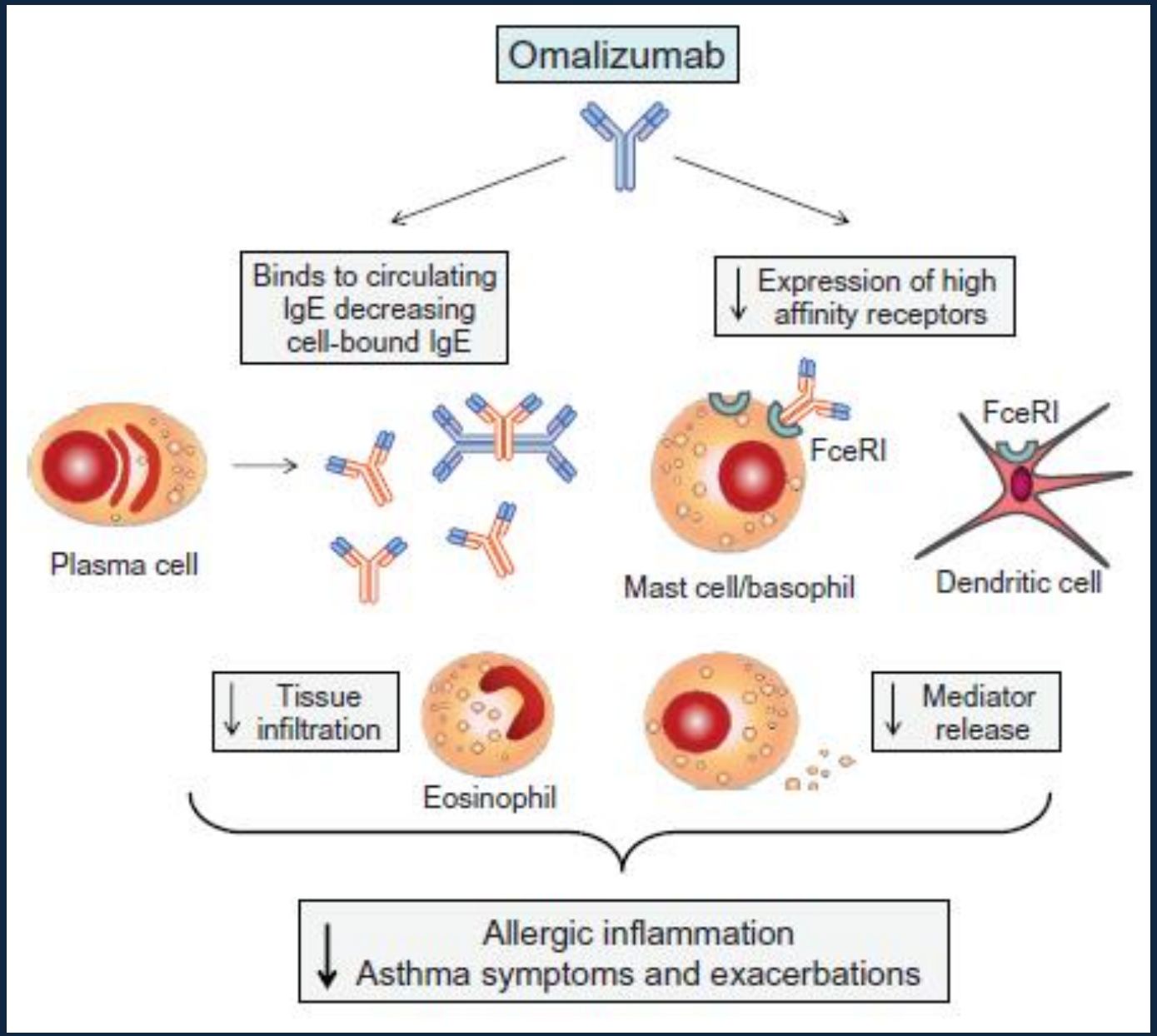
Pelaia G et al 2012 Nat Rev Drug Disc

Targeted Therapies for Severe TH2/Type 2 Asthma

Xolair (Omalizumab)

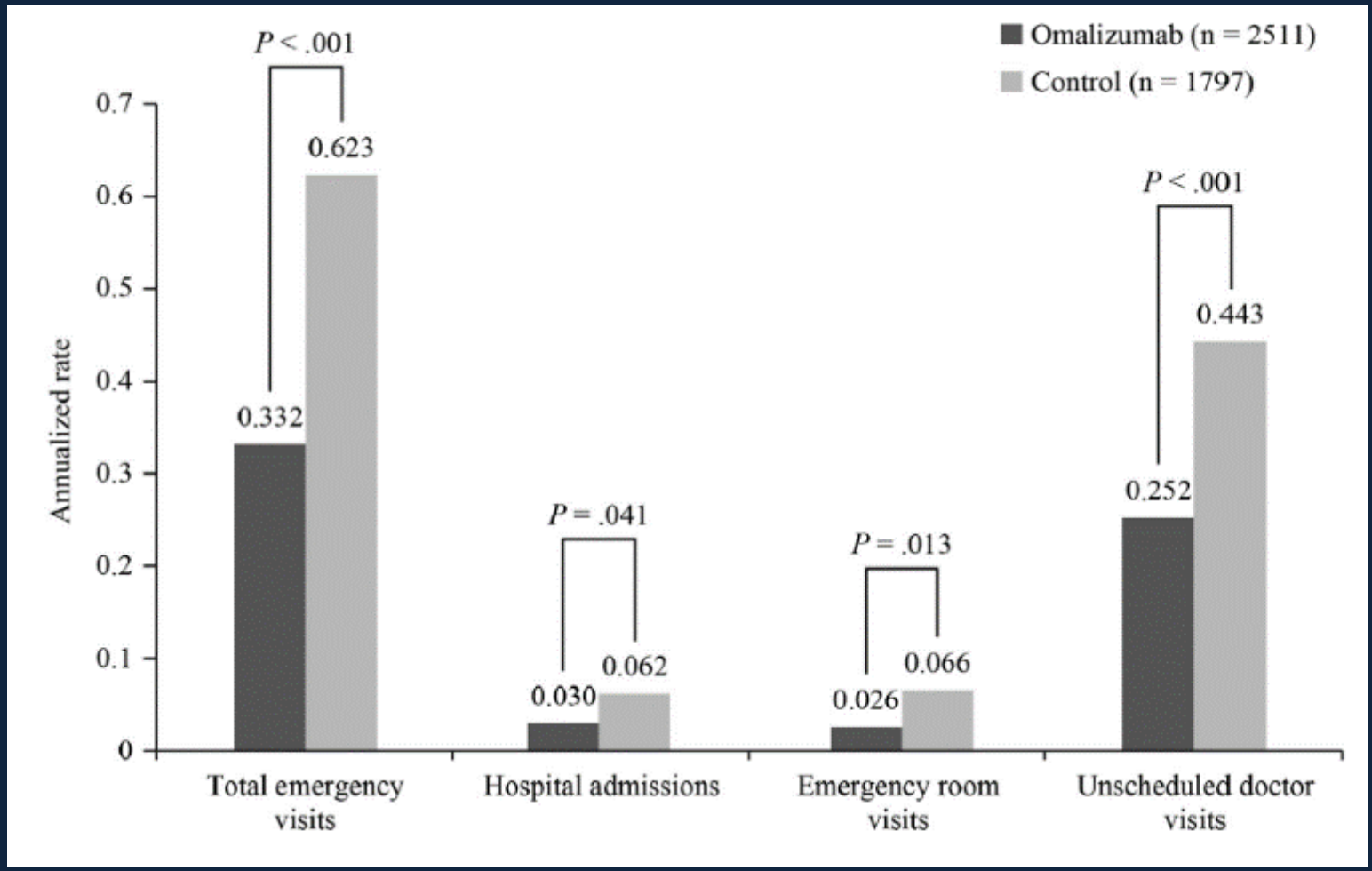


Segal M et al 2008 WAO Journal



Pelaia G et al 2011 Journal of Asthma and Aller

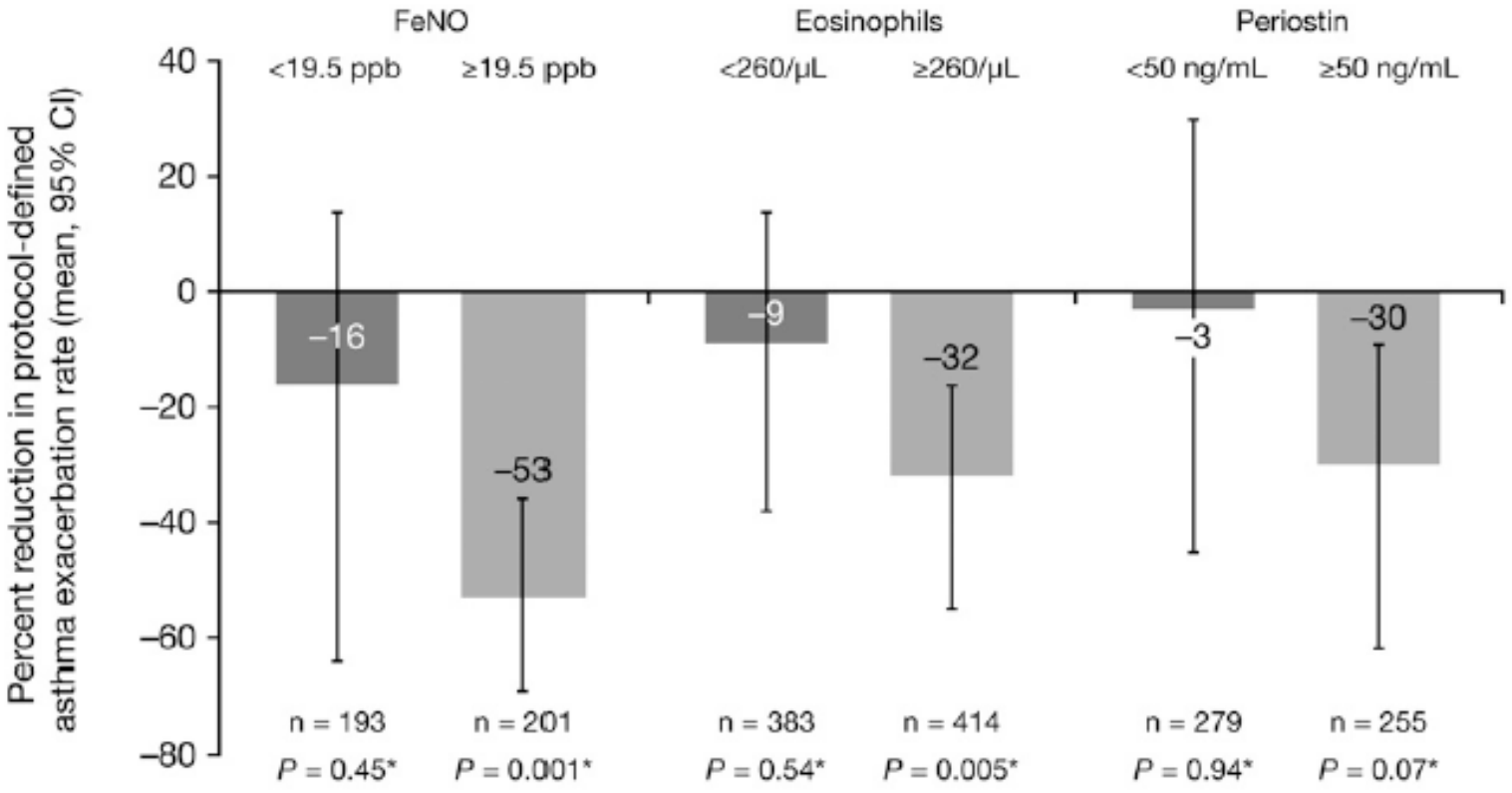
Omalizumab significantly reduces exacerbation rates



Incidence rates of asthma exacerbations and health care visits for the pooled population of patients in 7 randomized trials of omalizumab (n = 4308) by Poisson regression analysis

Humbert M et al 2014 JACI in Practice

Omalizumab efficacy correlates with TH2 biomarkers



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

Hanania NA 2013 Am J Resp Crit Care Med

Prescribing Omalizumab (Xolair)

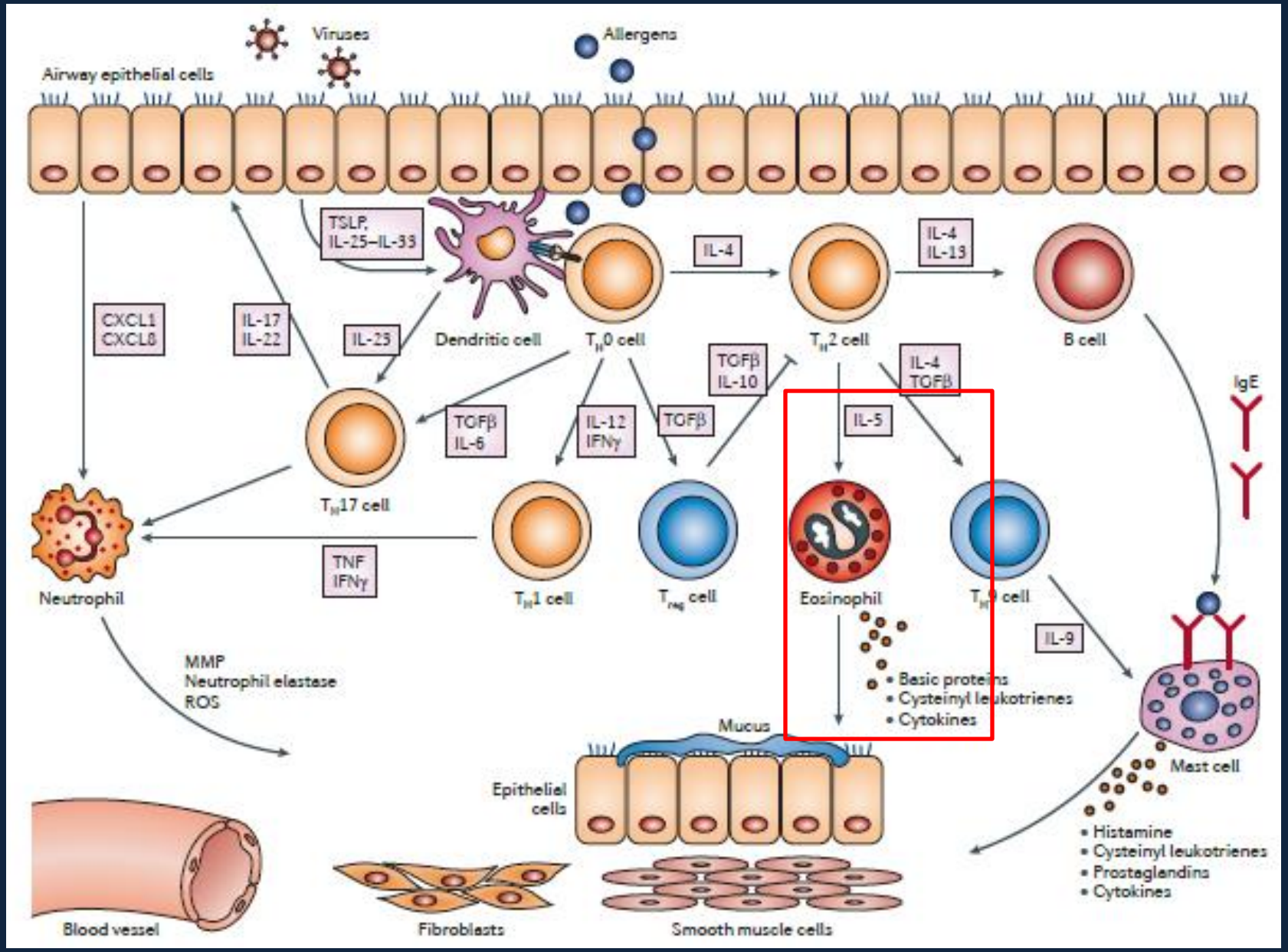
- 12 yrs old or older (recent approval for ages 6 and up!)
- Moderate-Severe persistent asthma (adjunctive therapy in GINA step 5/6)
- Total IgE 30-700
- Sensitized to a perennial allergen (ex dust mite, animal dander, cockroach, mold)

Given as 150mg – 375mg subcutaneously every 2-4 weeks

Adverse reactions:

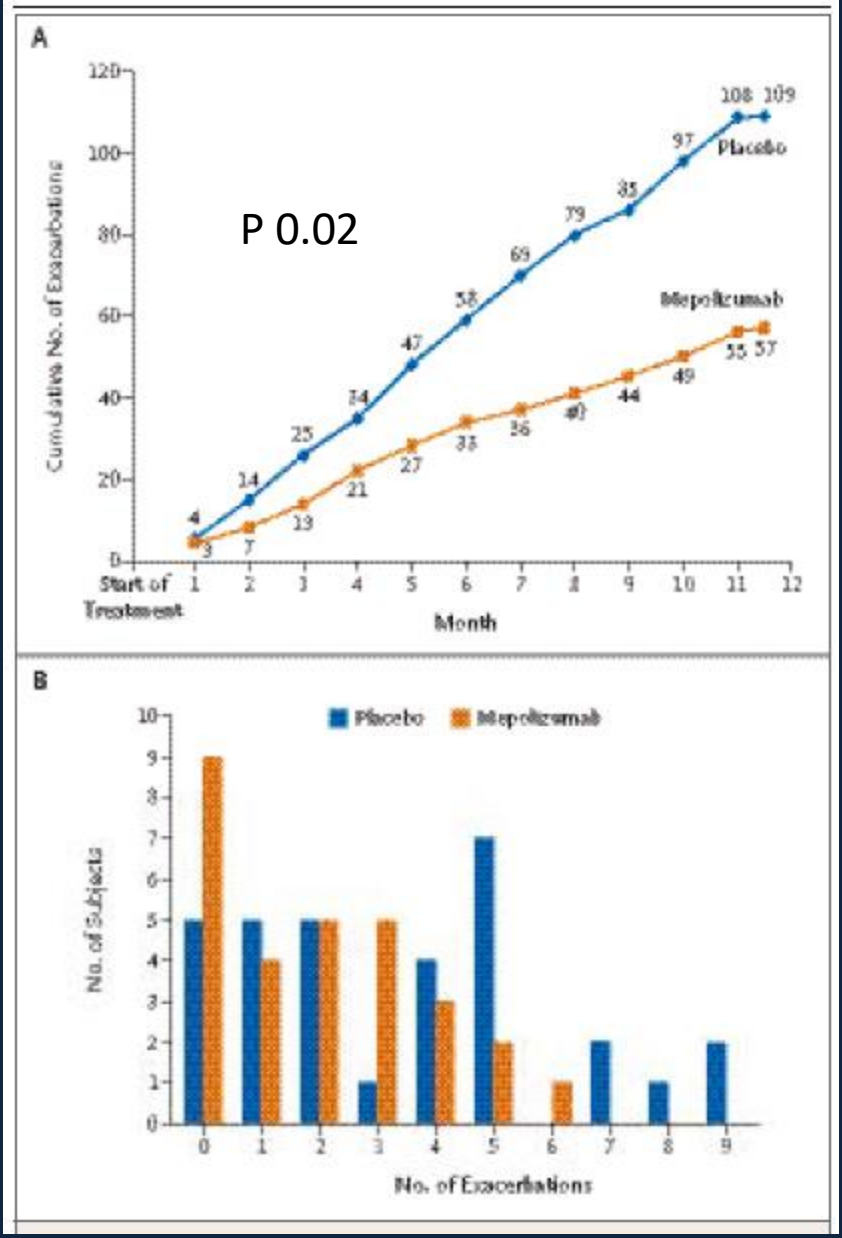
- Anaphylaxis (1-2/1000, lower than other biologics) – 3hr obs after 1st 3 doses, epi pen
- Malignancies (skin, breast, prostate) – NO per EXCELS study
- Cardiovascular (MI, UA, CVA, TIA, CV death) - HR 1.32 per EXCELS study

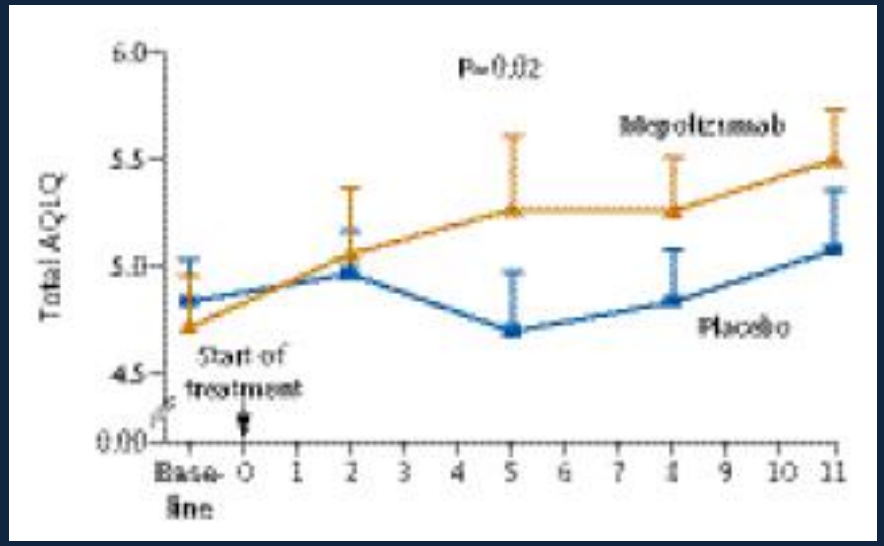
Asthma Immunobiology and Therapeutic Targets

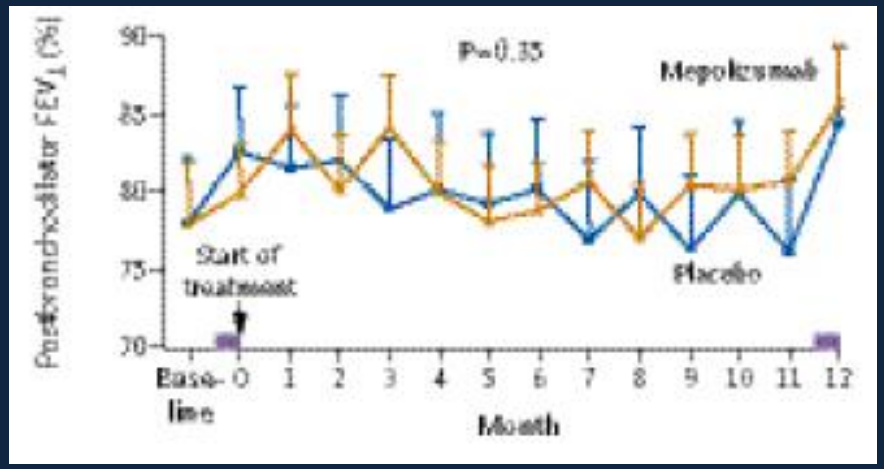


Pelaia G et al 2012 Nat Rev Drug Disc

Mepolizumab in severe *eosinophilic* asthma







Haldar P et al 2009 NEJM

Mepolizumab reduces the need for systemic glucocorticoids in severe eosinophilic asthmatics

Table 2. Primary and Secondary Outcomes.

Outcome	Placebo (N=66)	Mepolizumab (N=69)	Odds Ratio (95% CI)*	P Value
Reduction in oral glucocorticoid dose at 20 to 24 wk: primary outcome — no. (%)†			2.39 (1.25–4.56)	0.008
90 to 100%	7 (11)	16 (23)		
75 to <90%	5 (8)	12 (17)		
50 to <75%	10 (15)	9 (13)		
>0 to <50%	7 (11)	7 (10)		
No decrease in oral glucocorticoid dose, a lack of asthma control, or withdrawal from treatment	37 (56)	25 (36)		
Secondary outcomes				
Reduction in daily oral glucocorticoid dose of ≥50% — no. (%)‡	22 (33)	37 (54)	2.26 (1.10–4.65)	0.03
Reduction in daily oral glucocorticoid dose to a level ≤5 mg — no. (%)‡	21 (32)	37 (54)	2.45 (1.12– 5.37)	0.02
Reduction of 100% in oral glucocorticoid dose — no. (%)‡	5 (8)	10 (14)	1.67 (0.49–5.75)	0.41
Median percent reduction from baseline in daily oral glucocorticoid dose (95% CI)§	0.0 (–20.0 to 33.3)	50.0 (20.0 to 75.0)	NA	0.007

Bel E et al 2014 NEJM

Mepolizumab (NUCALA) FDA approved

- Add-on therapy for severe/refractory asthma with an eosinophilic phenotype (300/ul or more during prior 12 months or 150/ul or more at time of eval).

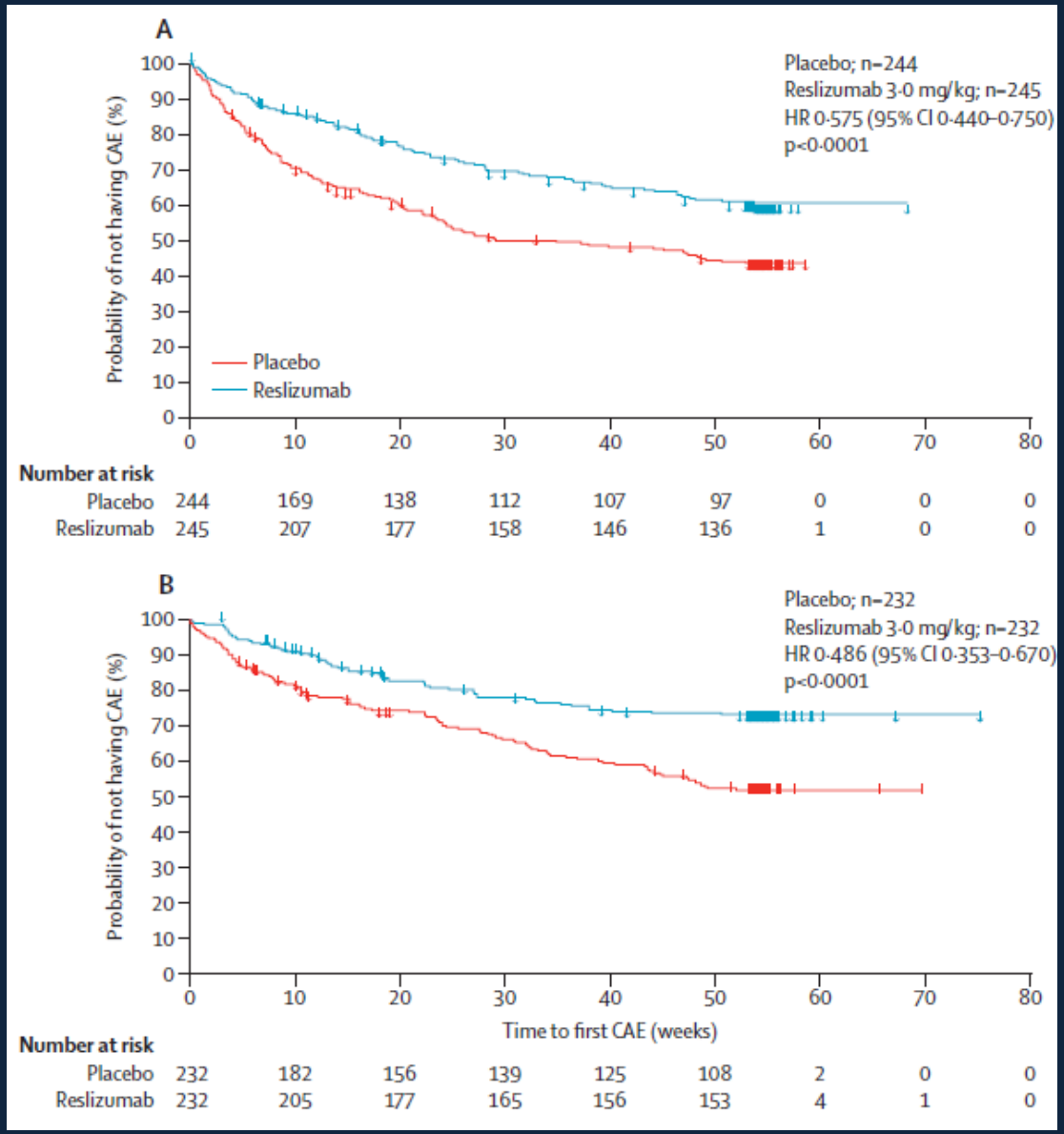
- Ages 12 and up

- 100mg subcutaneously every 4 weeks

- Headache, injection site pain and rare hypersensitivity reactions
- Zoster? Listed as Opportunistic infection. 2 patients (total) versus zero in placebo controls.
- Vaccinate if clinically indicated.

- Now approved at 300mg/month for EGPA

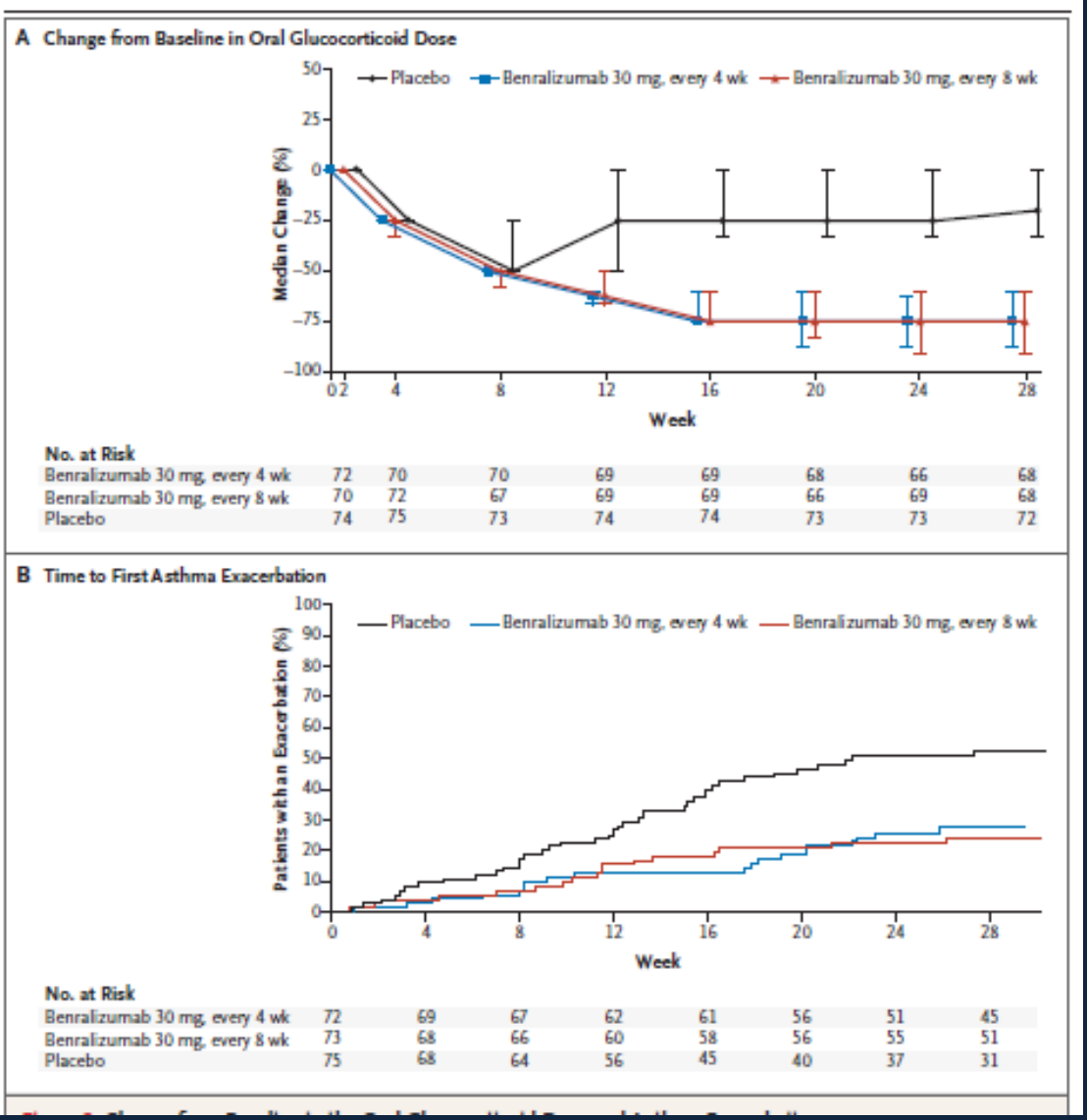
Another anti-IL5 option: Reslizumab (CINQAIR)



- IV delivery
- Monthly infusion
- Similarly efficacious
- **0.3% rate of anaphylaxis**

Castro M et al 2015 Lancet Respir Med

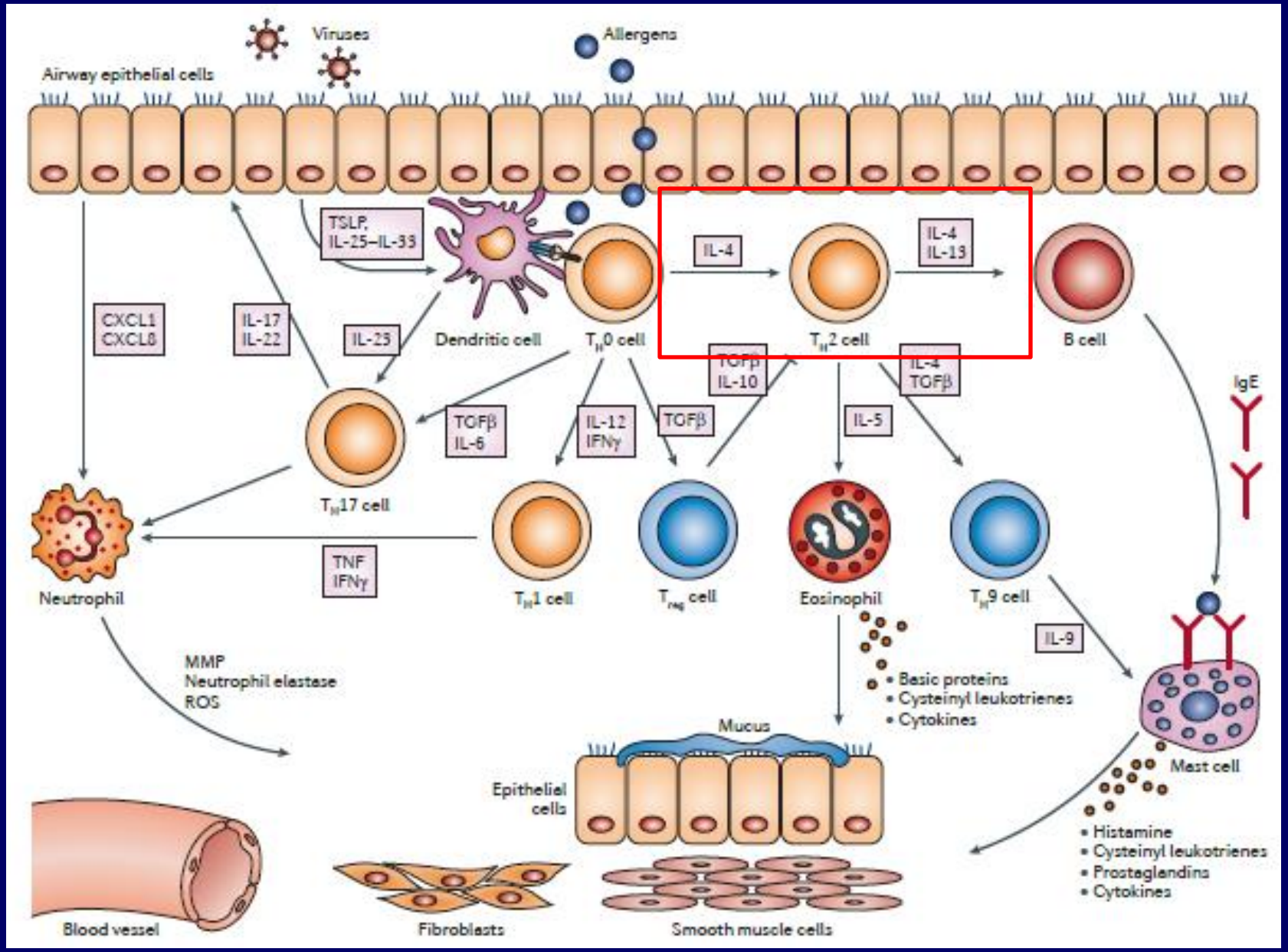
Another anti-IL5 option: Benralizumab (Fasenra)



- De-fucosylated humanized **anti-IL5ra**
- Targets eos (and baso's) for NK cell-mediated lysis (ADCC)
- Fast reduction in eosinophils
- 30mg SQ every 4 weeks for 3 doses, then every 8 weeks

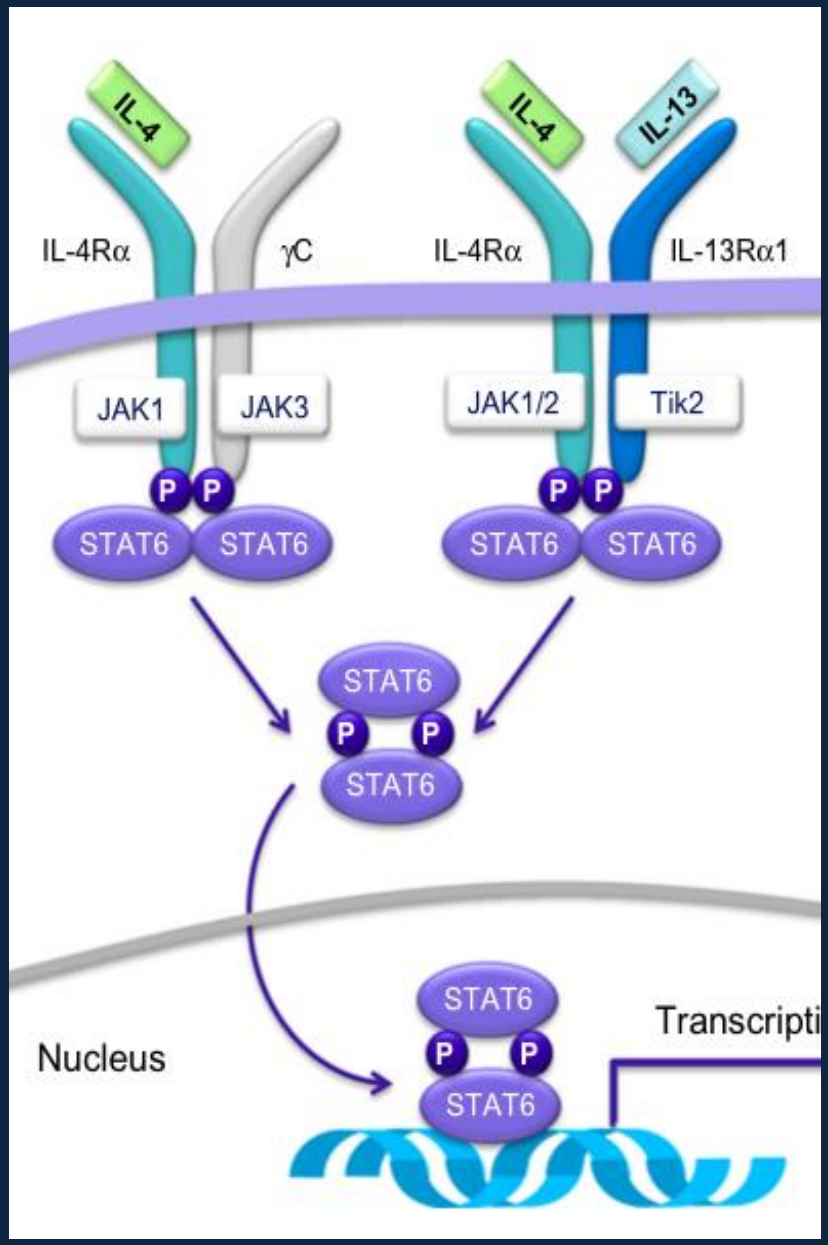
Nair P et al 2017 NEJM

Asthma Immunobiology and Therapeutic Targets

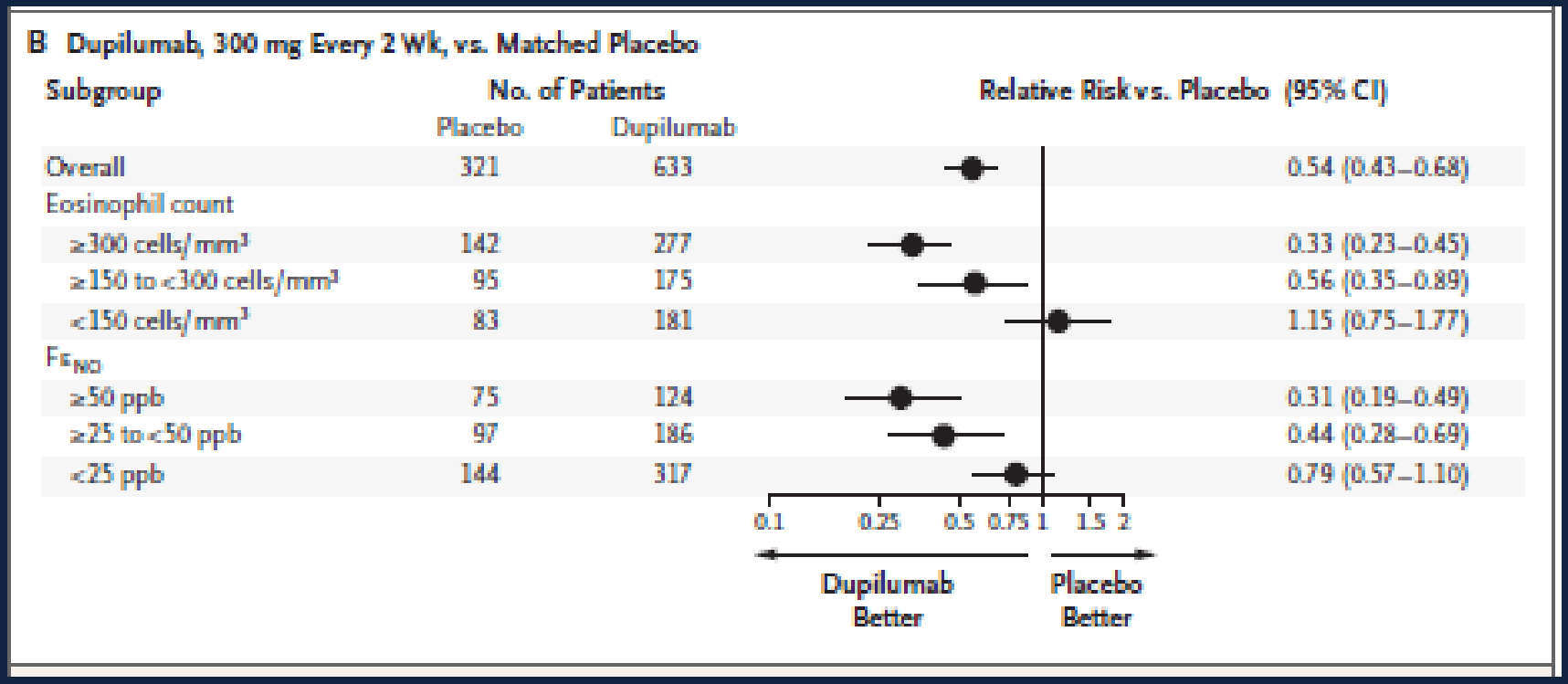


Pelaia G et al 2012 Nat Rev Drug Disc

Dupilumab



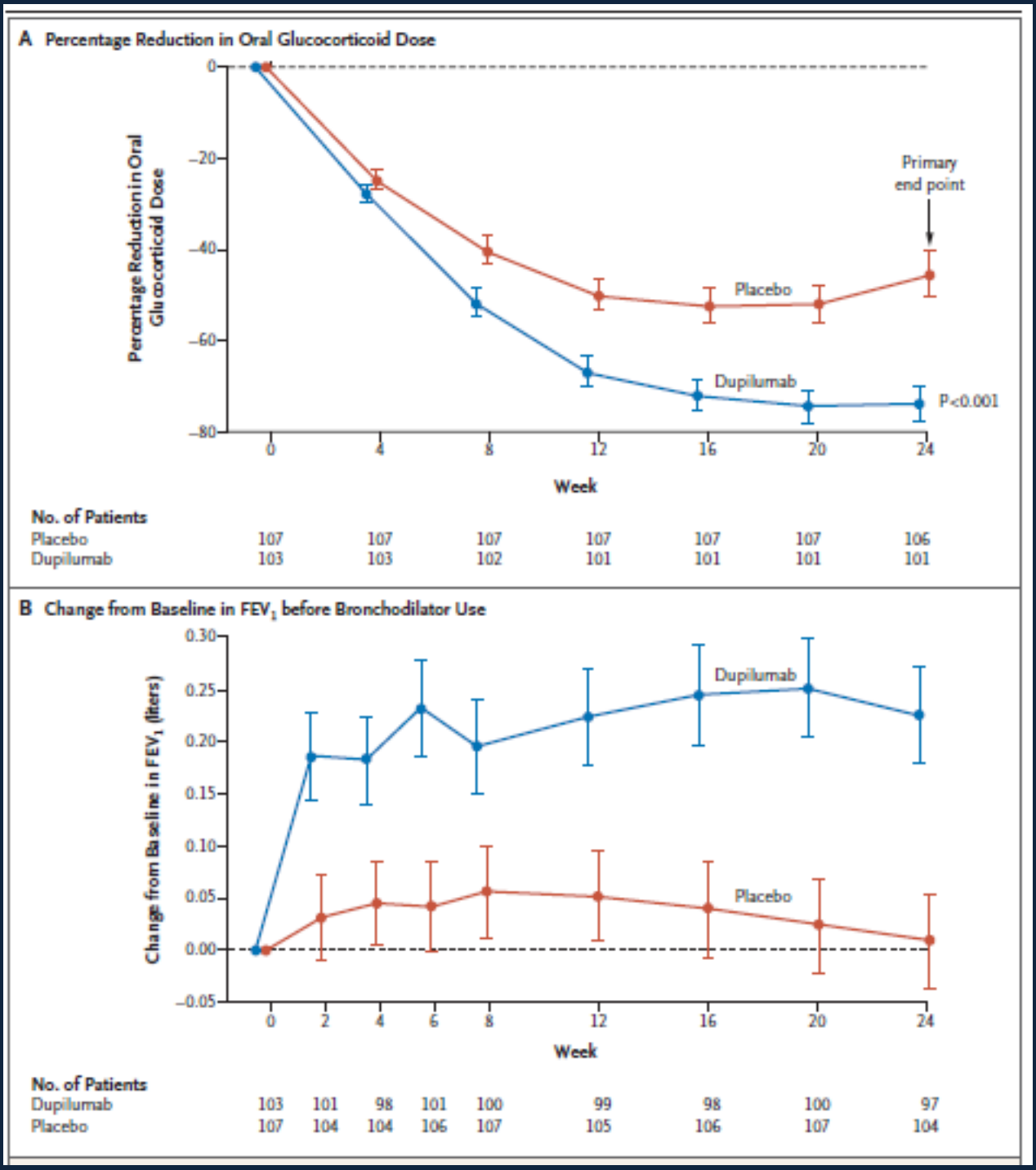
- Fully human mAb targeting IL-4Rα chain
- Effectively inhibits signaling via both IL4 and IL13.



Forrest plot relative risk of primary endpoint (severe asthma exacerbation) based on baseline blood eosinophils or FENO

Patients (ages 12 and up with mod-severe asthma on med-high dose ICS plus 2 other controllers).
Randomized: Dupilumab 200mg SQ q 2 wks (n=600); Dupilumab 300mg SQ q 2 wks (n=600), volume-matched control groups n=300 each).

Rabe K 2018 NEJM

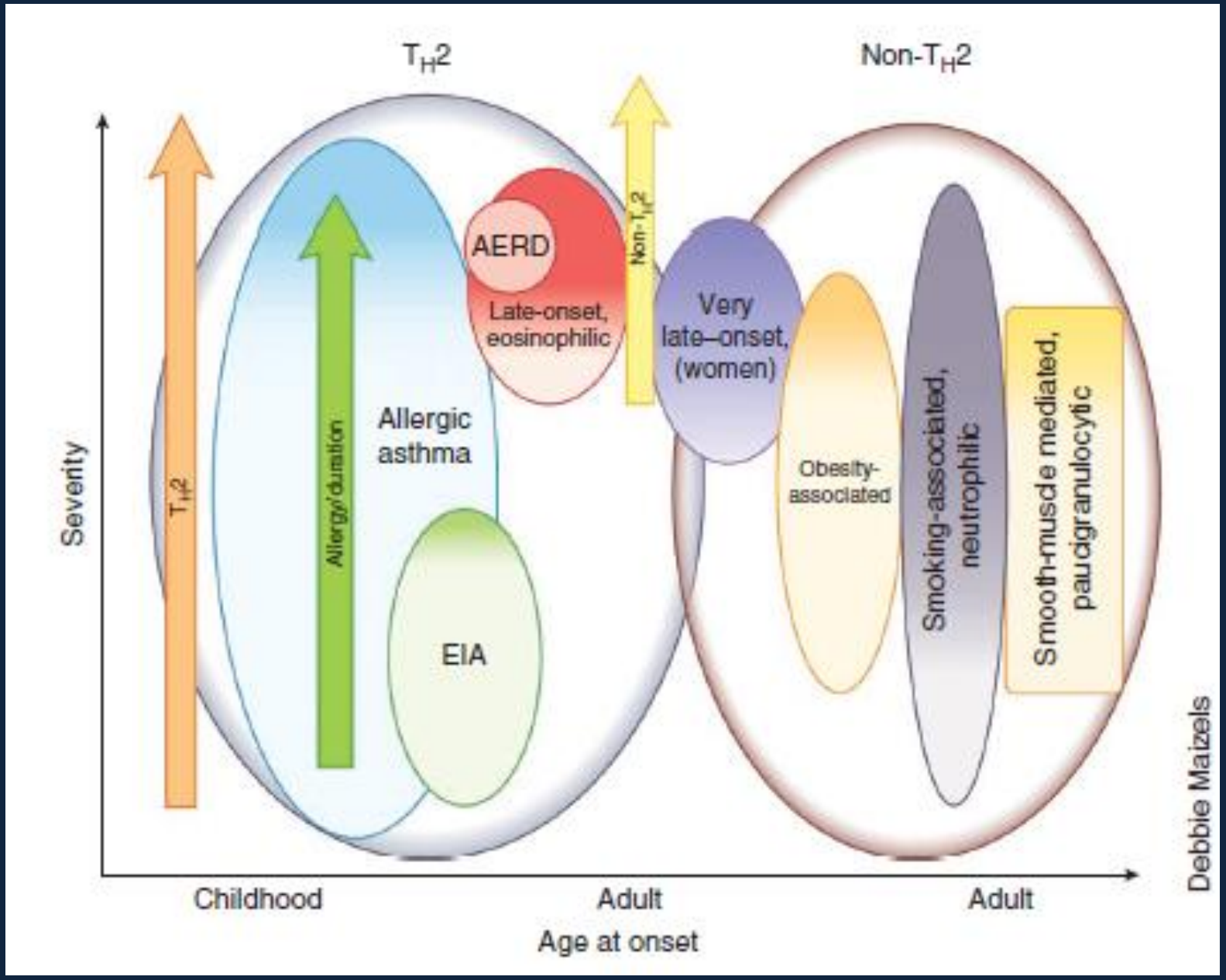


Rabe K 2018 NEJM

Dupilumab (recently approved by FDA for asthma in patients 12 and older as well as atopic dermatitis)

- Ages 12 and up as add-on for moderate to severe asthma with eosinophilic phenotype OR with oral steroid-dependent asthma.
- Also approved for atopic dermatitis and nasal polyp disease
- Adverse reactions: Conjunctivitis, keratitis (<1%), oral and other HSV infections, helminthic infections, transient eosinophilia

Asthma Phenotypes



Wenzell, SE 2012 Nature Medicine

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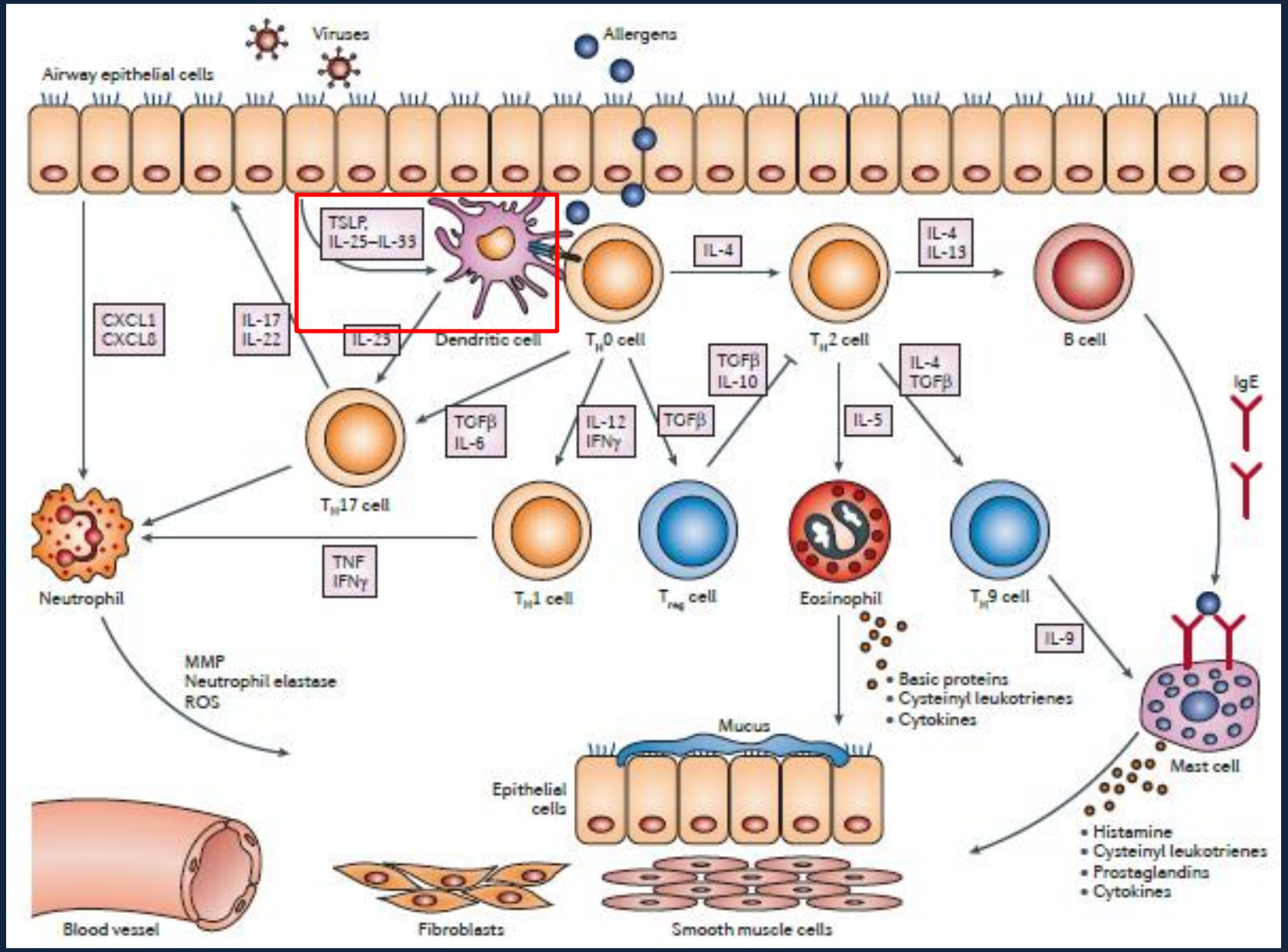
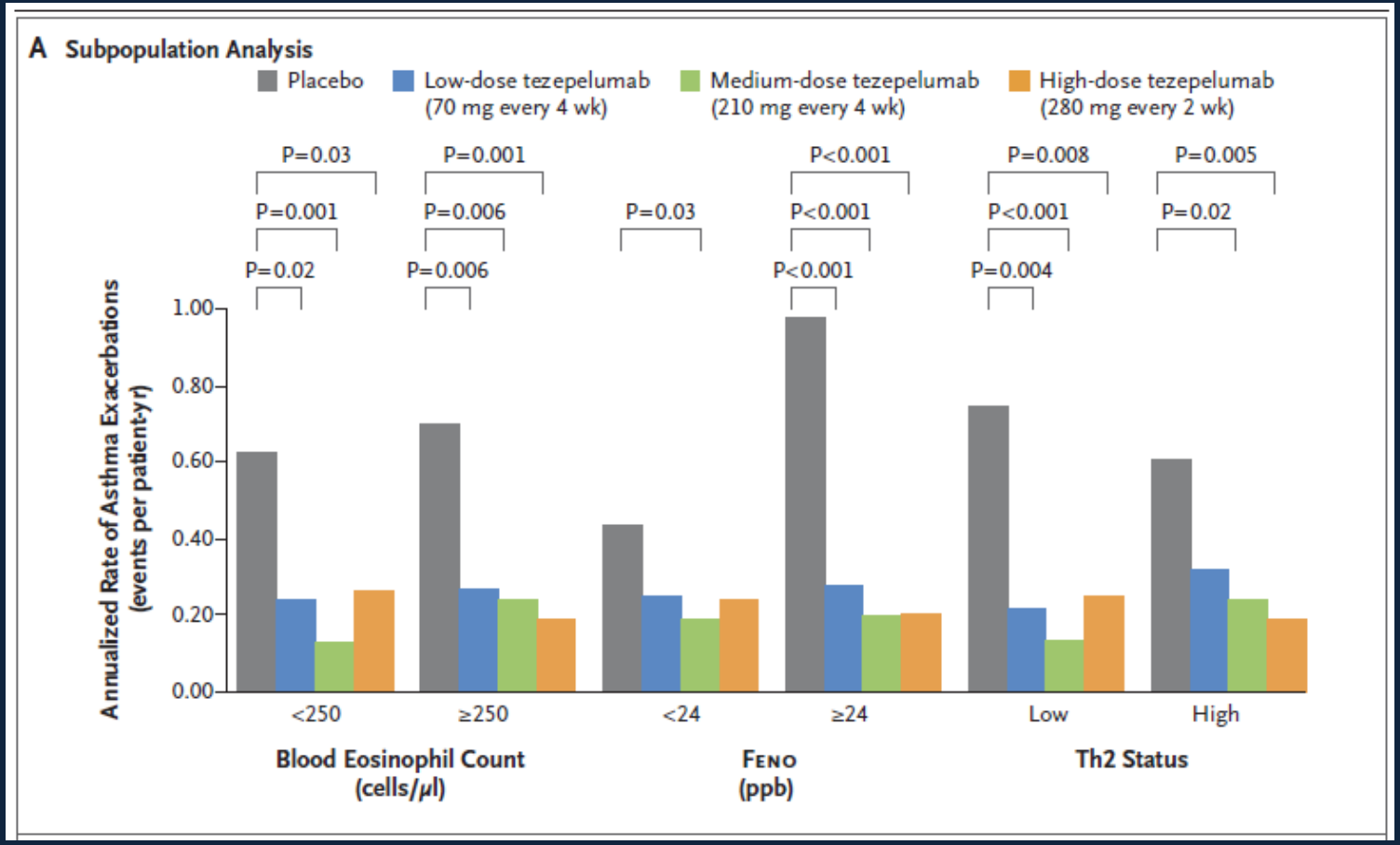


Pelaia G et al 2012 Nat Rev Drug Disc

Tezepelumab (human IgG2 anti-TSLP Mab)

- Adults 18-75yrs; poorly controlled asthma despite LABA + med to high dose ICS
- 2 exacerbations prior year (systemic steroid and/or hospitalization)
- SQ Tezepelumab (70mg, 210mg, 280mg or placebo) q 2 weeks x 52 weeks (n=145/group)
- Primary EP annualized rate of exacerbations



Corren J et al 2017 NEJM

Tezepelumab (human IgG2 anti-TSLP Mab)

- Lowered FENO, blood eosinophils and IgE starting week 4
- Unclear why non-TH2 asthmatics responded (TSLP effects on neutrophils and innate lymphoid cells?)
- Adverse events:
  - Most common bronchitis, nasopharyngitis, headache and asthma
  - Not different in Tezepelumab groups vs placebo
  - 3 serious events attributed to drug
    - Pneumonia and stroke (same patient, low dose Tezepelumab group)
    - Guillian Barre
  - 1 death (patient with Pneumonia and stroke, died 8 weeks after study period)

Corren J et al 2017 NEJM

Cost

- Omalizumab (Xolair): $540 per 150mg vial (thus between $1080 and 2700 per month)
- Mepolizumab (Nucala): $2500 per month
- Benralizumab (Fasenra): $2900 per month
- Dupilumab (Dupixent): $3083 per month
- Reslizumab (Cinquair): Variable (weight-based). $944 per 100mg.

Corren J et al 2017 NEJM

Non-allergic, non-Type 2 asthma remains a challenge

- **Tiotropium (antimuscarinic) shown to be efficacious as add-on to ICS/LABA**
- TNF inhibitors not well studied in asthma, anecdotally ineffective and the safety profile appears poor
- Anti-TH17-targeted antibody was not successful in 1 study
- **Azithromycin showed improvement specifically in non-eos asthma,** but ERS/ATS recommend against use due to concerns about resistant bacteria
- **Bronchial thermoplasty: FDA approved. Effective long term reduction in exacerbations. FEV1<60% and life-threatening exacerbations were exclusion criteria. Invasive. Exacerbations increased during the 9 week treatment period.**
- **Bariatric surgery/weight loss programs**

Obesity and asthma:

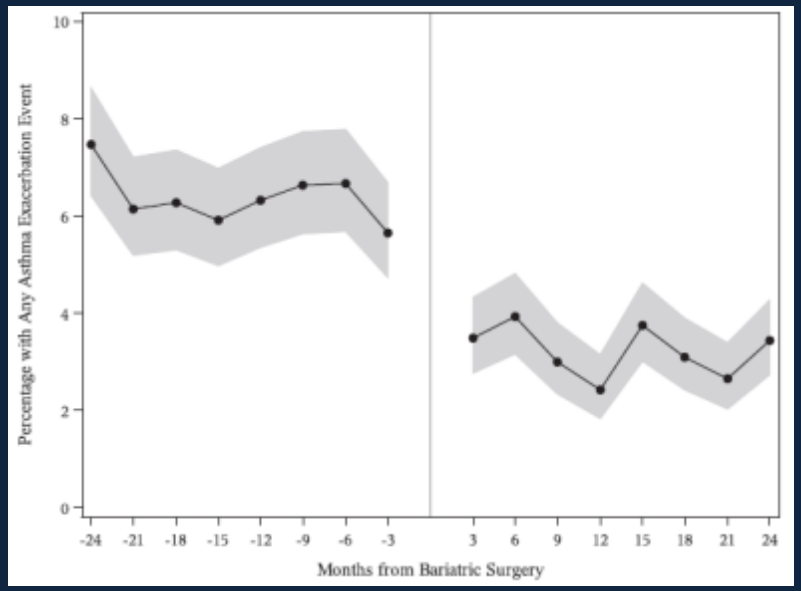
- 2.5 fold increased risk of asthma
- Increased severity
- Poorer control
- Less response to standard therapies

Can be a primary driver of asthma, and can compound pre-existing asthma.

- Immune/inflammatory changes
- Mechanical/physiologic changes
- Comorbidities (cardiovascular, diabetes, GERD).

Initial data on weight loss and asthma control was disappointing. Bariatric surgery, however, shows significant promise…..

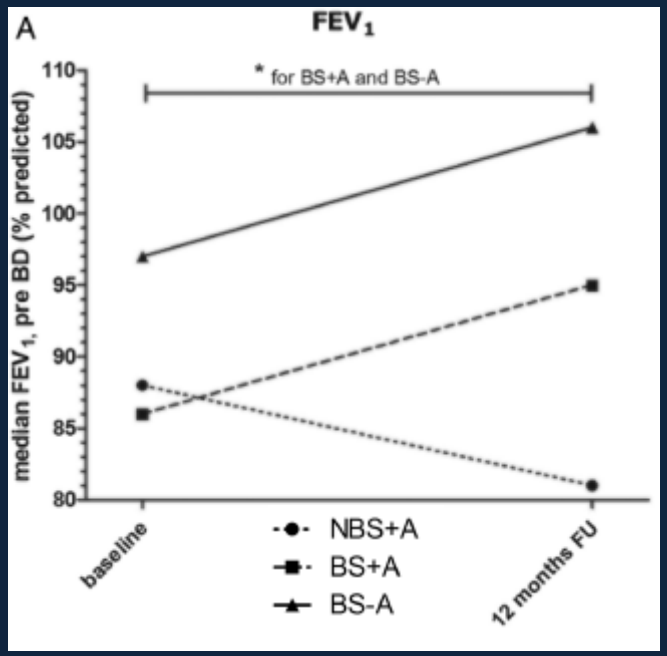
Bariatric Surgery and asthma

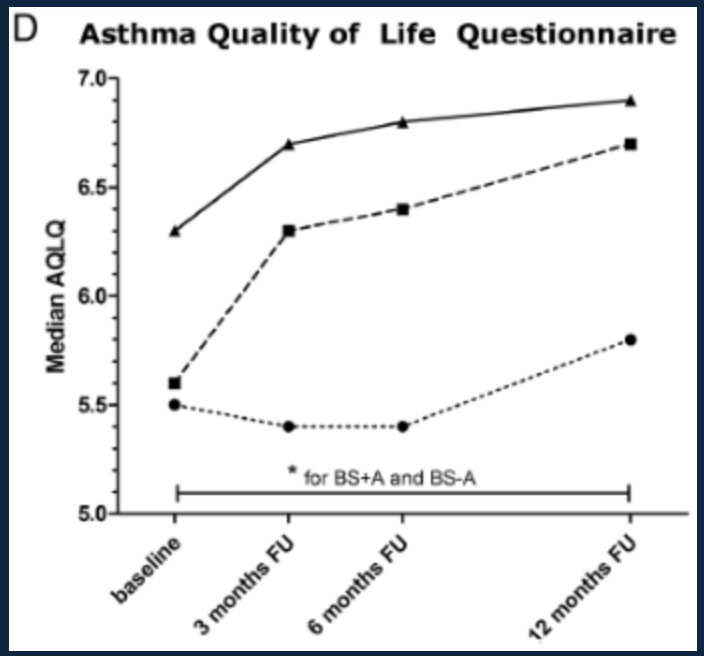


2260 patients with asthma and at least 1 ED visit in 5 yrs prior to enrollment.

Significant reduction in exacerbation rates in the 2 years after bariatric surgery.

J All Clin Imm 2015 136: 288-94





Thorax 2015 70: 659-67

Improvement in FEV1 and asthma symptom scores

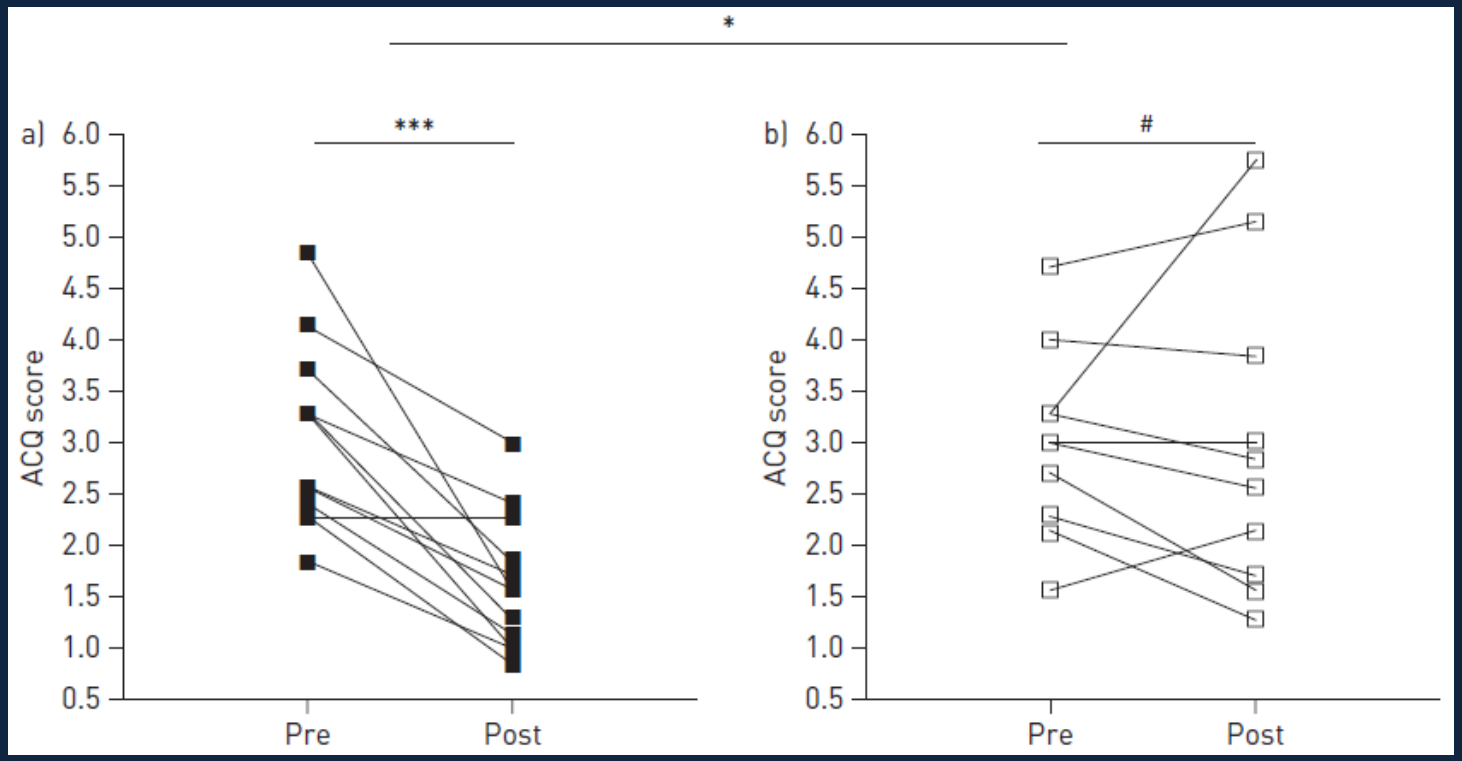
Non-invasive weight loss programs

Still need more data.

Benefits may be more likely in those achieving more significant weight loss.

Greater than 10% weight loss

Less than 10% weight loss

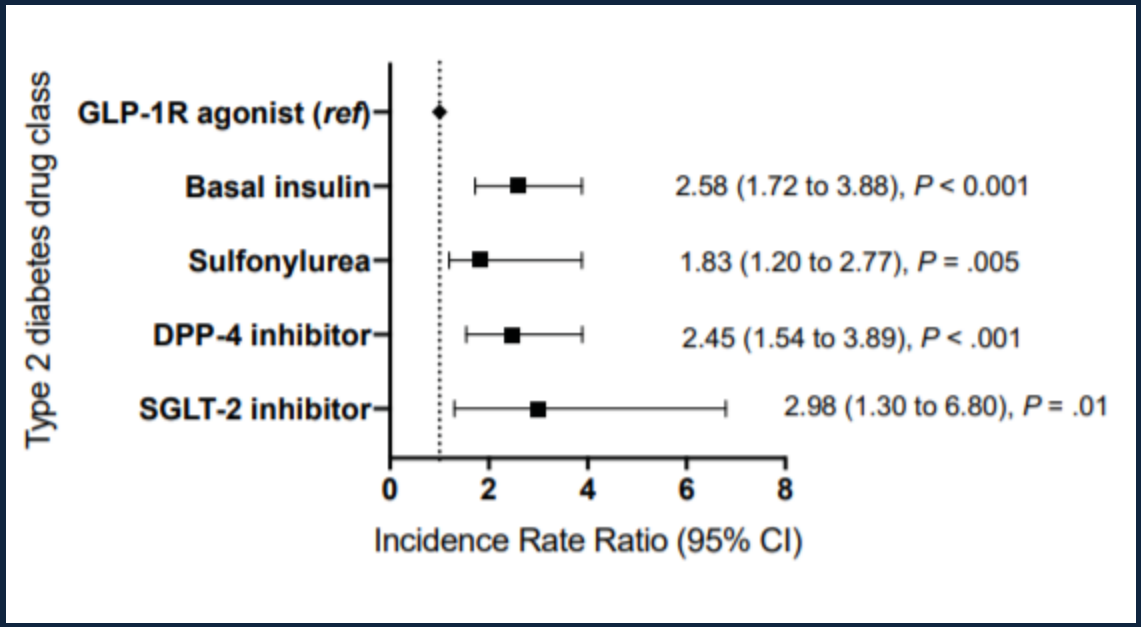


Eur Resp J 2014 43: 1368-77

Glucagon-like peptide receptor agonist

Retrospective EMR review (Brigham and Women's 2000-2018)

- GLPR1 agonist n=448
- Basal insulin n=2,692
- Sulfonylurea n=2,253
- DPP-4 inhibitor n=435
- SGLT-2 inhibitor n=112



Significantly reduced likelihood of asthma exacerbations

Eur Resp J 2014 43: 1368-77

Conclusions

- The study of asthma phenotypes has allowed significant steps forward in management of severe/refractory asthma.
- Biologic therapies targeting mediators of TH2/Type 2 asthma (anti-IgE, anti-IL5 and anti-IL4/13 monoclonals) reduce exacerbations, reduced systemic glucocorticoid exposure, and improve symptoms when used as add-on therapy.
- Small molecules are on the horizon…..
- **Non-TH2 asthma remains difficult.**
- Tiotropium (anti-muscarinic) as add-on shows some benefit
- Bariatric surgery (and hopefully non-invasive weight loss programs) shows significant promise in improving control in obese asthmatics
- Medications modulating metabolic pathways may hold promise as well
- **Bronchial thermoplasty** remains an option for otherwise refractory patients