Brigham and Women's Hospital
Founding Member, Mass General Brigham

Asthma in 2024

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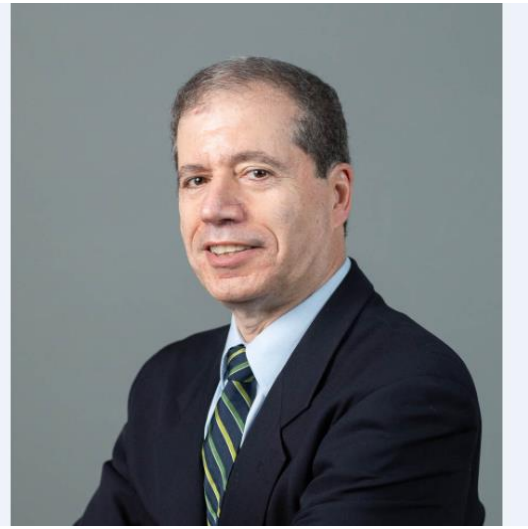
CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Elliot Israel, M.D.



Johns Hopkins University School of Medicine
Medicine Residency – Johns Hopkins Hospital, New York Hospital/Cornell
Pulmonary/Critical Care Fellowship - BWH
Allergy & Immunology Fellowship - BWH
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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

- Consultant

- AB Science
- Amgen
- Arrowhead Pharmaceuticals
- Cowen and Co
- Glaxo SmithKline
- Merck

- Consultant and Clinical Research Support

- AstraZeneca
- Avillion
- Novartis
- Genetech
- Regeneron
- Sanofi
- TEVA

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Abbreviations

- ACQ- Asthma Control Questionnaire
- ACT-Asthma Control Test
- ENT- ear, nose, and throat
- Eos- eosinophilic
- FeNO- fractional exhaled nitric oxide
- FEV1- forced expiratory volume in one second
- GI- gastrointestinal
- GINA-Global Initiative for Asthma
- ICS- inhaled corticosteroids
- IgE- immunoglobulin E
- IL4 - interleukin 4
- IL4RA- interleukin 4 receptor alpha
- IL5- interleukin-5
- LABA- long-acting beta agonist
- LAMA-long-acting muscarinic antagonists
- MDI- metered dose inhaler
- NAEPP- National Asthma Education and Prevention Program
- OCS- oral corticosteroids
- PRN- as needed
- RAST- radioallergosorbent test
- SABA- short-acting beta agonists
- TSLP- thymic stromal lymphopoietin

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Objectives

- Understand new non-biologic medications in asthma
- Understand new NAEPP and GINA guidelines for the treatment of asthma
- Understand biologics used in treatment of severe asthma
  - T2 and non-T2 inflammation
  - Mechanisms
  - Effects on biomarkers
  - Indications and precision medicine

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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

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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 ≤20 / >1.5
  - Lung function Reduced by >20%
  - Exacerbations >2/yr

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Control on ACT or ACQ

- ACT
  - 20 or more
  - 3 point change is considered MCID
- ACQ
  - ≤1.0
  - A 0.5 change is felt to be enough to make a change in therapy
    - Therefore 1.5 is inadequately controlled

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WHAT'S NEW IN MEDICATIONS

Super long-acting beta-agonist combinations for once a day

- Fluticasone furoate 100/vilanterol 25 and 200/25
  - Combined long-acting ICS and super-long acting (LA)BA.
  - Only approved in 18 yo and above
  - Dose equivalency
    - 1 puff 100/25 qd = 1 puff bid FP250/Salm 50 BID
    - 1 puff 200/25 qd = 1 puff bid FP500/Salm50 BID
- ICS/LAMA/LABA once a day now approved for asthma (FF/umeclidinium/vilaneterol)
  - (100/62.5/25 and 200/62.5/25)

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NAEPP Major Change in 2021 Update

- The use of as needed inhaled corticosteroids with a short-acting beta-agonist or a long-acting beta agonist (formoterol ONLY) in almost all severity levels

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AGES 12+ YEARS: STEPWISE APPROACH FOR MANAGEMENT OF ASTHMA

Treatment	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 12+ Years				
	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6■
Preferred	PRN SABA	Daily low-dose ICS and PRN SABA or PRN concomitant ICS and SABA▲	Daily and PRN combination low-dose ICS-formoterol▲	Daily and PRN combination medium-dose ICS-formoterol▲	Daily medium-high dose ICS-LABA + LAMA and PRN SABA▲	Daily high-dose ICS-LABA + oral systemic corticosteroids + PRN SABA
Alternative		Daily LTRA* and PRN SABA or Cromolyn,* or Nedocromil,* or Zileuton,* or Theophylline,* and PRN SABA	Daily medium-dose ICS and PRN SABA or Daily low-dose ICS-LABA, or daily low-dose ICS + LAMA,▲ or daily low-dose ICS + LTRA,* and PRN SABA or Daily low-dose ICS + Theophylline* or Zileuton,* and PRN SABA	Daily medium-dose ICS-LABA or daily medium-dose ICS + LAMA, and PRN SABA▲ or Daily medium-dose ICS + LTRA,* or daily medium-dose ICS + Theophylline,* or daily medium-dose ICS + Zileuton,* and PRN SABA	Daily medium-high dose ICS-LABA or daily high-dose ICS + LTRA,* and PRN SABA	
		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▲			Consider adding Asthma Biologics (e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13)**	

		Step 1	Step 2		Step 3	Step 4	Step 5
		INTERMITTENT	PERSISTENT				
≥12 years old	CONTROLLER	None	Preferred: Low-dose ICS	None	Low-dose ICS/formoterol	Medium-dose ICS/formoterol	Medium- to high-dose ICS/LABA + LAMA
	PRN RELIEVER	SABA	SABA	ICS & SABA (concomitant)	ICS/formoterol (up to 12 puffs per day)		"SABA"

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Considerations Regarding Single Maintenance and Reliever Therapy (SMART) with ICS/LABA

- Formoterol is the preferred LABA due to its rapid onset of action; salmeterol has a slower onset of action and should NOT be used
- FDA package insert warns against using budesonide/formoterol prn
  - Many insurers will not cover the extra inhaler
- Studies of SMART were almost exclusively performed with budesonide/formoterol;
  - Theoretically, other ICSs could be effective but they have not been studied

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Considerations Regarding Single Maintenance and Reliever Therapy (SMART) with ICS/LABA

- In moderate to severe asthma SMART was only studied in patients
  - With at least one exacerbation in the past year
  - Who were NOT using nebulizers for reliever medication
  - Who bronchodilated before entering the study

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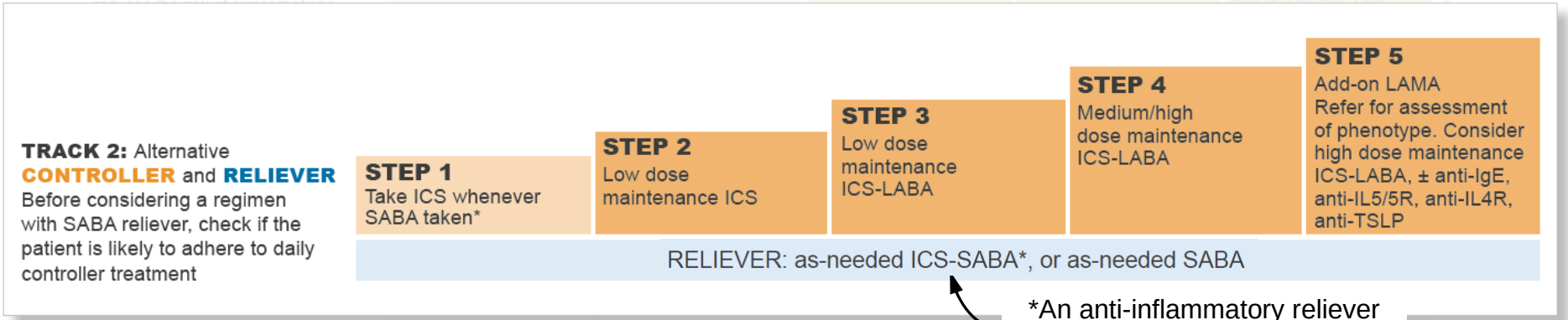
GINA HAS NOW INCORPORATED PRN ICS/SABA INTO TRACK 2 RECOMMENDATIONS

GINA 2023 – Adults and adolescents
Track 2

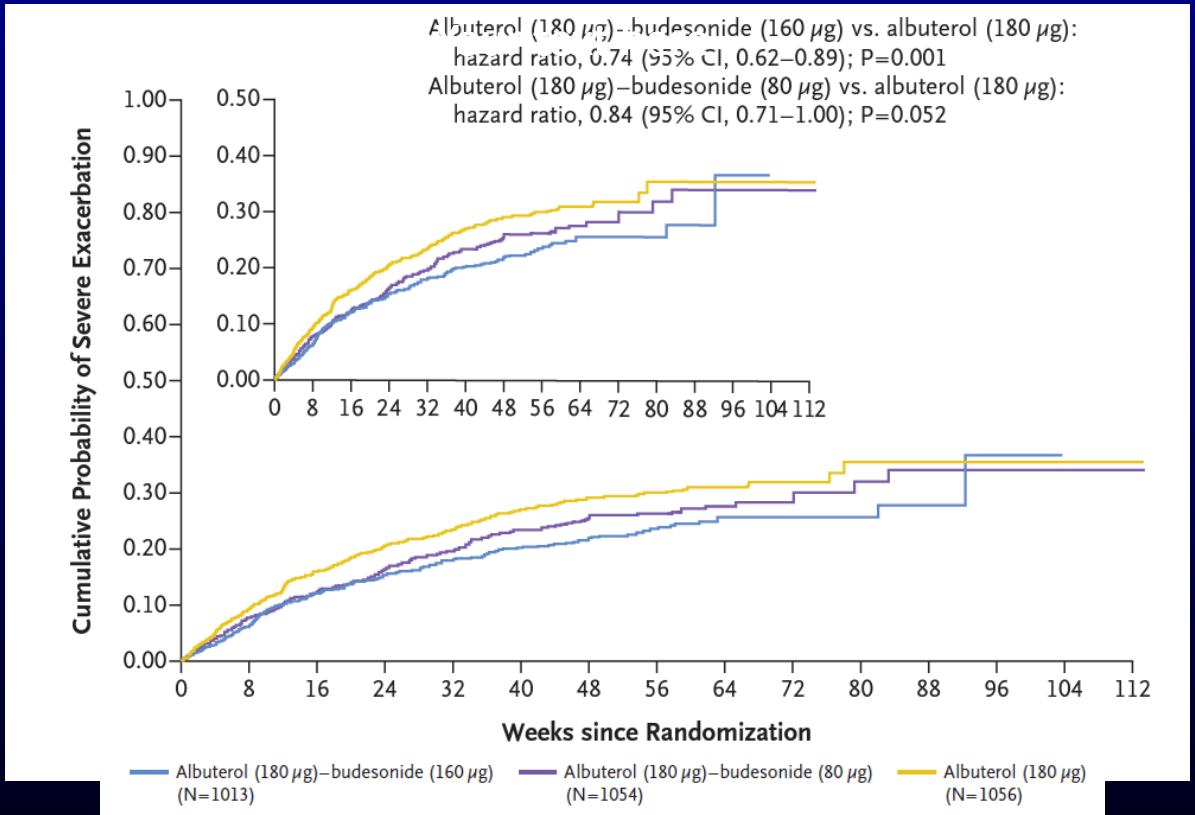


*An anti-inflammatory reliever (Steps 3–5)

Box 3-12 (3/4) Track 2

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

Added to Underlying ICS or ICS/LABA Reduced Exacerbations by 26% c/w Albuterol Alone (0.15/yr)



•Papi, NEJM, 2022

GINA Differs from NAEPP

- GINA does not recommend SMART for those 5-11 years old
- GINA recommends SMART at step 5 while NAEPP does not
- GINA advocates using ICS/formoterol instead of SABA as reliever therapy for *all* patients,12 years and older including those with intermittent asthma (it does not recommend ICS/formoterol as reliever therapy in those under 12)

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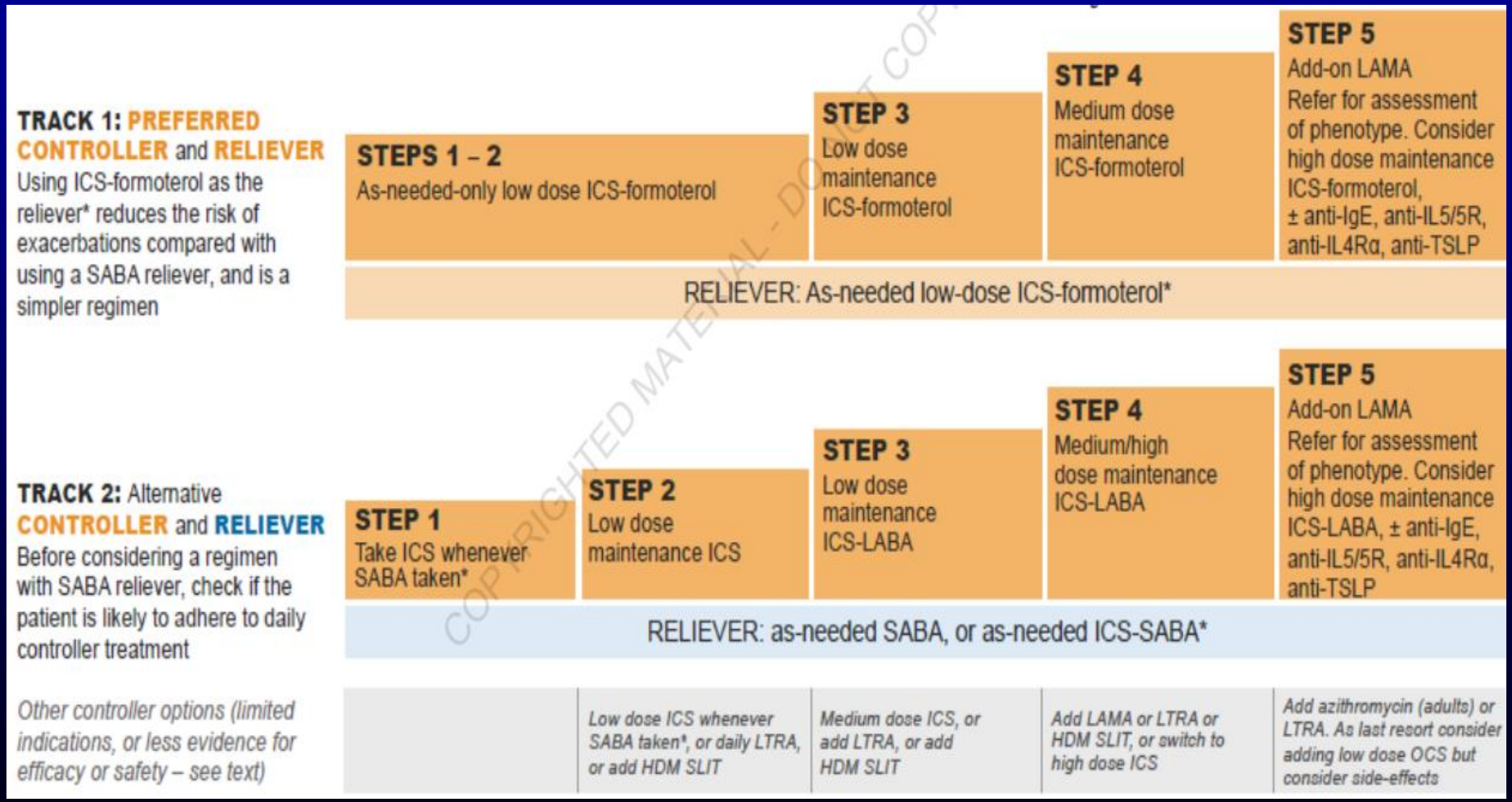
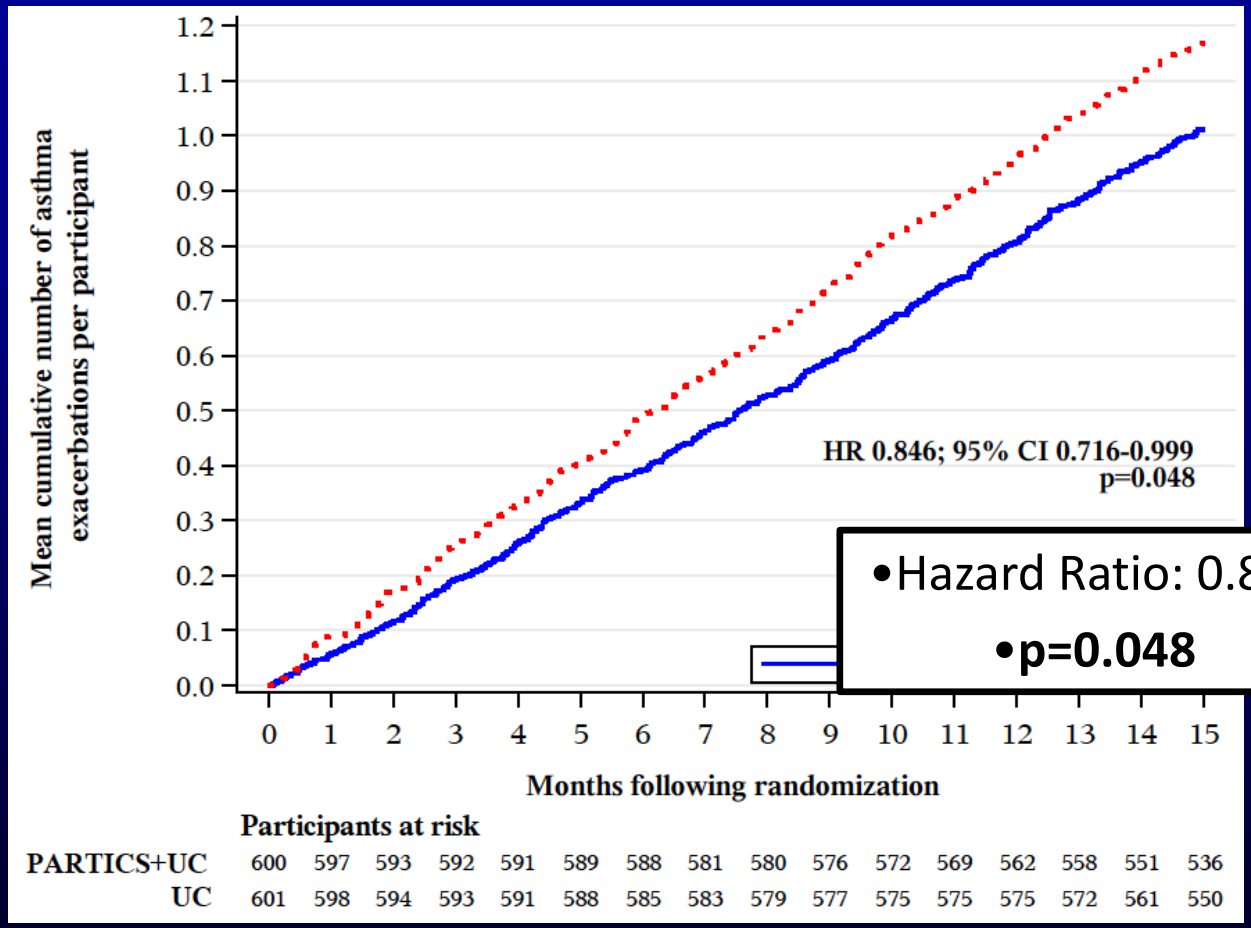
GINA Update 2023 (Addition of ICS/SABA as alternative reliever)



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



- Hazard Ratio: 0.846
- **p=0.048**

- **PARTICS** reduced severe exacerbations by 0.13/person/year
- This is **equal or greater** than the reduction in severe exacerbations seen in **SMART** studies cited by NAEPP (0.12/patient/year, weighted by sample size and duration)

- **PARTICS**: **P**atient **A**ctivated **R**eliever **T**riggered **ICS**

- Israel et al. NEJM 2022

Additional NAEPP Updates

- LAMA can be used in addition to ICS/LABA for some potential additional control in Step 5
- Allergy shots can be used in mild-moderate asthma with clinical worsening due to allergens but NOT in severe asthma
  - SLIT is not recommended for asthma
- Indoor allergen mitigation not that effective
  - Consider only for those with documented allergy to indoor substances
    - Pest control provides some benefit
    - Multi-strategy dust control provides some benefit

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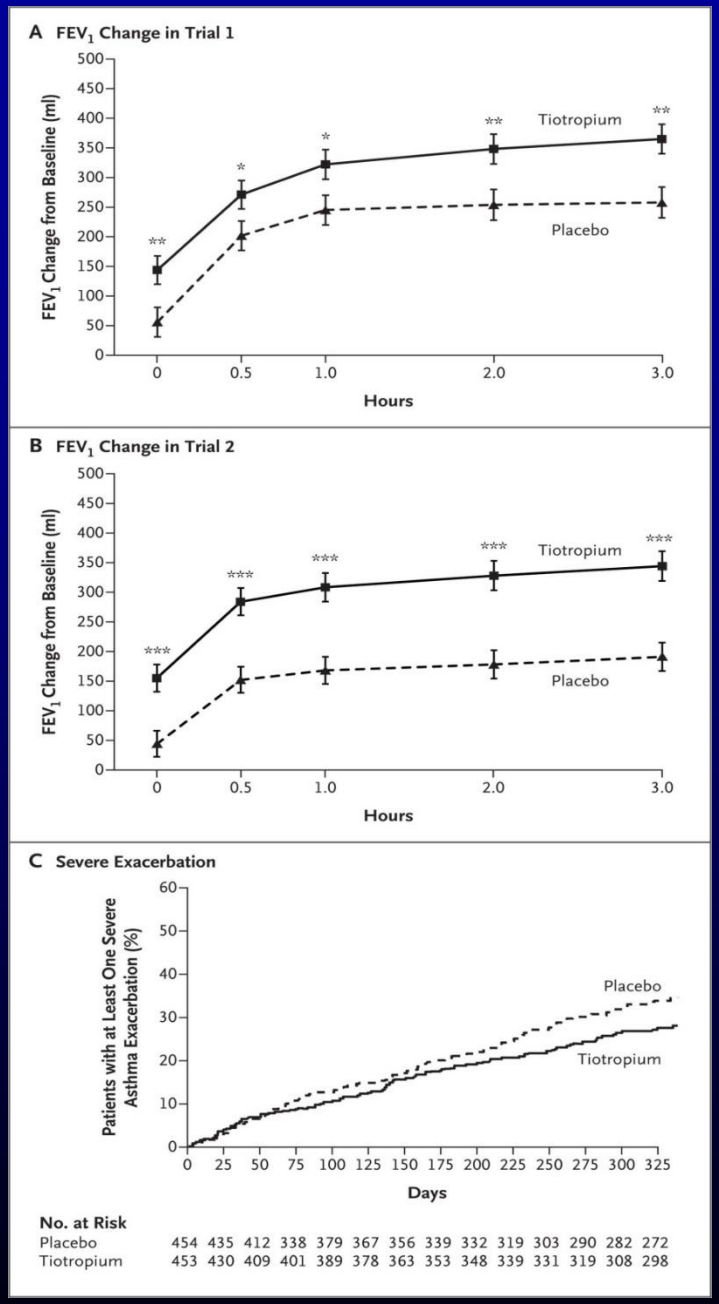

Long-acting AntiCholinergics

Improve FEV1 and Reduce Exacerbations in Patients uncontrolled on High-Dose ICS/LABA

Kerstjens HAM et al. N Engl J Med 2012;367:1198-1207

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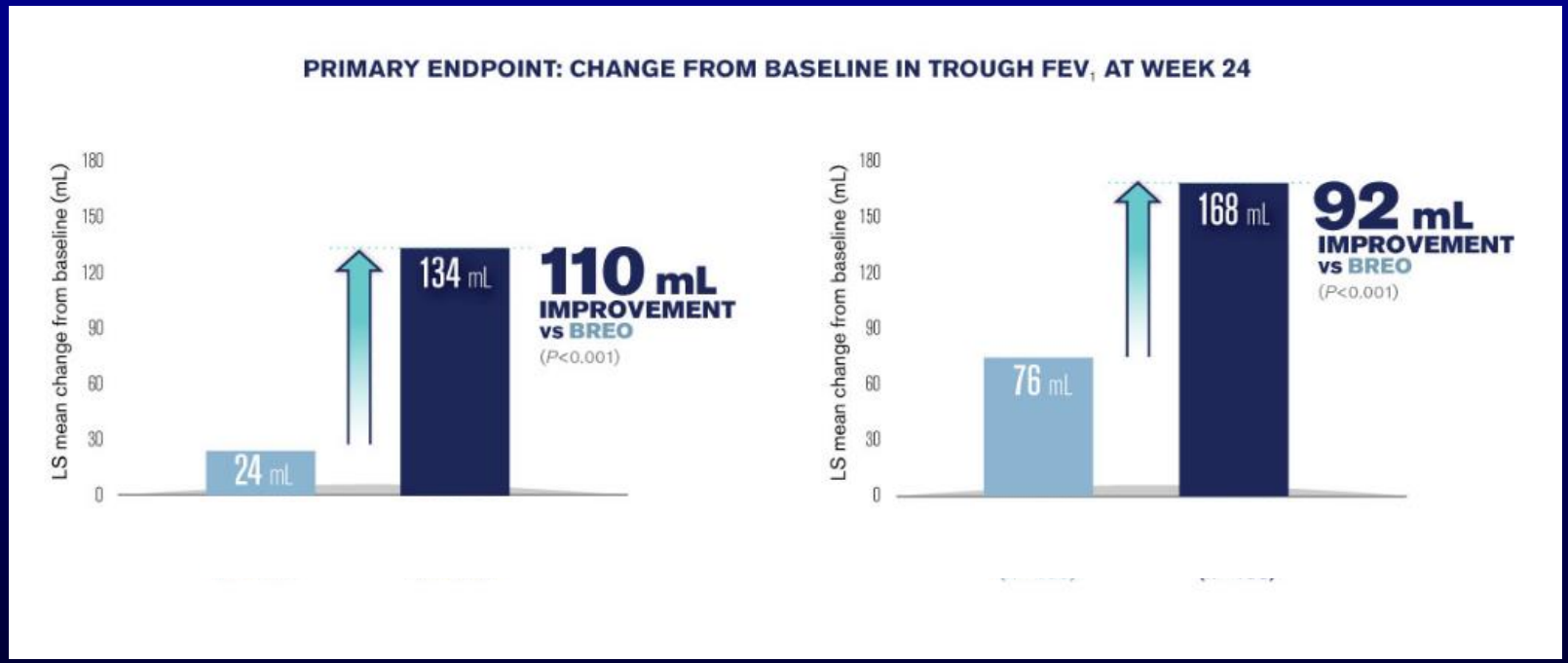
QD Triple Inhaler ICS/LABA/LAMA

F furoate/(umeclidinium)/vilanterol



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Additional NAEPP Updates

- FeNO can be used as an adjunctive measure to assist in diagnosis of asthma but should not be relied on primarily
- FeNO can be used as an adjunctive measure to follow patients Type 2 inflammation
  - High levels according to NAEPP are >50 in adults and >35 in kids
  - Need to be aware that allergic rhinitis can produce increased FeNO w/o asthma

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Use of Exhaled Nitric Oxide

- Markedly reduced by use of ICS
- Persistently high FeNO despite therapy is c/w non-compliance or pathobiology resistant to therapy
- May be a good predictor of response to therapy for patients considered for biologic aimed at Type 2 process (Anti- IgE / Anti - IL4/IL13

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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^H2) CD4+ 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.

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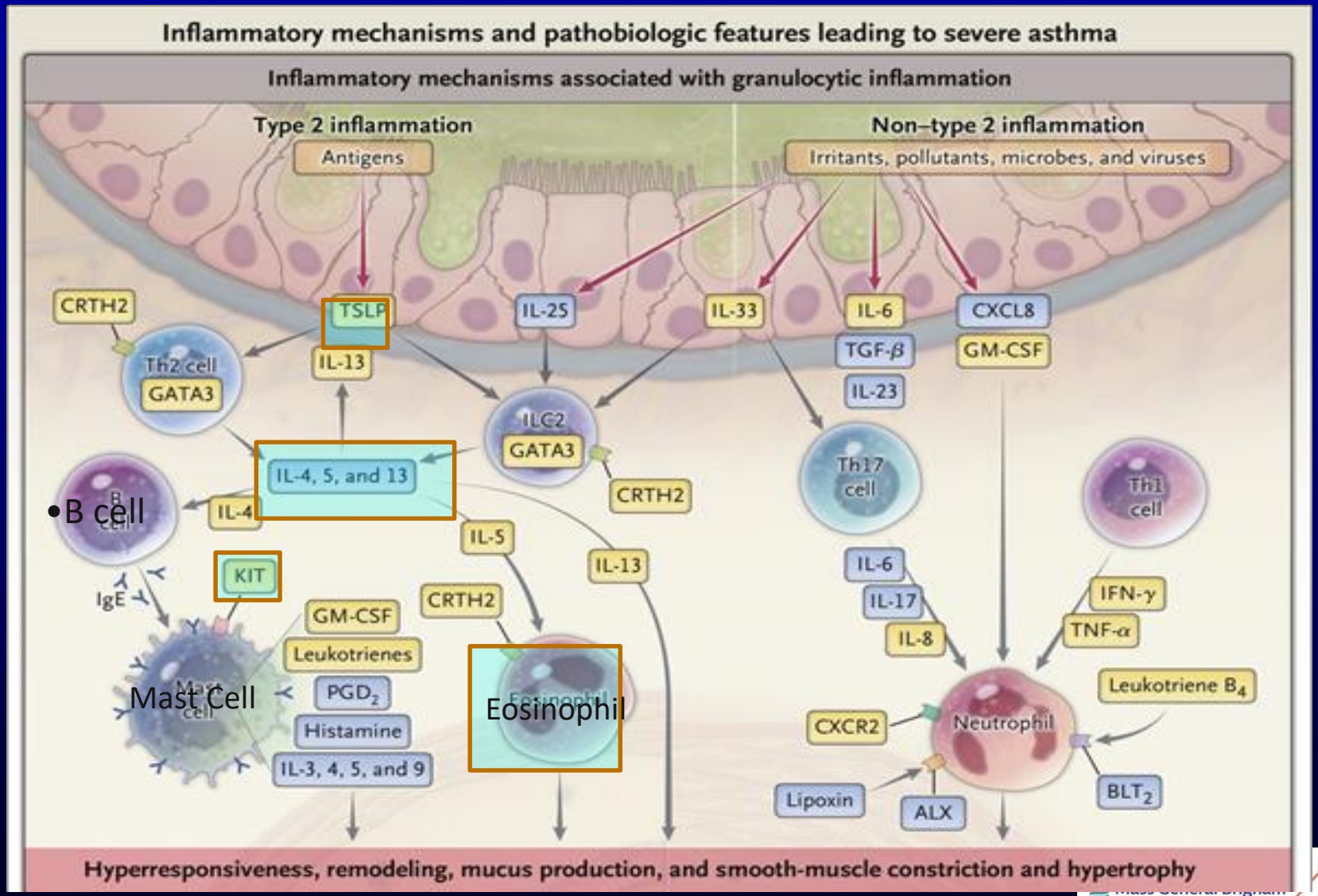
Gandhi

Type 2 Inflammatory Targets



•Israel & Reddel, NEJM, 2017

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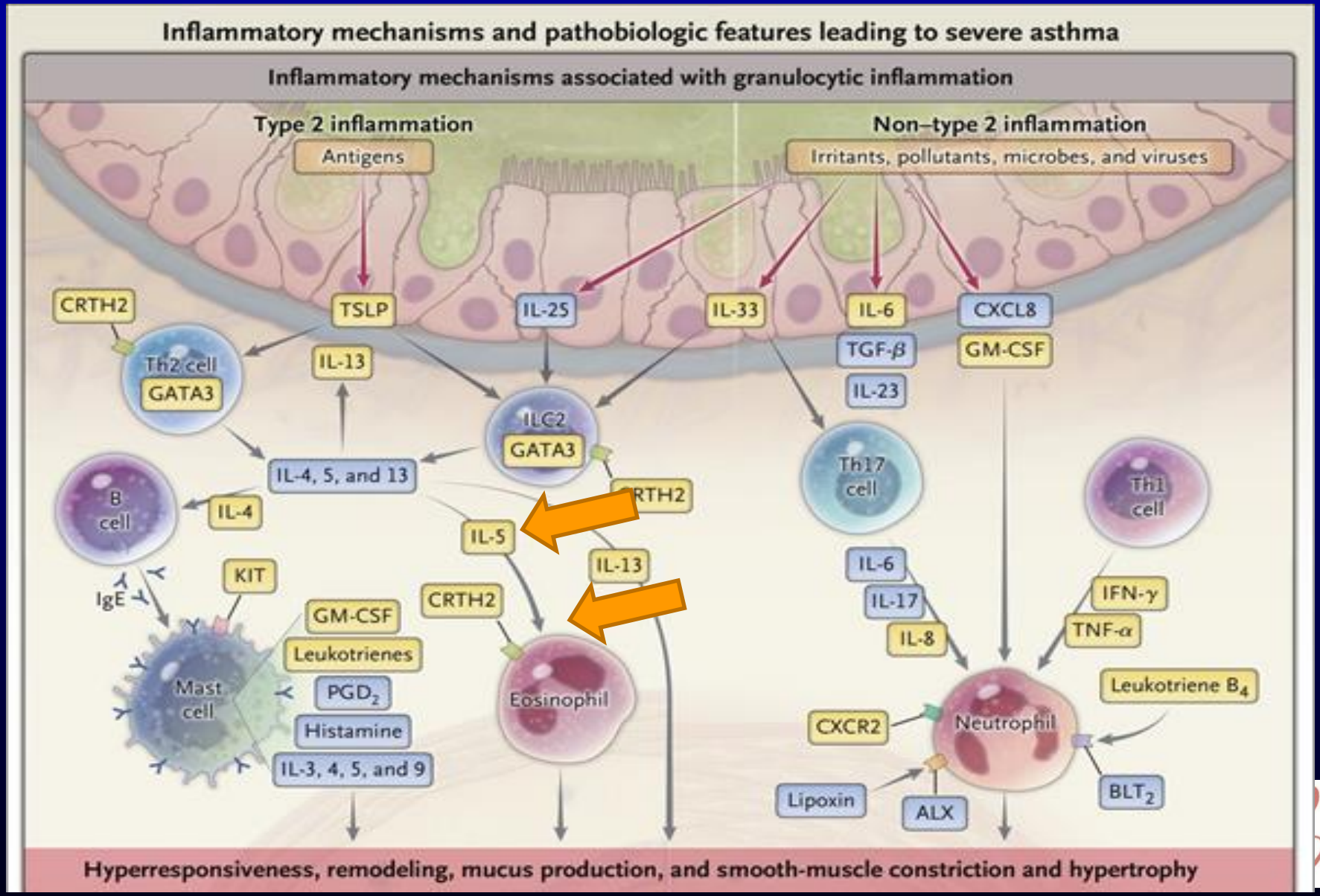
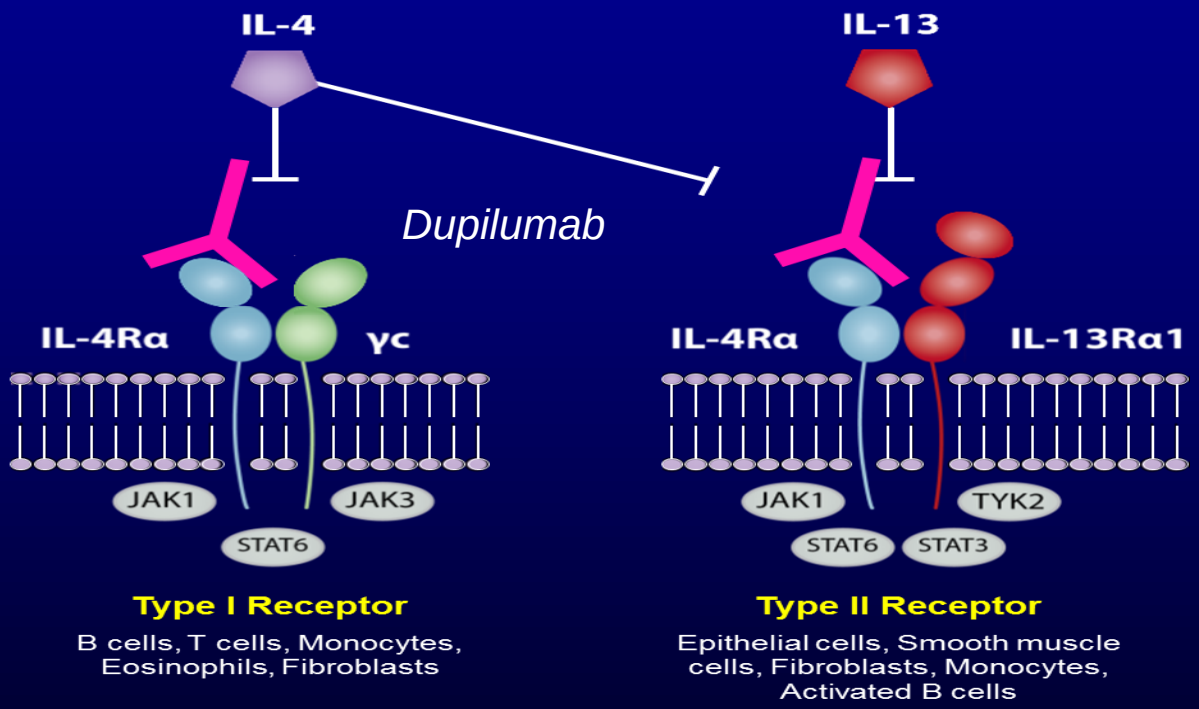
Type 2 Inflammatory Targets – IL5



•Israel & Reddel, NEJM, 2017

Blocking IL-4Ralpha (Dupilumab) Blocks both IL4 and IL13



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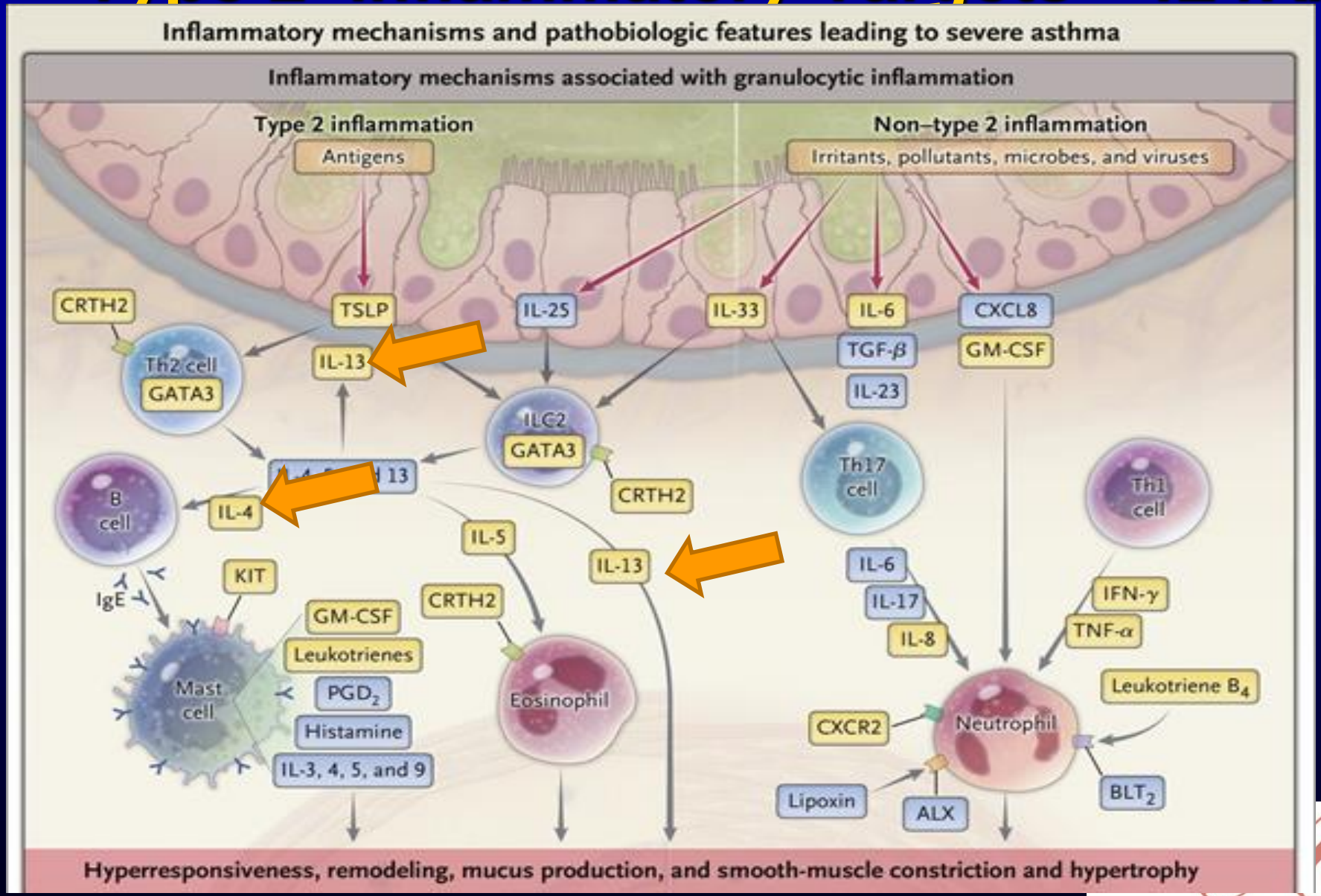
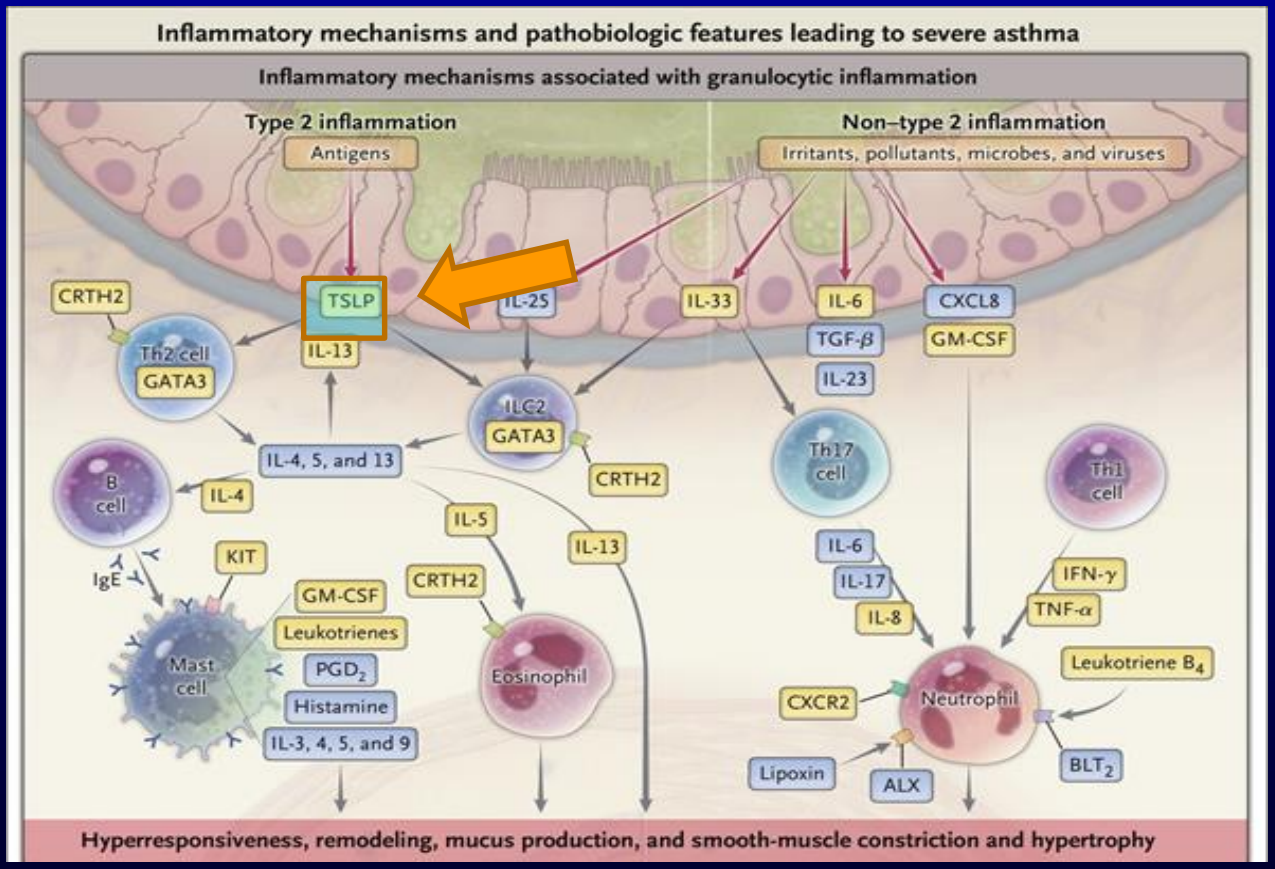
Type 2 Inflammatory Targets – IL4RA



•Israel & Reddel, NEJM, 2017

Type 2 Inflammatory Targets - TSLP



•Israel & Reddel, NEJM, 2017

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Outcomes in Patients with Eosinophils ≥300/ul

- (Studies Required 1-2 exacerbations, ≥12% Bronchodilator Response and ACQ ≥1.5 on Study Entry)

	IgE	IL5			IL4RA	TSLP
	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab	Tezepelumab
% Reduction in Exacerabation	32	61	~55 (In eos >400/ul)	~35	66	70
FEV1 (cc)	40	202	126	~138	~225	230
ACQ	0.36	~0.48	~0.24	~0.2	~0.4	0.33

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OCS-Sparing Effects (Regardless of Blood Eosinophil Count)

- Effective
  - Mepolizumab
  - Benralizumab
  - Dupilumab
- Did not Show Effectiveness in Pivotal Trial
  - Tezepelumab
- Not tested
  - Reslizumab

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Administration of the Biologics in Severe Asthma

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab	Tezepelumab
Lowest age	6	6	18	12	6	12
Frequency	2-4 wks	4 wks	IV 4 weeks	8 wks after first months	2 wks	4 wks
Mode	SC	SC	IV	SC	SC	SC
Home Administration	Y	Y	N	Y	Y	Y
Anaphylaxis	0.1-0.3%	NR	0.3%	NR	NR	NR
Additional Notes	-	-	-	-	-Temporary increase in eosinophil - Conjunctivitis	

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Effects on Biomarkers

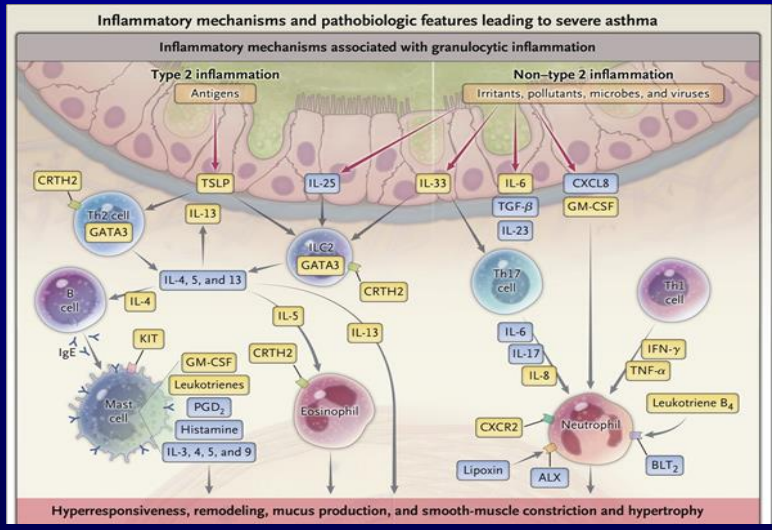
Effect of the Biologics on Biomarkers in Severe Asthma

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab	Tezepelumab
IgE	+++[X]	=	=	=	+[#]	+[#]
FeNO	+[#]	=	=	=	+	++
Eosinophils	+[#]	+++	+++	+++/+++	-/+*	++

[X]Reduction in free IgE (commercial assays detect TOTAL igE)

[#]**Gradually reduced**

*Eosinophils may rise especially in those with high baseline eosinophils



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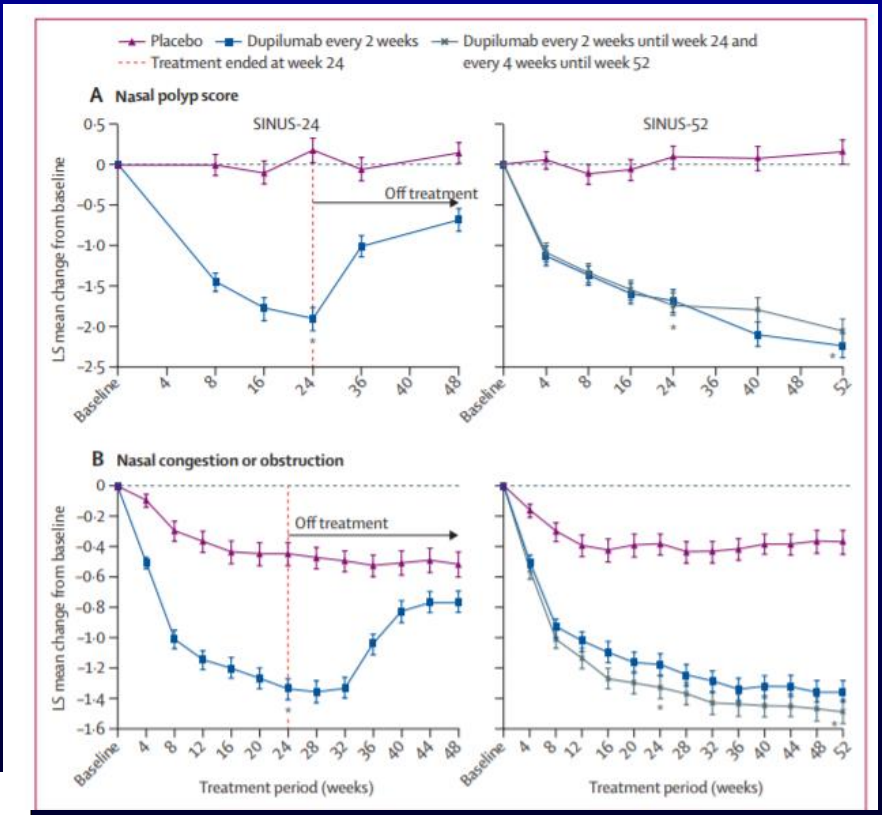
Effects on Co-Morbidities

Dupilumab First Shown Effective in Nasal Polyposis

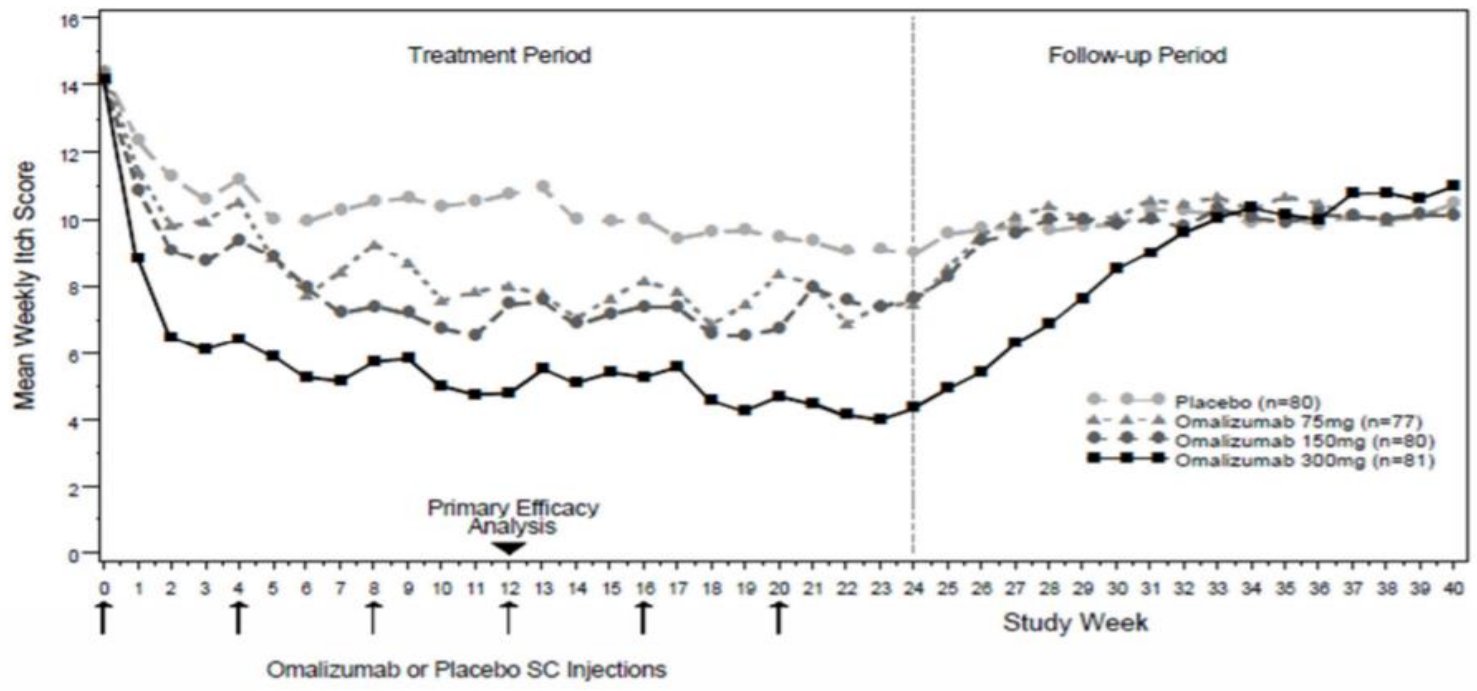


Now shown for:
-Mepolizumab
-Omalizumab

Bachert, Lancet, 2019

Omalizumab is Effective in Chronic Idiopathic Urticaria

Figure 2. Mean Weekly Itch Severity Score by Treatment Group
Modified Intent to Treat Patients in CIU Trial 1



SEVERE ASTHMA PROGRAM

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Dupilumab is Very Effective in Atopic Dermatitis and Is Approved for that Indication in Age 6 months and above

-Also approved for eosinophilic esophagitis age 12+

-Approved for prurigo nodularis

Biomarkers of Patients Likely To Respond

- **ALL PATIENTS STUDIES HAD TO HAVE ≥1-2 EXACERBATIONS AT BASELINE AND BD BY ≥12%**

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

Anti-IgE

- Qualifications – IgE 30 to 700 and a positive skin test or RAST to an inhalant allergen

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Neutrophilic or Non-Type 2 Asthma

- More than half of asthma patients have asthma that involves inflammation mediated by Type 2 cytokines (IL4,5, and 13) ⩾ IgE/Eosinophils
- Forty to 50% may have neutrophilic or paucigranulocytic inflammation
  - May be less responsive to steroids

Points to Remember

- SMART is recommended in Step 3 and 4 therapy by NAEPP but may have implementation and patient characteristic limitations
- IgE >30 or Eos ≥300 (150) may be candidates for biologics especially with 2 or more exacerbations per year
- Consider co-morbidities in use of biologics
- While tezepelumab is most effective in T2 high asthma it appears to have significant effectiveness in T2 low asthma with high exacerbations
- Pts on OCS candidates for biologics regardless of eosinophil count

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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 or 1 844 BWH-LUNG**

Question #1

Which of the following is NOT generally considered part of the conditions for recommendation of anti-IL5 therapy?

a. Persistent symptoms on high dose ICS/LABA or two types of asthma controllers
b. Eosinophils ≥300
c. 2 or more exacerbations
d. High FeNO

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Answer Question #1

- D

- – 2 or more exacerbations in the context of eosinophils ≥300 AND failure on Step 5 therapy identify patients most likely to have a reduction in exacerbation.
  - High FeNO does NOT identify patients likely to respond to anti-IL5

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Question #2

55F symptomatic on Step 5 therapy with 2 exacerbations in the last year, IgE 300, Eos 100, FeNO 55, RAST negative. Comorbidities include hypertension and atopic dermatitis. Which of the numbered options would you choose?

1. Omalizumab
2. Anti-IL5 therapy
3. Dupilumab
4. Tezepelumab

a. **Any of them**
b. **#3 or #4**
c. **#3**
d. **#4**

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Answer Question #2

- C - Dupilumab

-She has the requisite number of exacerbations and medication use for all of them. However, RAST is negative so not omalizumab. Eos are too low for anti-IL5.

FeNO is high enough for Dupilumab and Tezepelumab but concomitant atopic dermatitis makes dupilumab the preferred choice.

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Short List of References

- 2020 Focused Updates to the Asthma Management Guidelines: : A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. Cloutier M et al. J All Clin Imm 2020: 146: 1217-1270

- Israel E, Reddel HK. Severe and Difficult to Control Asthma in Adults, N Engl J Med 2017; 377:965-976

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