

# Asthma Update

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**CONTINUING MEDICAL EDUCATION  
DEPARTMENT OF MEDICINE**



**HARVARD MEDICAL SCHOOL  
TEACHING HOSPITAL**

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Pulmonary/Critical Care Fellowship - BWH  
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Professor of Medicine, Harvard Medical School  
Gloria M. and Anthony C. Simboli Distinguished Chair in Asthma Research  
Clinical focus: Severe Asthma  
Research focus:

- Clinical and Translational Research related to severe asthma
- Pharmacogenetics of asthma therapy
- Precision medicine and adaptive trial design in asthma
- Asthma in disadvantaged communities

# DISCLOSURES

Amgen	Consultant and
Clinical Research Support	
Anaptys Bio	Consultant
Apogee Therapeutics	Consultant
Arrowhead Pharmaceuticals	Consultant
AstraZeneca	
Consultant and Clinical Research Support	
Bain Capital	Consultant
Cowen	Consultant
GlaxoSmithKline	Consultant
Jasper Therapeutics	Consultant
Leerink Partners	Consultant
Orbimed	Consultant
Regeneron	Consultant
Sanofi	Consultant
TEVA	
Consultant and Clinical Research Support	
Yuhan	Consultant

# Objectives

- Understand paradigm shift discouraging the use of beta-agonist reliever medication without inhaled corticosteroid in asthma
- Understand the concept of type 2 (T2) inflammation and how we clinically assess for its presence in asthma
- Review the biologics available in asthma that mostly target T2 inflammation, how they work, and how they are used

# Definition of Asthma

Chronic inflammatory disorder of the airways

Characterized by:

- Airflow limitation,
  - reversible either spontaneously or with treatment
- Airway inflammation
- Increased responsiveness to a variety of stimuli

# Rule of 2's for Lack of Control and Escalation of Medications

- Lack of Control
  - Nighttime awakenings >2/mo
  - SABA use for sxs (not pre-exercise) >2/wk
  - Sx >2 wk
  - ACT / ACQ  $\leq 20$  /  $>1.5$
  - Lung function Reduced by >20%
  - Exacerbations >2/yr

# Control on ACT or ACQ

- ACT
  - 20 or more
  - 3 point change is considered MCID
- ACQ
  - $\leq 1.5$
  - MCID 0.5

# PROGRESSION in NAEPP

- SABA
  - Daily ICS + prn SABA
- or
- Low dose formoterol/ICS or SABA with ICS
- Regular ICS/formoterol + prn ICS/formoterol
  - Increase strength of ICS in the ICS/formoterol
  - Add LAMA
  - Consider biologic



## **43 yo woman with hypertension and mild asthma seeking f/u of her hypertension**

- One steroid requiring exacerbation in the past and it was in the last year with a cold
- She has several unopened/unexpired salmeterol/fluticasone inhalers at home from the exacerbation and they are her insurer's preferred ICS/LABA with a low co-pay
- Needs her albuterol inhaler once a week or so and sometimes after exercise
- ACT is 21
- Asks you to renew her albuterol (she has refilled it once in the last year)

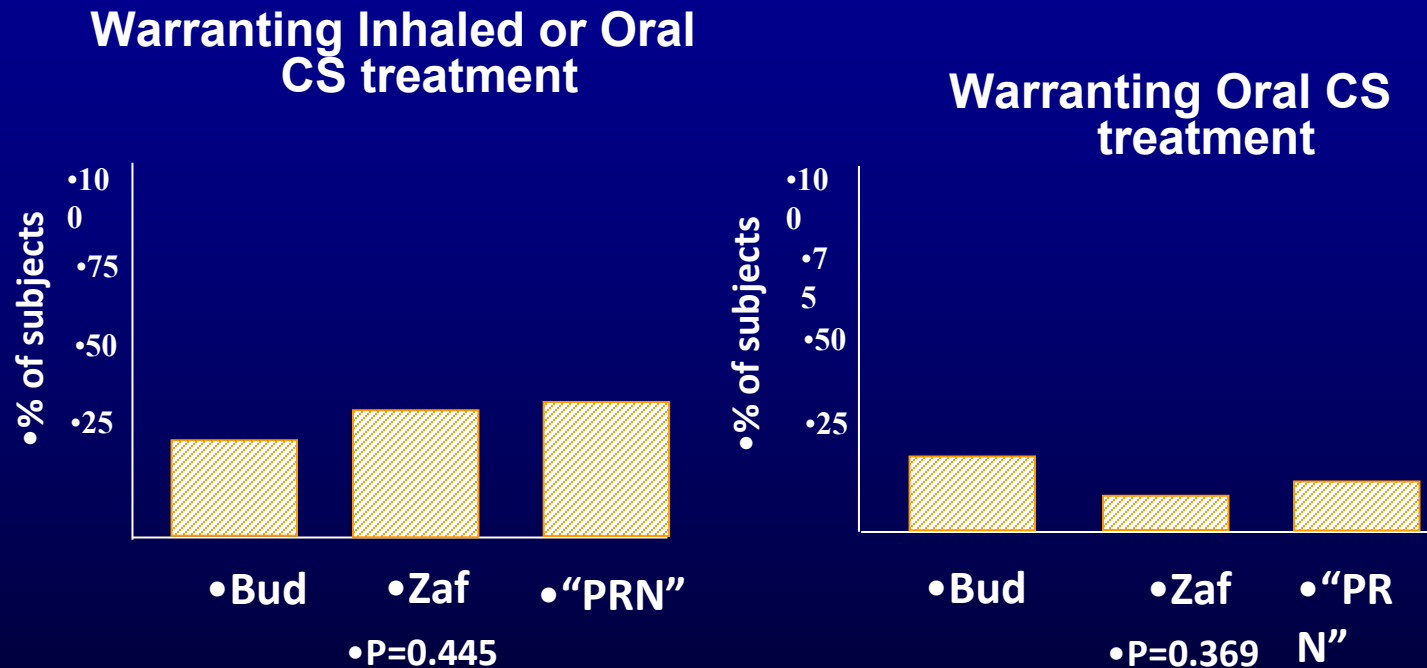
# Would you?

- A. Renew albuterol
- B. Suggest that she use her low-cost salmeterol/fluticasone inhaler as needed instead of albuterol
- C. Prescribe formoterol/ICS inhaler and tell her to use it prn instead of the albuterol
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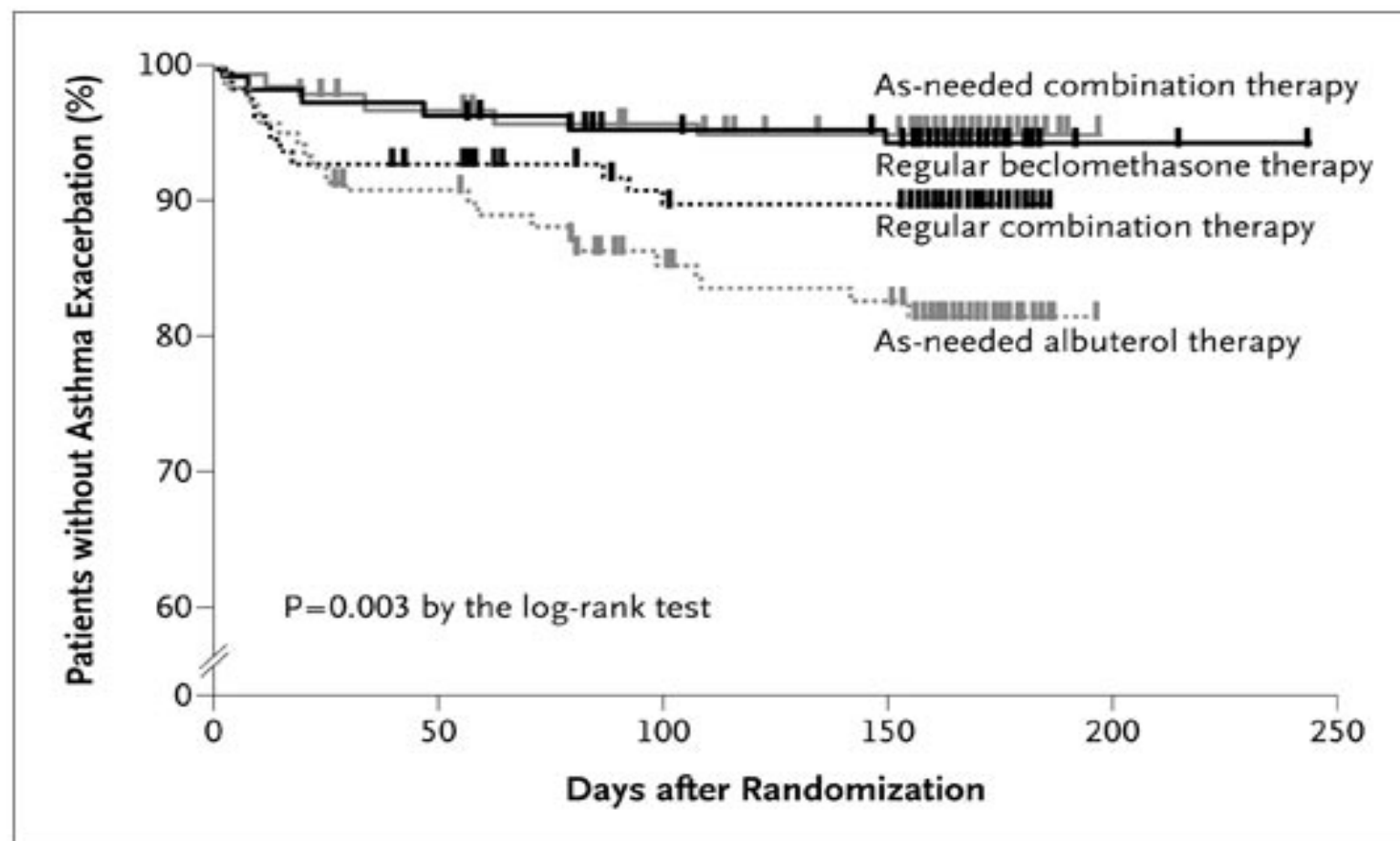
# Anti-Inflammatory Reliever Therapy AIR

- Paradigm Shift
- Concept that reliever bronchodilator therapy should almost always be accompanied by an anti-inflammatory drug (inhaled corticosteroid)
  - Increased beta agonist use without concomitant ICS is associated with increased asthma morbidity
  - Using ICS every time you use a reliever reduces asthma exacerbations

# IMPACT Study Showed That Using PRN ICS Could be As Effective as Regular ICS in Mild Asthma



## BEST: Albuterol-Triggered ICS was as Effective for Preventing Asthma Exacerbations as Regular Use in Mild Asthma



- ICS use was reduced by >75% in Triggered group as c/w regular group
- No difference in SFD, rescue medication use, of symptom scores between regular and triggered

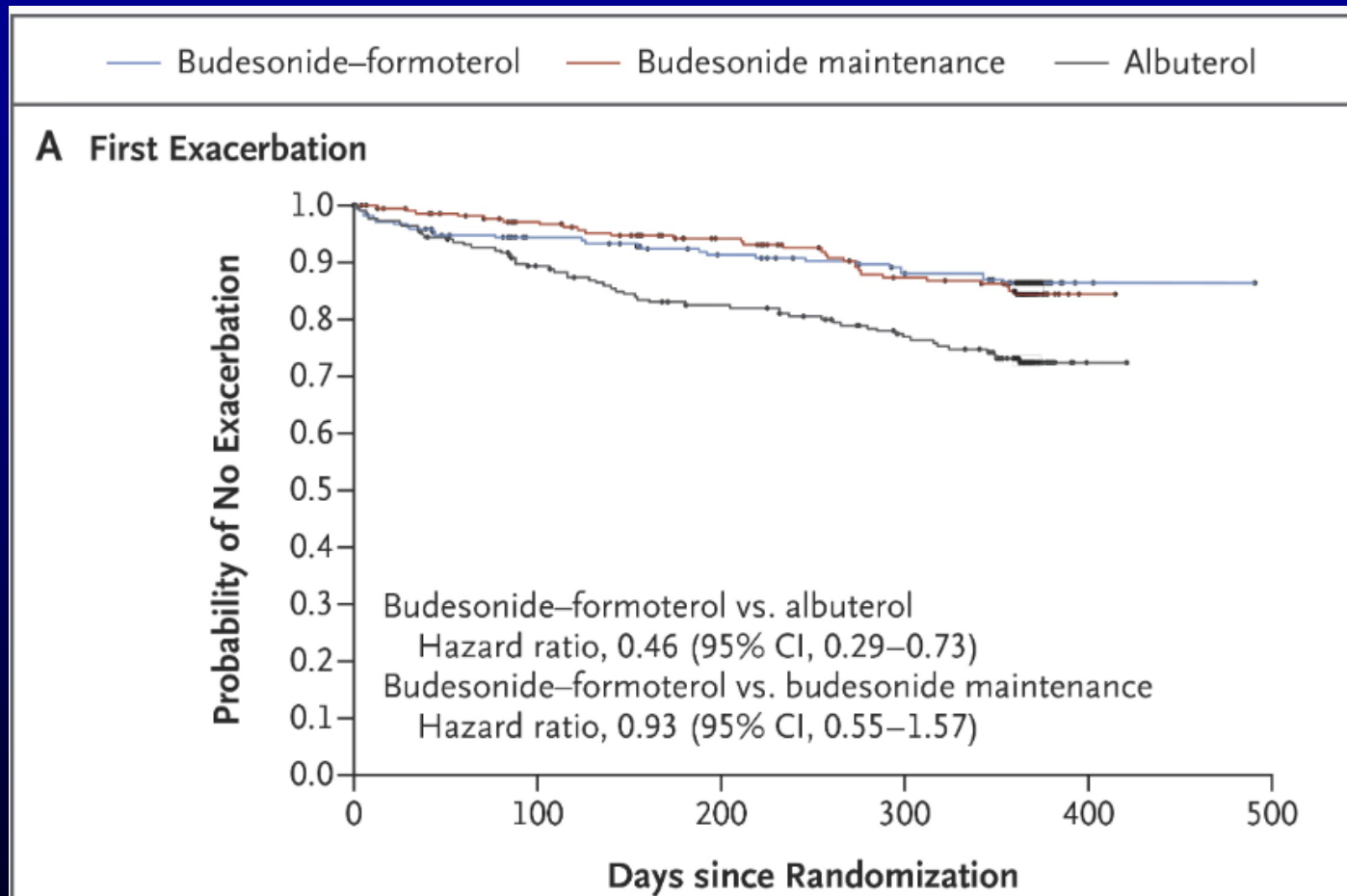
# ICS/formoterol and the evolution to (S)MART (Single) Maintenance And Reliever Therapy

- While formoterol is a long-acting beta-agonist (LABA), as compared to the other LABA (salmeterol), formoterol has a quick onset of action
- Studies were undertaken to examine whether ICS/formoterol could be used instead of albuterol and simultaneously as background therapy
- Studies showed that ICS/formoterol prn was as effective as regularly used ICS in preventing exacerbations and resulted in a 50 to 75% reduction in ICS exposure

## (S)MART

- Further it was shown that substituting ICS/f for SABA reduced exacerbations by 30% or more
- Studies also showed that using ICS/f instead of SABA was as, or more, effective than increasing the ICS dose of ICS/f while decreasing ICS exposure
- These led to recommendations that patients at level 3 or 4 (requiring ICS/LABA) should be on MART.

# PRN ICS/f Was As Effective As Regular ICS in a Real World 2019 Study in Mild (and Intermittent) Patients





# NAEPP 2020

## AGES 12+ YEARS: STEPWISE APPROACH FOR MANAGEMENT OF ASTHMA

	Intermittent Asthma	Management of Persistent Asthma In Individuals Ages 12+ Years				
Treatment	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6 <sup>■</sup>
Preferred	PRN SABA	Daily low-dose ICS and PRN SABA or PRN concomitant ICS and SABA <sup>▲</sup>	Daily and PRN combination low-dose ICS-formoterol <sup>▲</sup>	Daily and PRN combination medium-dose ICS-formoterol <sup>▲</sup>	Daily medium-high dose ICS-LABA + LAMA and PRN SABA <sup>▲</sup>	Daily high-dose ICS-LABA + oral systemic corticosteroids + PRN SABA
Alternative		Daily LTRA <sup>▲</sup> and PRN SABA or Cromolyn,* or Nedocromil,* or Zileuton,* or Theophylline, <sup>▲</sup> and PRN SABA	Daily medium-dose ICS and PRN SABA <sup>▲</sup> or Daily low-dose ICS-LABA, or daily low-dose ICS + LAMA, and PRN SABA <sup>▲</sup>	Daily medium-dose ICS-LABA or daily medium-dose ICS + LAMA, and PRN SABA <sup>▲</sup> or Daily medium-dose ICS-LABA, or daily low-dose ICS + LAMA, and PRN SABA <sup>▲</sup>	Daily medium-high dose ICS-LABA or daily high-dose ICS + LTRA <sup>▲</sup> and PRN SABA	
			<div>ICS/formoterol</div> <div>GINA – Global Initiative for Asthma</div>			
					Steps 2–4: Conditionally recommend the use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals ≥ 5 years of age whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy <sup>▲</sup>	
					Consider adding Asthma Biologics (e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13)**	

**Except possibly for mildest cases of asthma the general consensus is that albuterol should not be used without an ICS**

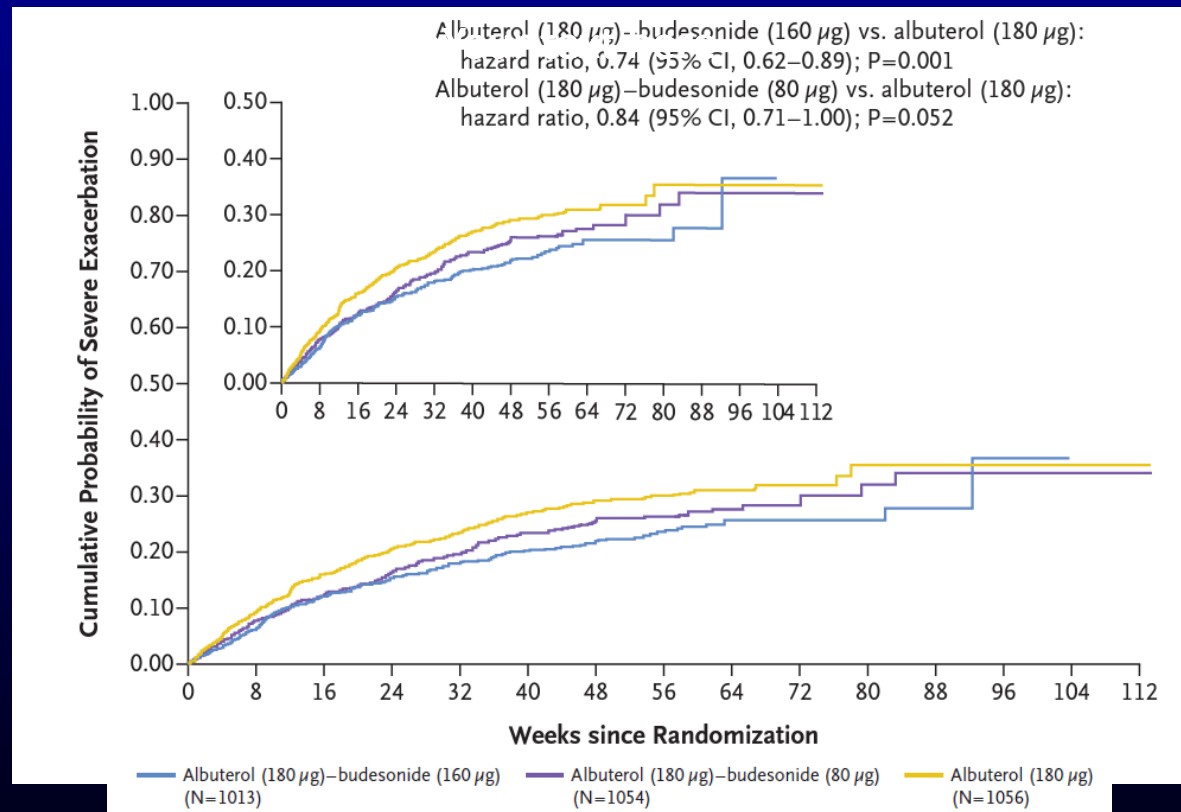
In most cases of mild asthma AIR approach should be used

# Three Ways to Administer AIR

- Single inhaler with beta-agonist and ICS
  - Formoterol/ICS inhaler
    - Formoterol/budesonide (Breyna or Symbicort)
    - Formoterol/mometasone (Dulera)
  - Cannot use Salmeterol containing combination (Advair) since salmeterol is not quick acting enough
  - Albuterol/ICS
    - Albuterol/budesonide (AirSupra)
- Instructing patient to take ICS every time they use their reliever (PARTICS) – Patient Activated Reliever Triggered ICS

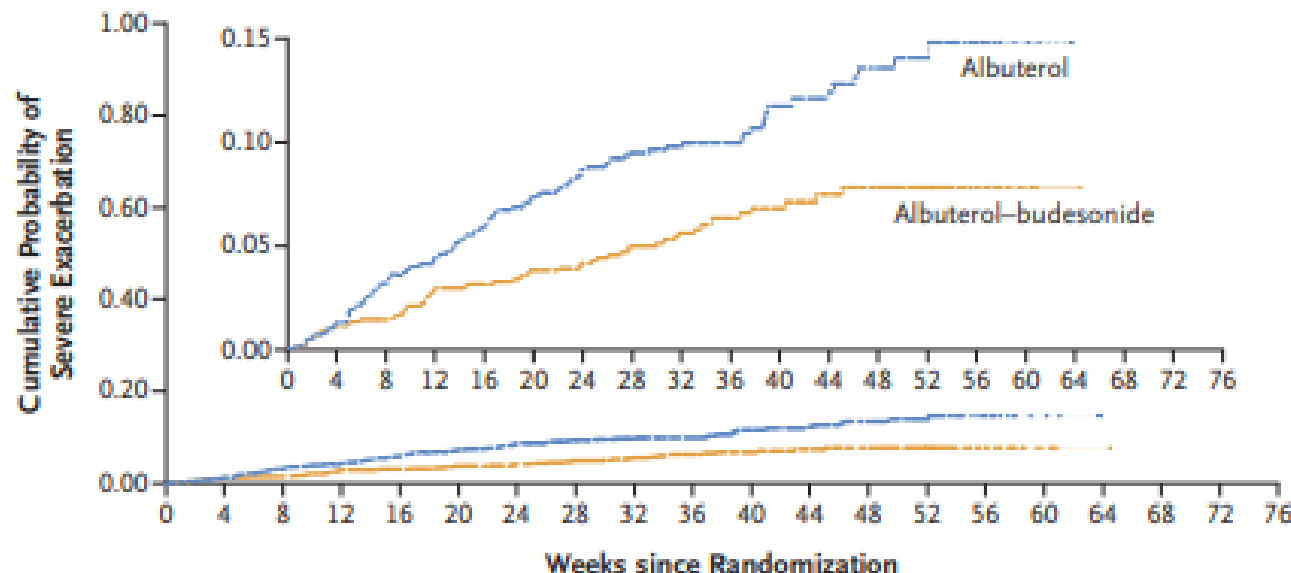
# ICS/Albuterol Fixed Combination Introduced in the US as PRN Reliever + ICS

Added to Underlying ICS or ICS/LABA (not on nebulizers)  
Reduced Exacerbations by 26% c/w Albuterol Alone (0.15/yr)



# Albuterol/budesonide PRN in Symptomatic Patients Using Albuterol or Low Dose ICS Reduced Exacerbations by 47%

**A On-Treatment Efficacy Population**



No. of Participants  
with Event (%)

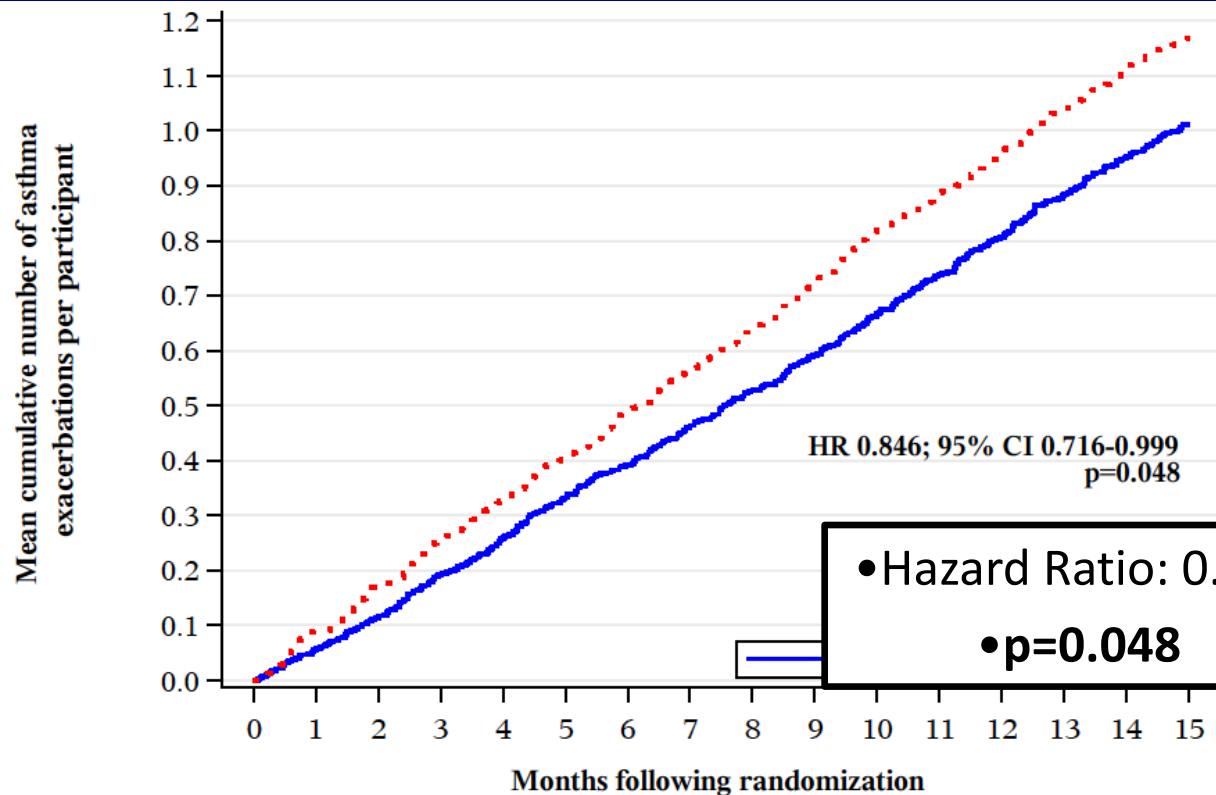
Group	No. of Participants with Event (%)
Albuterol	110 (9.1)
Albuterol-Budesonide	62 (5.1)

Hazard ratio with albuterol-budesonide,  
0.53 (95% CI, 0.39-0.73)  
P<0.001

No. at Risk

Weeks since Randomization	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76
Albuterol	1212	1158	1035	939	863	799	712	619	512	418	309	250	198	119	15	3	0	0	0	0
Albuterol-budesonide	1209	1176	1070	961	909	837	763	663	553	445	328	268	215	121	19	5	1	0	0	0

# Patient Activated Reliever Triggered ICS (QVAR 80 puff for puff w/MDI and 5 puffs w/neb) reduced asthma exacerbations



Participants at risk															
PARTICS+UC	600	597	593	592	591	589	588	581	580	576	572	569	562	558	551
UC	601	598	594	593	591	588	585	583	579	577	575	575	575	572	561

- **PARTICS** reduced severe exacerbations by 0.13/person/year

- This is **equal or greater** than the reduction in severe exacerbations seen in **MART** studies cited by NAEPP (0.12/patient/year, weighted by sample size and duration)

• Israel et al. NEJM  
2022

• **PARTICS: Patient Activated Reliever Triggered ICS**

# Implementation Considerations Regarding AIR

- Formoterol is the ONLY LABA for use due to its rapid onset of action
- FDA package insert warns against using budesonide/formoterol prn
  - Many insurers will not cover the extra ICS//f inhaler
- Studies of MART were almost exclusively performed with budesonide/formoterol;
  - Theoretically, other ICS/formoterol combinations such as mometasone/formoterol could be effective but they have not been studied
- Albuterol/budesonide is approved in the USA but may not be covered by all insurance
- MART may not be effective in patients who use a nebulizer during exacerbations (those patients may benefit from PARTICS)
- Telling patients to use their ICS every time they use their albuterol (tying a rubber band around them), PARTICS, is also effective
  - Can only use PARTICS or budesonide/albuterol if person on triple therapy

# iCARE

- We are conducting a real-life study comparing MART to PARTICS in patients on ICS/LABA with a history of an exacerbation
- 1 888 99 ASTHMA



# What about AIR for the mild intermittent patient?

## AGES 12+ YEARS: STEPWISE APPROACH FOR MANAGEMENT OF ASTHMA

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		Steps 2–4: Conditionally recommend the use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals ≥ 5 years of age whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy <sup>▲</sup>			Consider adding Asthma Biologics (e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13)**	

ICS/formoterol  
GINA – Global Initiative for Asthma

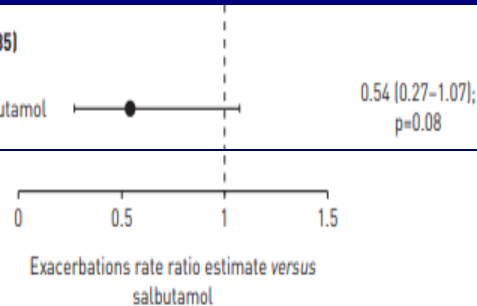
# In Mild Intermittent Patients Air Appears to Reduce Exacerbations by 50% (NS) but Absolute Rate is Low

## All Exacerbations

0.265 vs 0.143

Intermittent asthma subgroup (n=335)

Budesonide-formoterol versus salbutamol

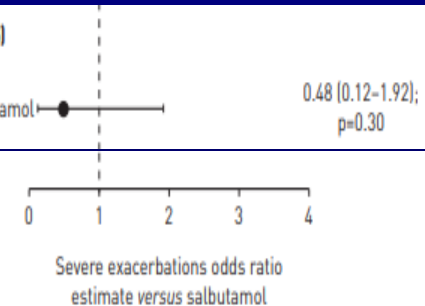


## Severe Exacerbations

6.1% vs. 3.1%

Intermittent asthma subgroup (n=335)

Budesonide-formoterol versus salbutamol



## 25.5 mg of budesonide/yr (0.35 puffs/d)

- Post-Hoc Analysis Novel Start ICS/f in Mild Intermittent Patients ( $\leq 2$  puff/wk and no exacerbations)

# Considerations for AIR in Intermittent Asthma vs. PRN SABA

- Shared decision making
- Even if well controlled, still at risk for an exacerbation especially if had an exacerbation in the past 1-2 years
- Reduces but does not eliminate risk of an exacerbation
- May be less appropriate for patients who are well controlled but use SABA frequently prophylactically e.g before exercise since may get more ICS than they need
- Can consider any of the 3 methods of AIR

## **43 yo woman with hypertension and mild asthma seeking f/u of her hypertension**

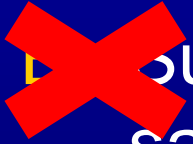
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# Triple Inhalers Approved for Asthma

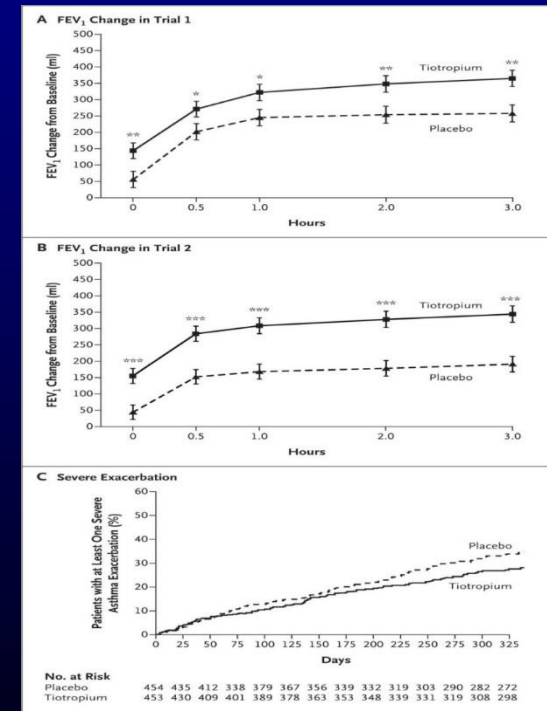
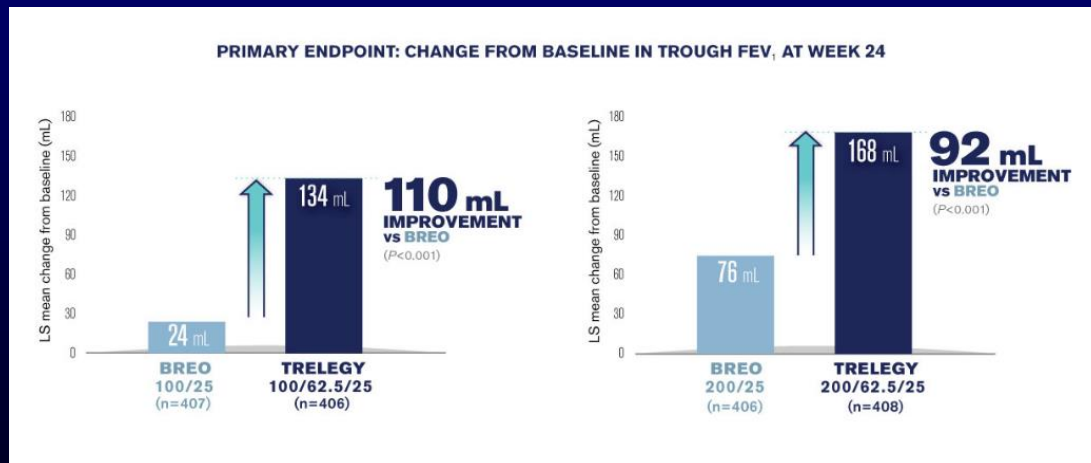
- ICS/LAMA/LABA

- (FF/umeclidinium/vilanterol)

- (100/62.5/25 and 200/62.5/25 once daily)

- Bud/glycopyrrolate/formoterol (approved April 2026)

- 160/18/4.8 – 2puffs twice a day
  - Glycopyrrolate dose is twice the COPD dose (18 instead of 9)



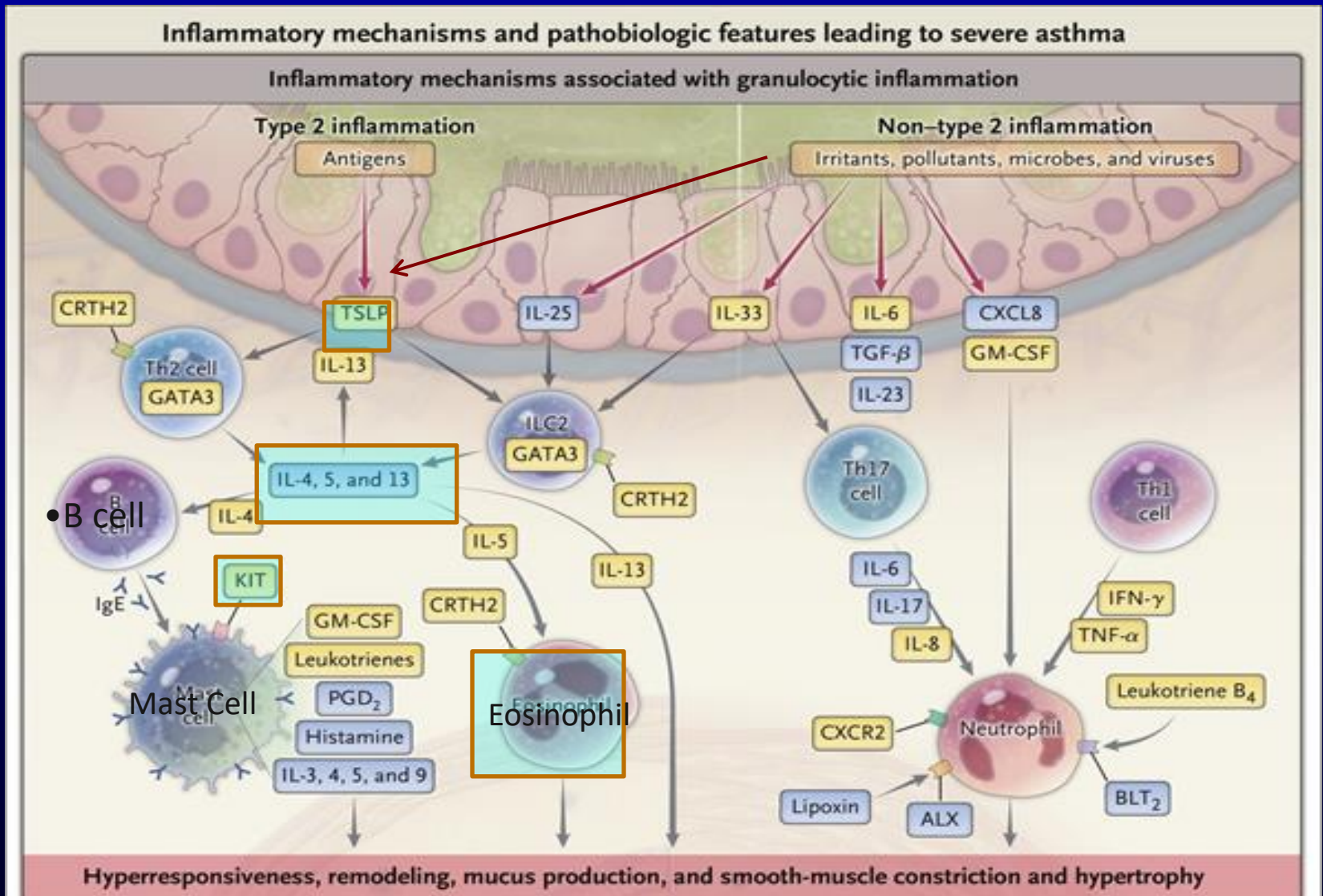
# BIOLOGICS



# Definition of Type 2 Immunity

- Immune response involving the innate and the adaptive arms of the immune system to promote barrier immunity on mucosal surfaces
- Cells
  - T helper 2 (T<sup>H</sup>2) CD4<sup>+</sup> T cells and B cell production of the immunoglobulin E (IgE) antibody subclass.
  - Innate response includes ILC 2 innate lymphoid cells, eosinophils, basophils, mast cells and interleukin-4 (IL-4)-and/or IL-13-activated macrophages.
- Associated with IL-4, IL-5, and IL-13.

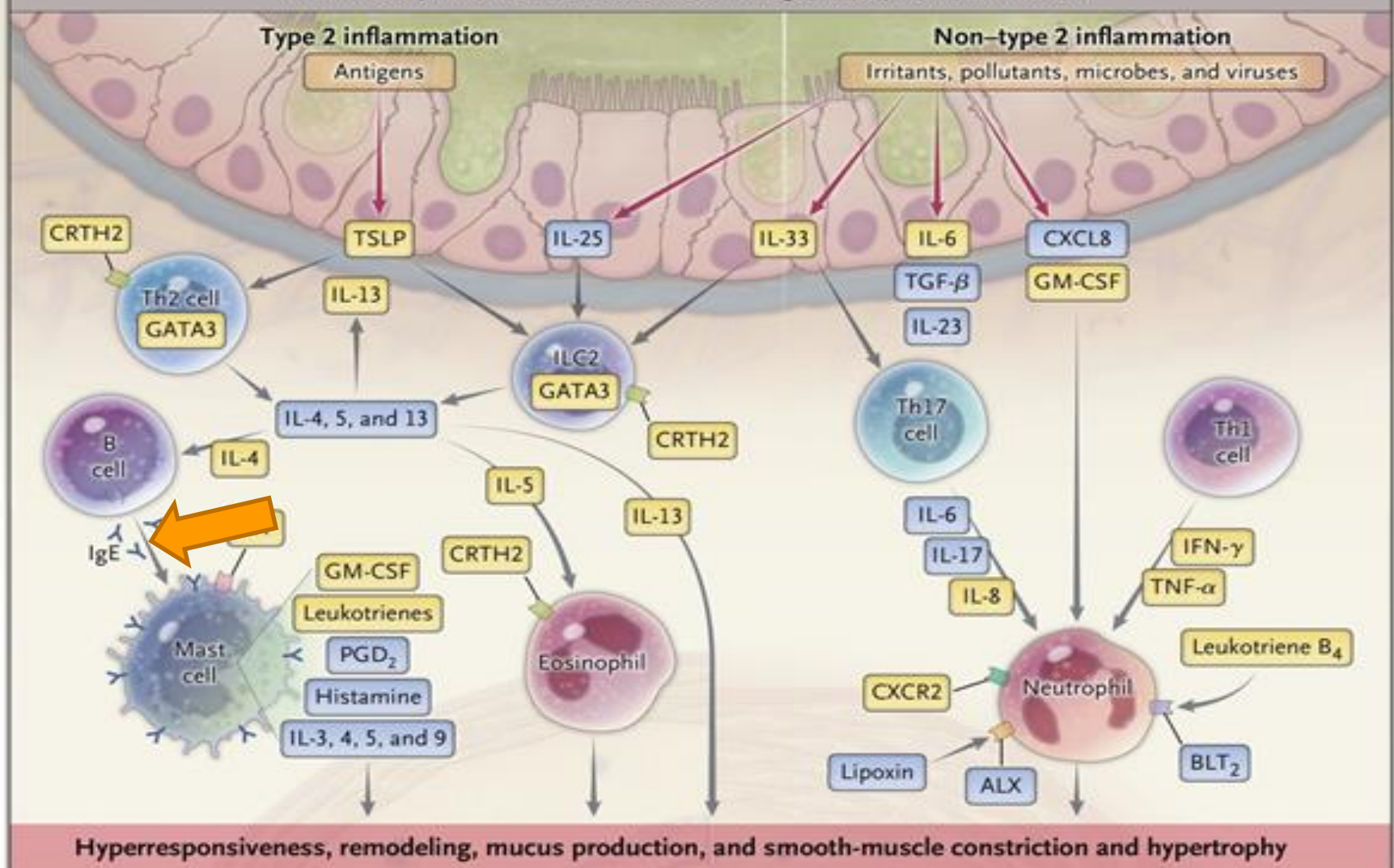
# Type 2 Inflammatory Targets



# Type 2 Inflammatory Targets – IgE

Inflammatory mechanisms and pathobiologic features leading to severe asthma

Inflammatory mechanisms associated with granulocytic inflammation

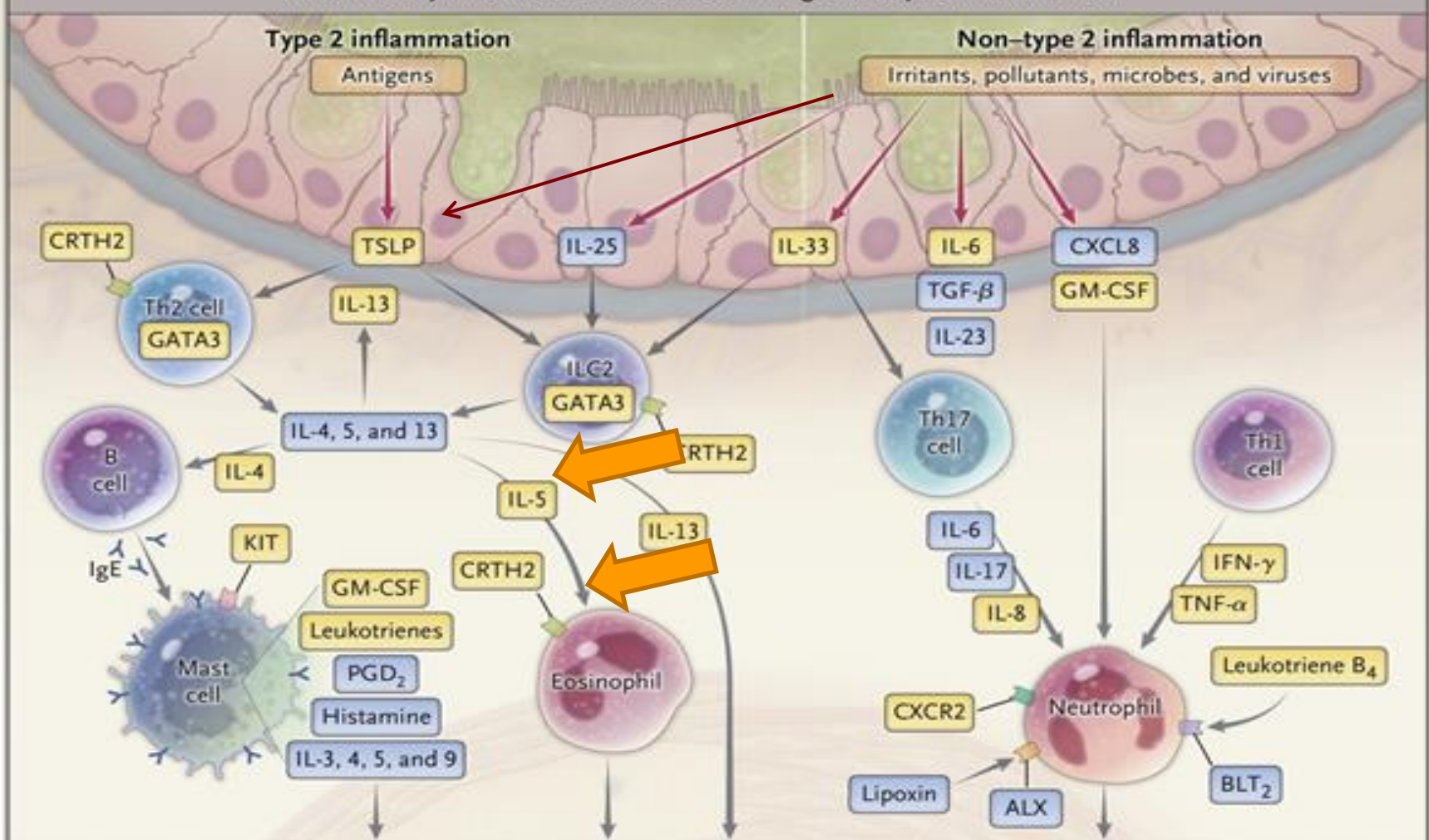




# Type 2 Inflammatory Targets – IL5 Mepolizumab, Reslizumab, Benralizumab, Depemokimab

Inflammatory mechanisms and pathobiologic features leading to severe asthma

Inflammatory mechanisms associated with granulocytic inflammation

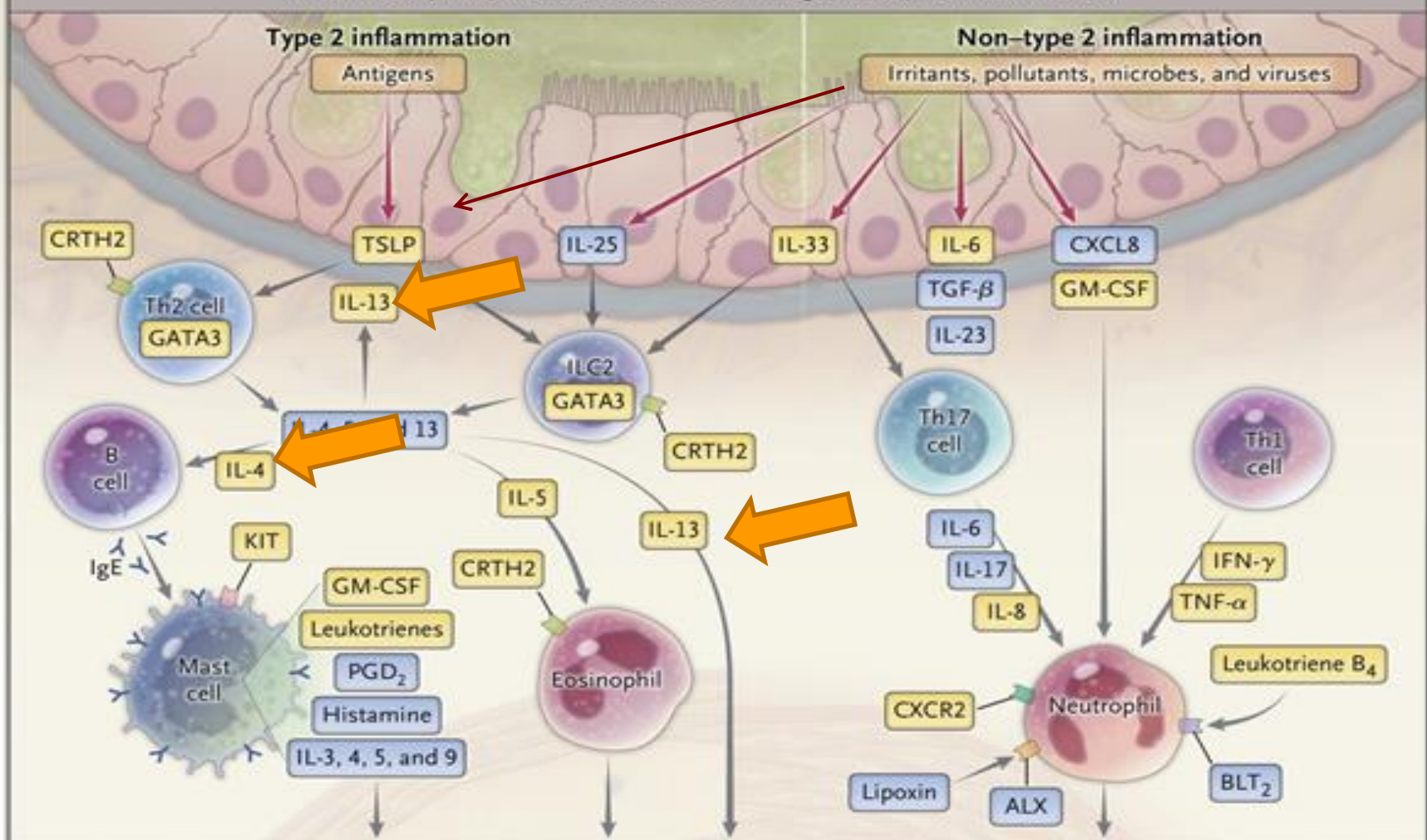


Hyperresponsiveness, remodeling, mucus production, and hypertrophy • Israel & Reddel, NEJM, 2017

# Type 2 Inflammatory Targets – IL4RA Dupilumab

Inflammatory mechanisms and pathobiologic features leading to severe asthma

Inflammatory mechanisms associated with granulocytic inflammation



•Israel & Reddel, NEJM, 2017

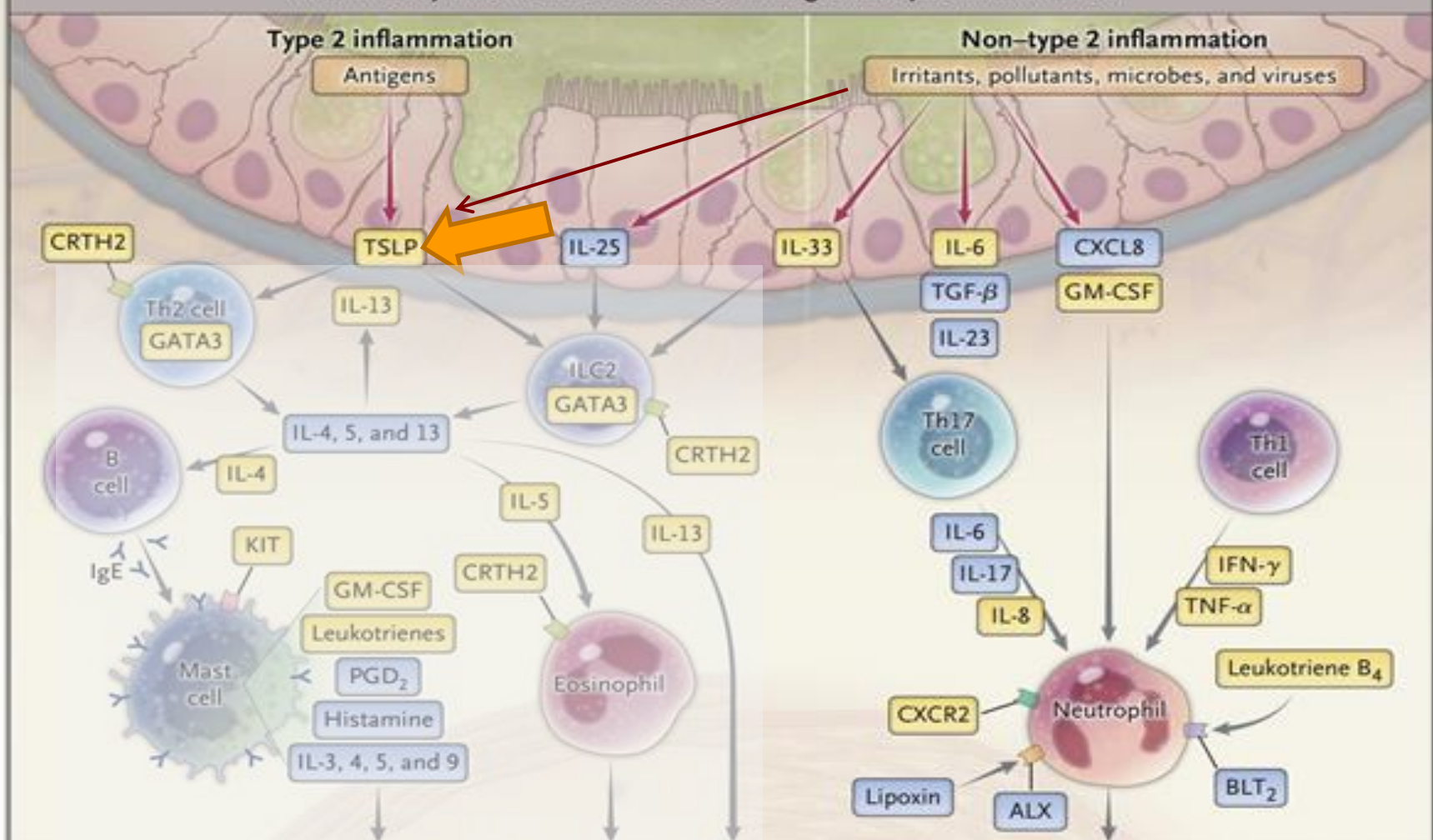
Hyperresponsiveness, remodeling, mucus production, and smooth-muscle constriction and hypertrophy



# Type 2 Inflammatory Targets – TSLP Tezepelumab

## Inflammatory mechanisms and pathobiologic features leading to severe asthma

### Inflammatory mechanisms associated with granulocytic inflammation



•Israel & Reddel, NEJM, 2017

Hyperresponsiveness, remodeling, mucus production, and smooth-muscle constriction and hypertrophy

# Biomarkers of Patients Likely To Respond

- ALL PATIENTS STUDIES HAD TO HAVE  $\geq 1$ -2 EXACERBATIONS AT BASELINE

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Depemokimab	Dupilumab	Tezepelumab
Eosinophils $\geq 300$ ( $>150$ w/3+ exac)	++	+++	+++	+++	+++	+++	+++
Low Eos/Hi FeNO (FeNO $>20$ -25)	0	0	0	0	0	++	+++
Low Eos/Low FeNO	0	0	0	0	0	0	+/-
OCS Dependent (regardless of T2)	N.D.	+	N.D.	+	N.D.	+	-

# Outcomes in Patients with Eosinophils $\geq 300/\mu\text{l}$

- (Studies Required 1-2 exacerbations,  $\geq 12\%$  Bronchodilator Response and ACQ  $\geq 1.5$  on Study Entry (except Depemokimab))

	IgE	IL5				IL4RA	TSLP
	Omalizu mab	Mepolizu mab	Reslizum ab	Benralizum ab	Depemoki mab	Dupilum ab	Tezepelu mab
% Reduction in Exacerbation	32	61	~55 (In eos >400/ $\mu\text{l}$ )	~35	54	66	70
FEV1 (cc)	40	202	126	~138	30	~225	230
ACQ	0.36	~0.48	~0.24	~0.2	-0.08	~0.4	0.33



# Effects on Co-Morbidities

- Omalizumab
  - CRSwNP
  - Chronic idiopathic urticaria (CIU)
  - Food allergies
- Mepolizumab
  - CRSwNP
  - COPD
  - EGPA
- Benralizumab
  - EGPA
- Dupilumab
  - CRSwNP
  - Eczema
  - COPD
  - CIU
  - Eosinophilic Esophagitis
  - Prurigo Nodularis
- Tezepelumab
  - CRSwNP

# Administration of the Biologics in Severe Asthma

	Omalizum ab	Mepolizu mab	Reslizuma b	Benralizuma b	Depemokim ab	Dupilum ab	Tezepelu mab
<b>Lowest age</b>	<b>6</b>	<b>6</b>	<b>18</b>	<b>12</b>	<b>12</b>	<b>6</b>	<b>12</b>
<b>Frequency</b>	<b>2-4 wks</b>	<b>4 wks</b>	<b>IV 4 weeks</b>	<b>8 wks after first 3 months</b>	<b>6 months</b>	<b>2 wks</b>	<b>4 wks</b>
<b>Mode</b>	<b>SC</b>	<b>SC</b>	<b>IV</b>	<b>SC</b>	<b>SC</b>	<b>SC</b>	<b>SC</b>
<b>Home Administratio n</b>	<b>Y</b>	<b>Y</b>	<b>N</b>	<b>Y</b>	<b>N</b>	<b>Y</b>	<b>Y</b>
<b>Anaphylaxis</b>	<b>0.1-0.3%</b>	<b>NR</b>	<b>0.3%</b>	<b>NR</b>	<b>NR</b>	<b>NR</b>	<b>NR</b>
<b>Additional Notes</b>	-	-	-	-		-Temporary increase in eosinophil - Conjunctivit is	

# Patient Eligible for Biologics for Asthma

- Adherent on maximal non-biologic therapy (high dose ICS/LABA Air)
- 2 or more steroid requiring exacerbations in the past year or chronic oral corticosteroids
- Except for tezepelumab, blood eosinophils  $>150-300$  or FeNO  $\geq 25$  ppb
  - Tezepelumab has no biomarker requirement but is more effective the higher the T2 biomarkers

# Implementation Points Regarding Biologics

- Except for reslizumab and Depemokimab all can be administered at home
- All contraindicated with in patients with active parasitic infestation
- FDA package insert does not recommend live vaccines with dupilumab or tezepelumab but that is not based on any data but rather study design

# Summary

- Almost all patients with asthma should not be using a beta-agonist without an ICS
  - Potential exceptions are patients who use it prophylactically for exercise but are very well controlled and have not had exacerbations
- When prescribing anti-inflammatory reliever using a LABA/ICS ONLY formoterol can be in the combination
- ICS/f may be most convenient but other factors may affect shared decision making
- Patients with 2 or more steroid-requiring exacerbations in the past year who are adherent to maximal therapy should be considered for biologics for their asthma

# Severe Asthma Program

State of the Art Multidisciplinary  
Evaluation and Treatment of Patients  
with Severe Asthma

- Pulmonary

- Allergy

- ENT

- GI

- Psychiatry

- Alternative Medicine

• [severeasthma@bwh.harvard.edu](mailto:severeasthma@bwh.harvard.edu) or **1 844 BWH-LUNG**

# References

- **Global Initiative for Asthma. *Global Strategy for Asthma Management and Prevention*, 2025. Updated 15 November 2025. Available from: [www.ginasthma.org](http://www.ginasthma.org).**
- **Israel E, Wechsler ME, Jackson DJ, et al. Anti-cytokine biologics for asthma in adults. *The Lancet*. 2025; 406(10516): 2282–2294. [DOI: 10.1016/S0140-6736\(25\)01625-3](https://doi.org/10.1016/S0140-6736(25)01625-3).**