It's Not About T2!
Low T2 Asthma Phenotype Pathophysiology

Thomas B. Casale, MD
Professor of Medicine and Pediatrics
University of South Florida Morsani College of Medicine
Tampa, FL USA

Learning Objectives:

Upon completion of this learning activity, participants should be able to:

- **Describe T2 inflammation in the context of pathogenesis and therapy of allergic and respiratory diseases.**
- **Review where are we today with biologic treatments for T2lo asthma**
- **Discuss what is needed to better treat patients for T2lo asthma**

Case Presentation: "JILL"

Jill is 51 yo obese female presents with a 25-year H/O asthma

3 steroid bursts in last 12 months

Current ACT score is 17

Medications:

- Budesonide/formoterol160/4.5 BID and PRN
- Albuterol 2 puffs Q4h PRN

PMH: Chronic rhinitis and multiple "sinus infections" annually

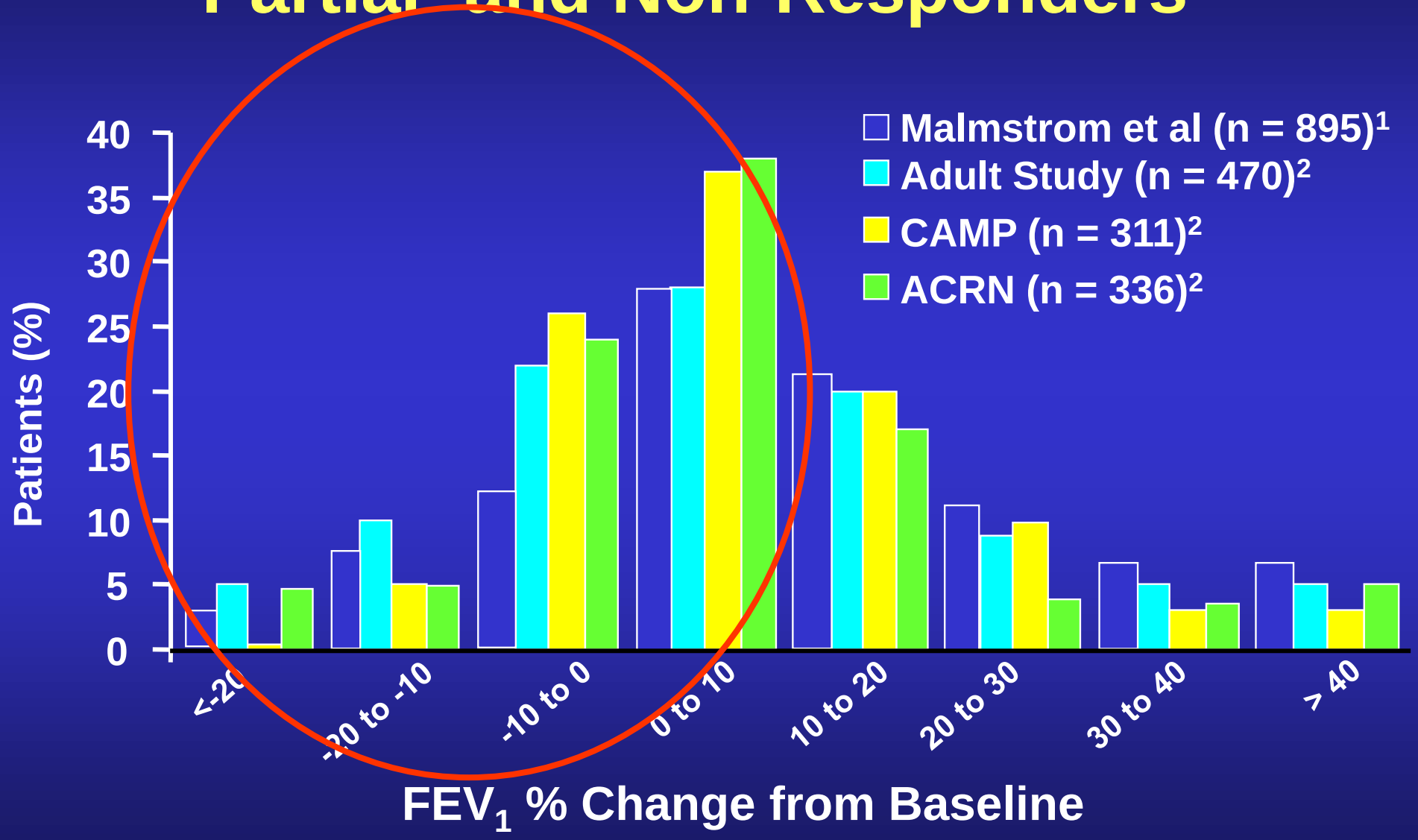
PE: Diffuse wheezing on expiration

Meds: mometasone 2 spr each nostril QD; atorvastatin QD

Spirometry:

- FEV 65 %FVC 75%
- FVC 75%
- FEV/FVC: 0.7

Analysis of Inhaled Corticosteroid Partial- and Non-Responders



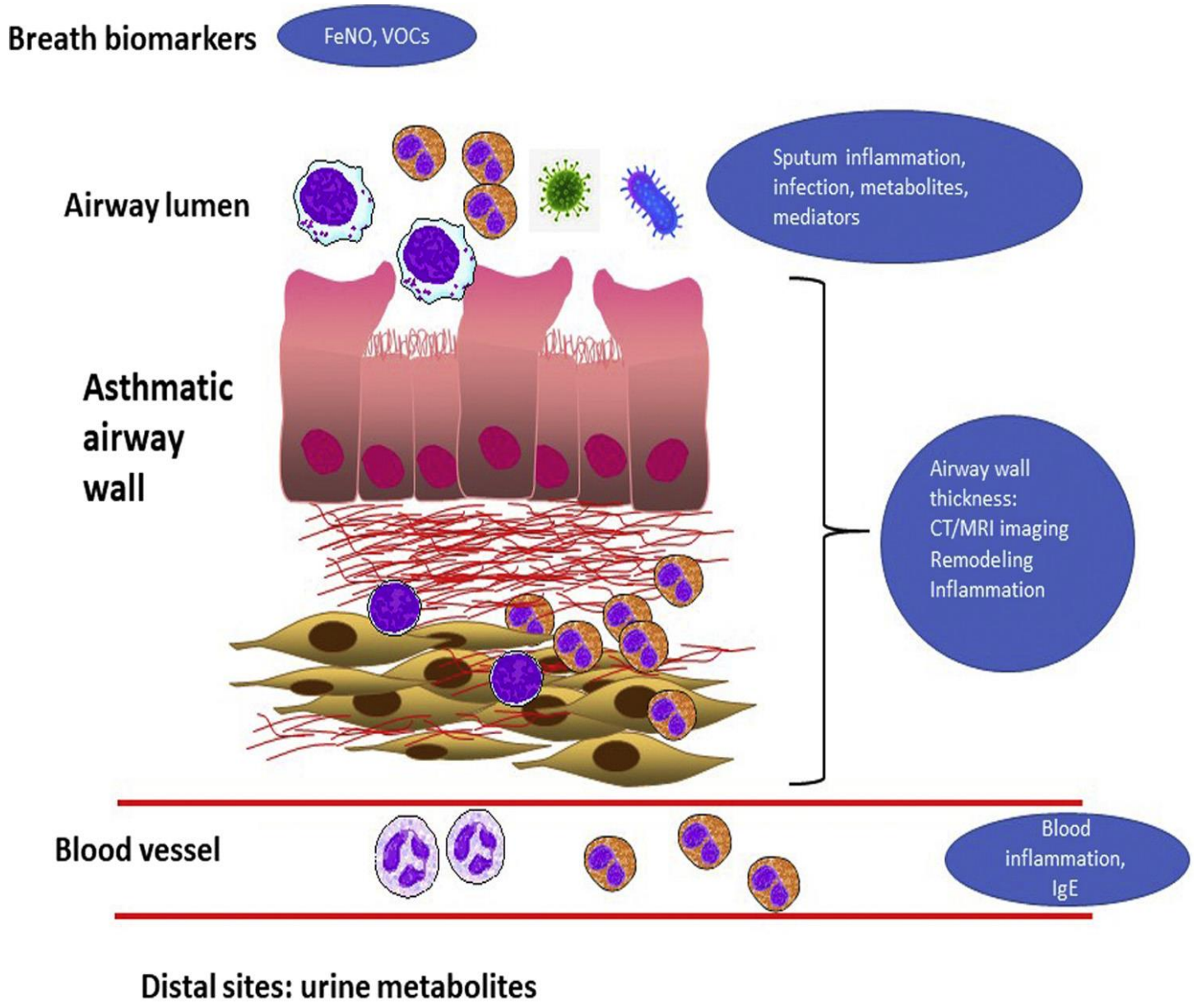
[1]Malmstrom K, et al. *Arch Intern Med.* 1999;130:487-95.
[2]Tantisira KG, et al. *Hum Mol Genet* 2004;13:1353–9.

Next steps to consider

- Check reversibility
- Do complete PFTs with DLCO
- Measure FeNO
- Measure blood eosinophils
- Do allergy testing
- Measure total IgE
- Rhinoscopy
- Sinus CT

Asthma Biomarkers: *Not where we need to be!*

- ***Allergic:* IgE 30-1300**
- ***Eosinophilic:***
  Bld ≥150/sputum>1%
- ***Type 2 hi:***
  Bld eos ≥150/FeNO>20
- ***Type 2 lo:***
  None of the above!

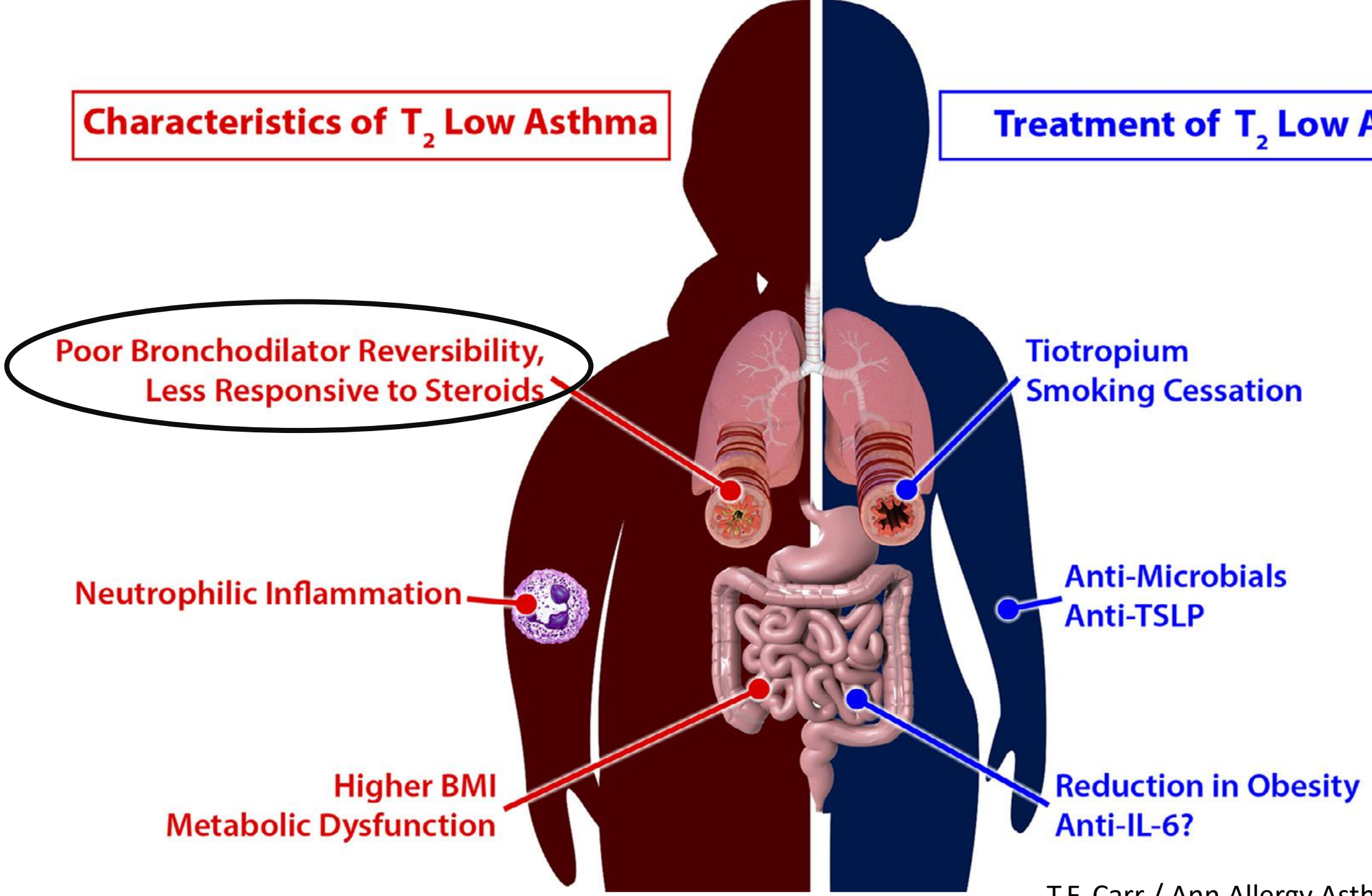


Agache et al, Allergy, 2020; Casale et al, Allergy, 2018

Custovic et al, JACI. 2/2022

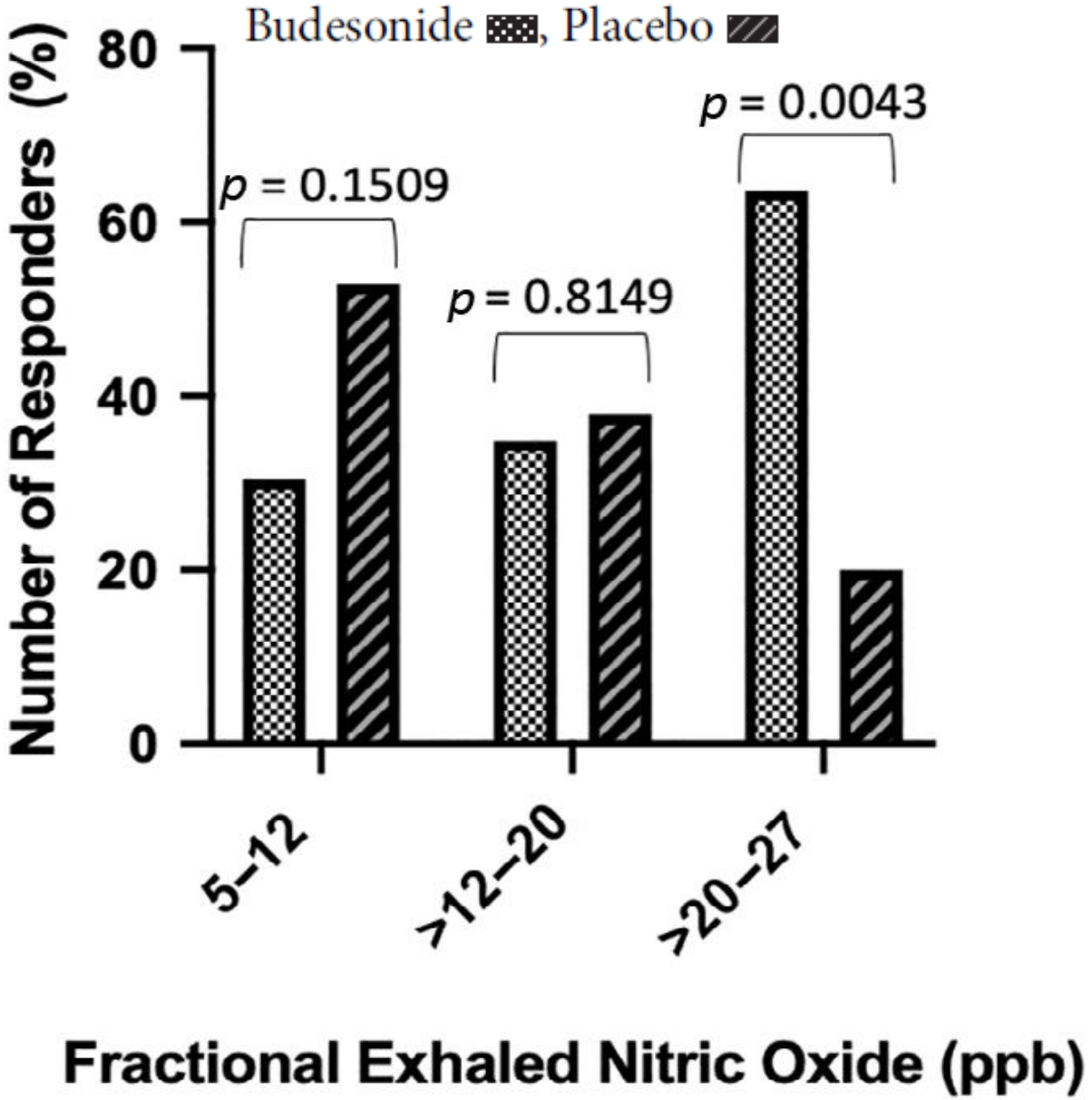
Next steps to consider for JILL

- Check reversibility: 10% and 125mL
- Do complete PFTs with DLCO: Did not do
- Measure FeNO: 18
- Measure blood eosinophils: 125
- Do allergy testing: Negative
- Measure total IgE: 30
- Rhinoscopy: Did not do
- Sinus CT: Did not do



T.F. Carr / Ann Allergy Asthma Immunol 2021.

Response to ICS according to baseline FeNO tertiles



Respirology. 2021;26:666–672

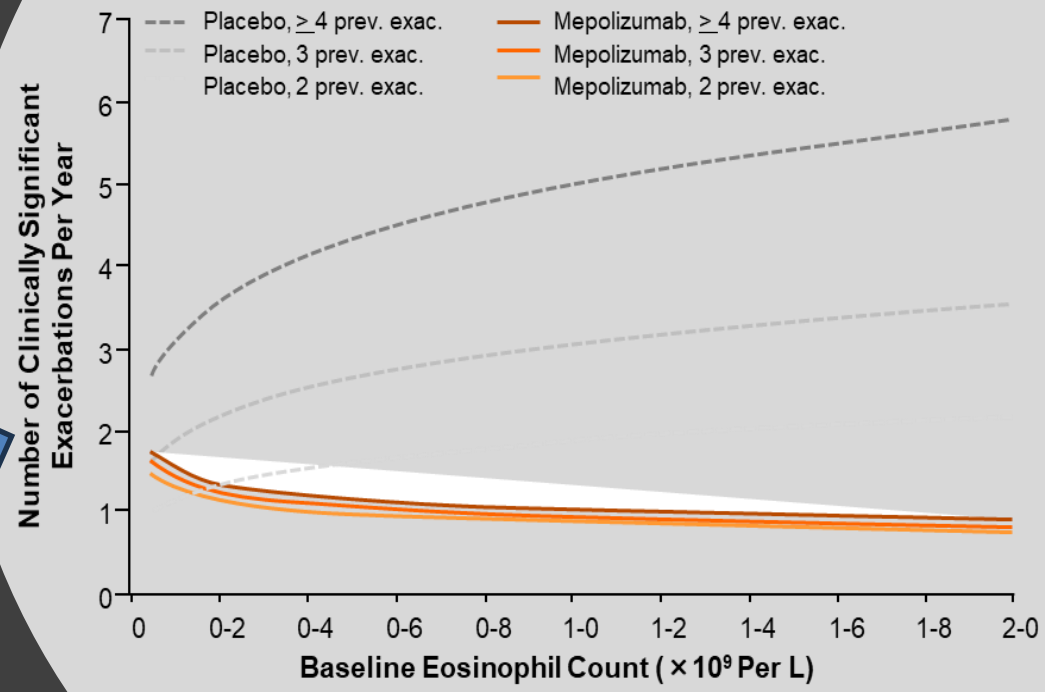
The T2lo Biomarker Conundrum

We lack T2lo biomarkers

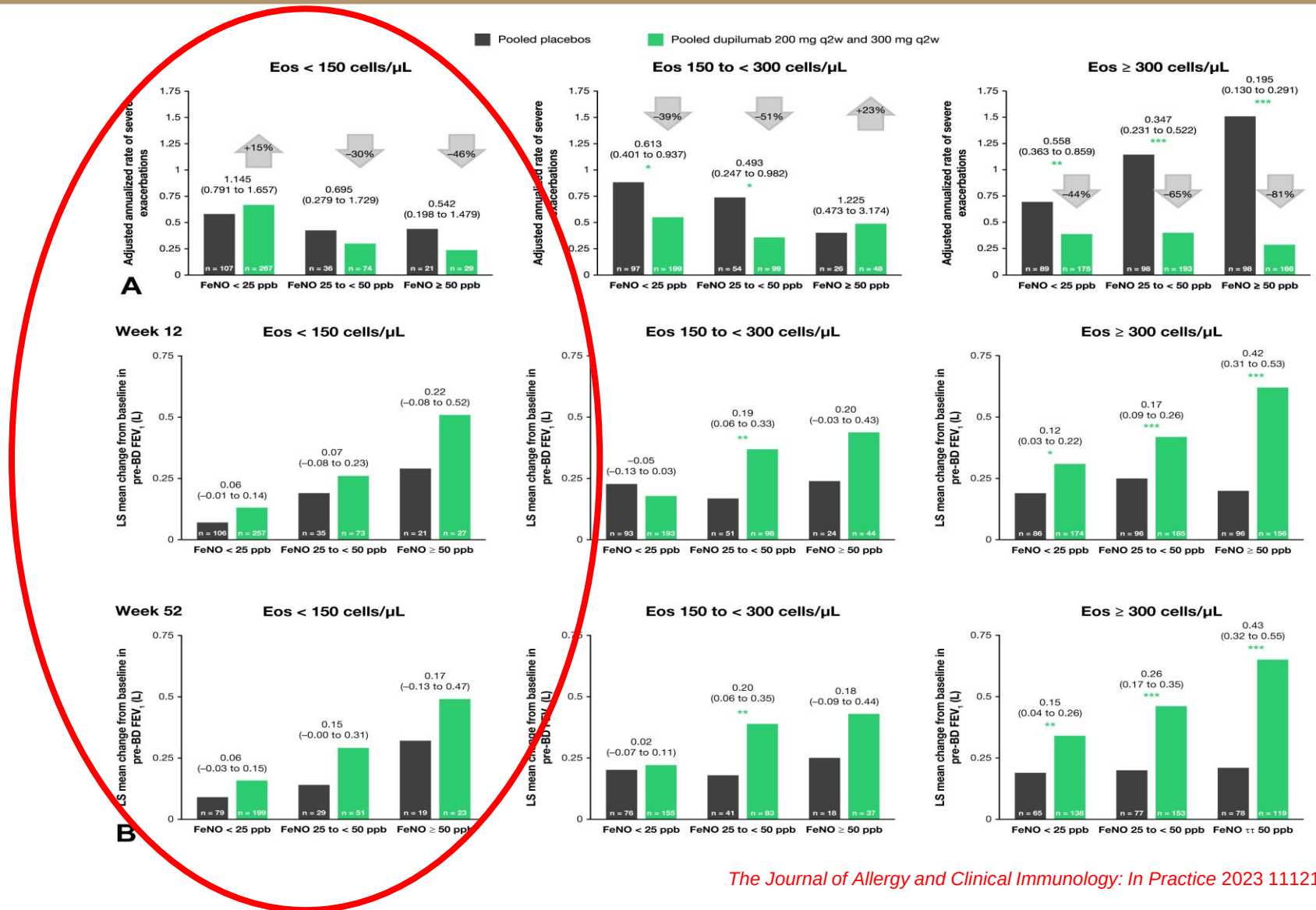
No specific biomarker to predict exacerbations in T2lo patients

Improved clinical responses with the current T2 hi biomarkers are largely driven by the placebo

Eos are a good biomarker to predict exacerbations



Response To Dupilumab Based On Biomarkers

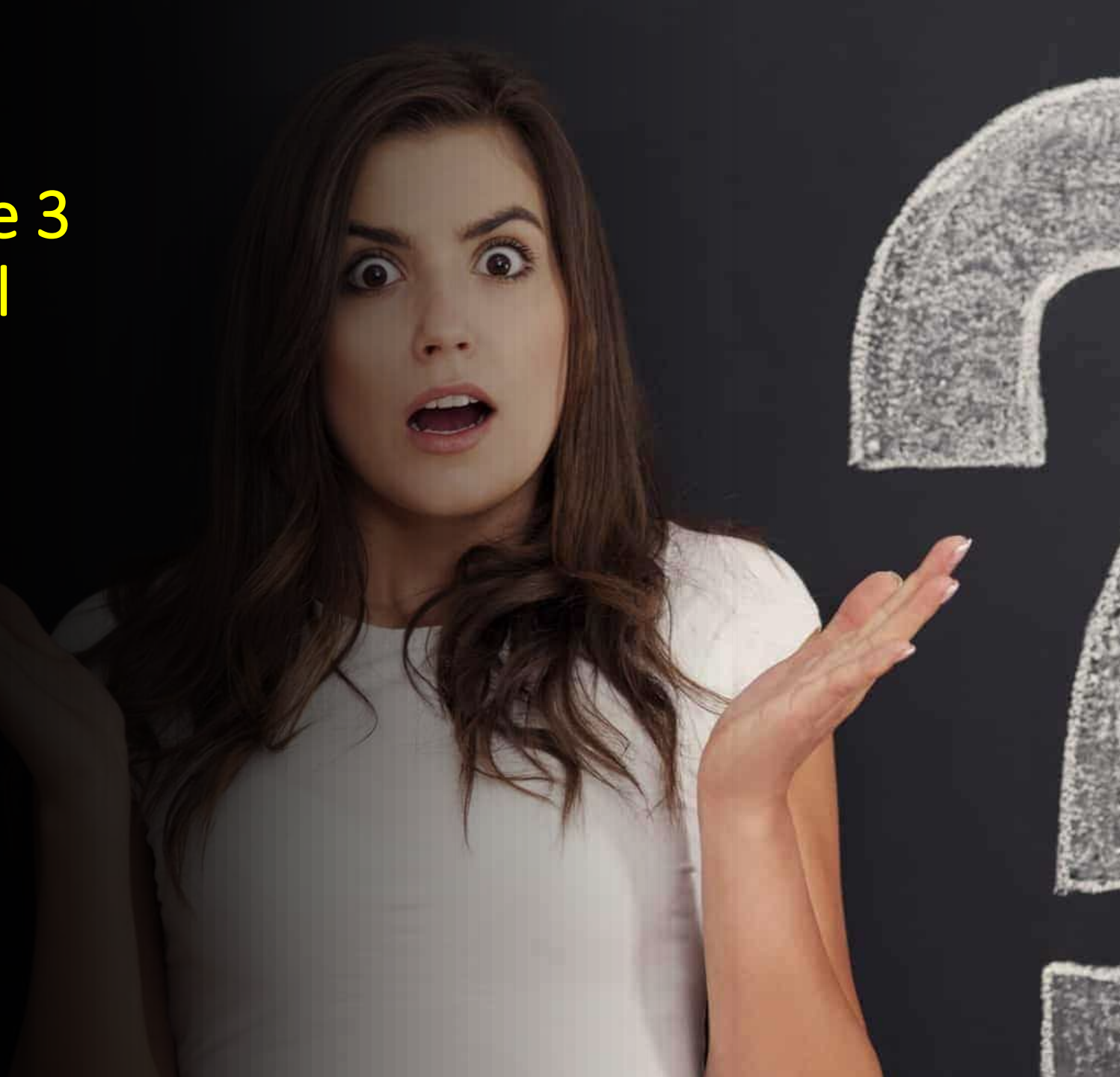


The Journal of Allergy and Clinical Immunology: In Practice 2023 111213-1220.e2DOI: (10.1016/j.jaip.2022.11.043)

Good news!
Your asthma has stayed the same,
But the research findings have changed!

Which to Choose When the 3 Biomarkers Are Not Helpful

- Patient preferences (shared decision making)
- What is the end game for the patient?
  - Data-driven choices
- Co-morbidities
- Exacerbation Triggers
- Insurance coverage!



Effects of Biologics Approved for Asthma on Comorbidities

Comorbidity	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab	Tezepelumab
Atopic dermatitis	+/−	−	No data	No data	Indicated	Failed
CRSwNP (nasal polyposis)	Indicated	Indicated	+	++	Indicated	No data
Food allergy	++	No data	No data	No data	+	No data
Allergic rhinoconjunctivitis/ allergic rhinitis	++	No data	No data	No data	+	No data

Differences Between The 2 Main CRS Phenotypes

Characteristics	CRSsNP	CRSwNP
Predominant inflammatory profile[1-4]	**Th1**	**Th2**
Common comorbidities[2,3,5]	Asthma: 22% Allergic rhinitis: 52% Asthma + allergic rhinitis: 68%	Asthma: 56% Allergic rhinitis: 76% Asthma + allergic rhinitis: 82% A/NSAID-ERD: 8%–26%

1. Benjamin MR, et al. *J Allergy Clin Immunol Pract.* 2019;7:1010-1016. **2**. Cho SH, et al. *J Allergy Clin Immunol Pract.* 2016;4:639-642. **3**. Orlandi RR, et al. *Int Forum Allergy Rhinol.* 2016;6(Suppl 1):S22-S209. **4**. Hopkins C. *N Engl J Med.* 2019;381:55-63. **5**. Laidlaw TM, et al. *J Allergy Clin Immunol Pract.* 2021;9:1133-1141.

Therapeutic Considerations

- Add LAMA
- OCS burst
- Change INCS dose and agent
- Consider a biologic
  - **Which one????**
- Antibiotics
- Refer to ENT
- Other?

Low-Dose Cumulative OCS Exposure Is Associated With Significant Adverse Effects[1,a]

44% of adults with asthma reported OCS use in the past 12 months[2]

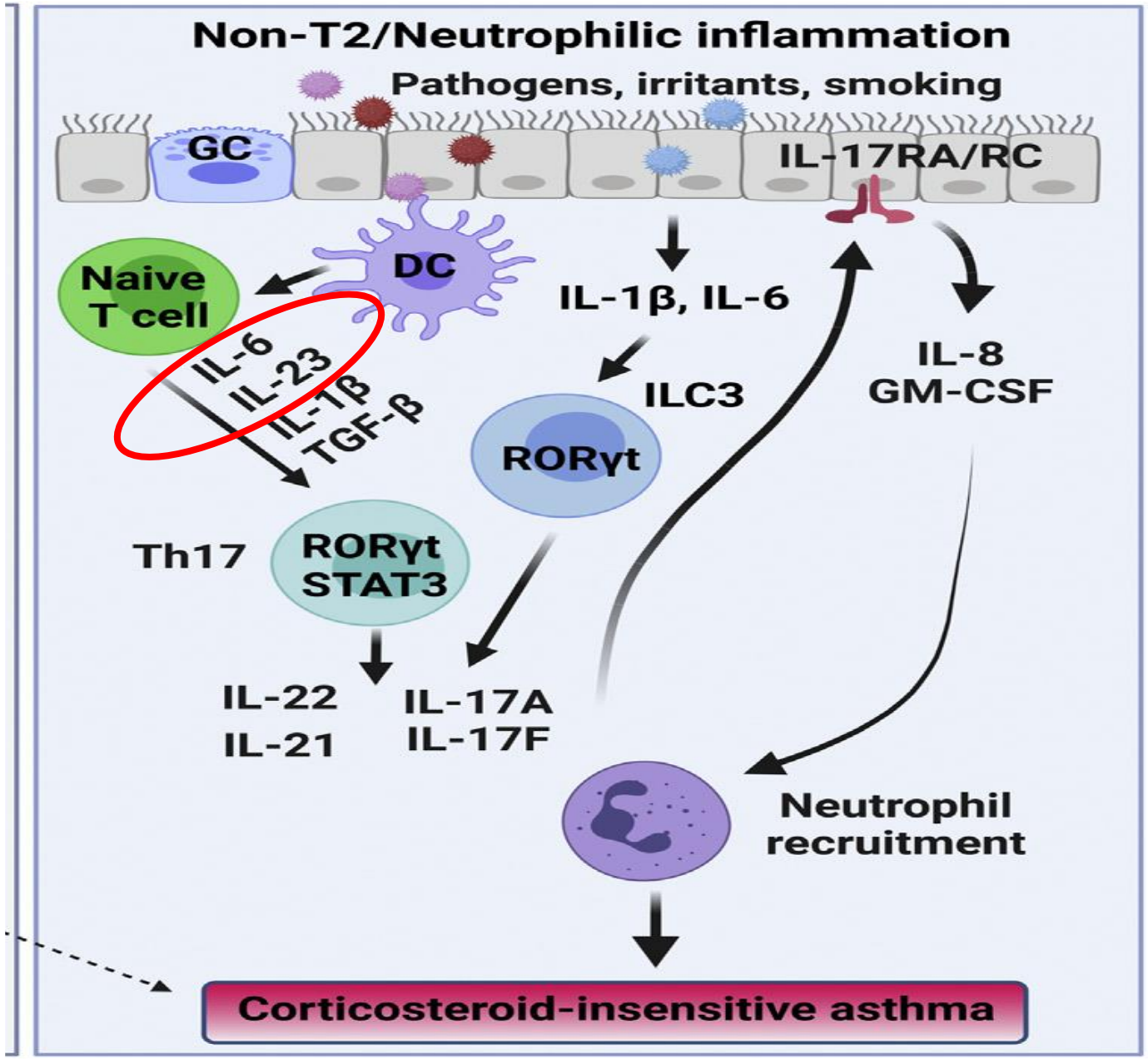
Cumulative OCS Exposure*	Osteoporosis Diagnosis and Fracture	Pneumonia	Type 2 Diabetes Mellitus	Cardio-/Cerebrovascular Disease
HR (95% CI) vs reference of >0 to <0.5 g cumulative OCS exposure				
0.5 to <1.0 g	1.34 (0.74-2.44)	1.17 (0.97-1.42)	1.16 (1.01-1.34)	1.14 (0.98-1.32)
1.0 to <2.5 g	2.60 (1.48-4.56)	1.70 (1.41-2.05)	1.37 (1.18-1.58)	1.42 (1.22-1.66)
2.5 to <5 g	2.39 (1.20-4.79)	2.52 (2.02-3.14)	1.34 (1.11-1.63)	1.79 (1.49-2.14)
5 to <10 g	4.96 (2.56-9.63)	3.36 (2.65-4.26)	2.03 (1.65-2.50)	1.96 (1.59-2.41)
≥10 g	5.79 (2.82-11.88)	3.98 (3.09-5.14)	2.59 (2.07-3.24)	2.23 (1.79-2.77)

Most adverse effects become significant above 0.5 to <1.0 g, equal to 4 lifetime "bursts"[1]

HR, hazard ratio.

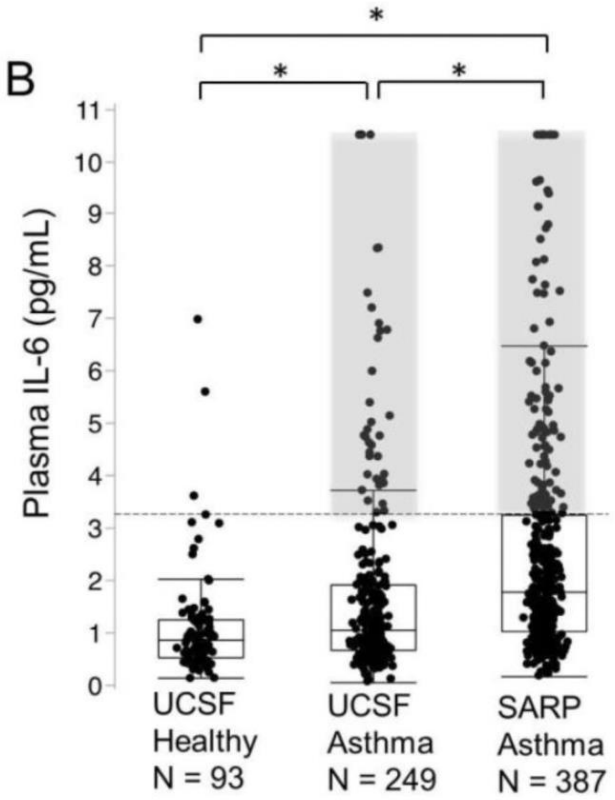
[a]For cumulative systemic CS exposure, HR are presented per 1.0 g increase in cumulative SCS dose as a continuous variable.[1]

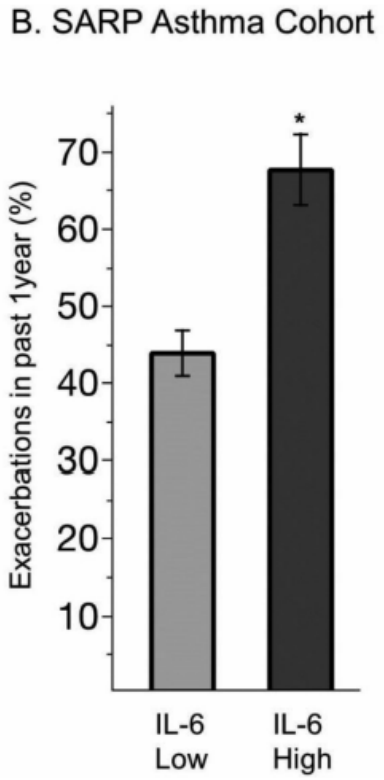
1. Price DB et al. *J Asthma Allergy*. 2018;11:193-204. 2. Price D et al. *NPJ Prim Care Respir Med*. 2014;24:14009.

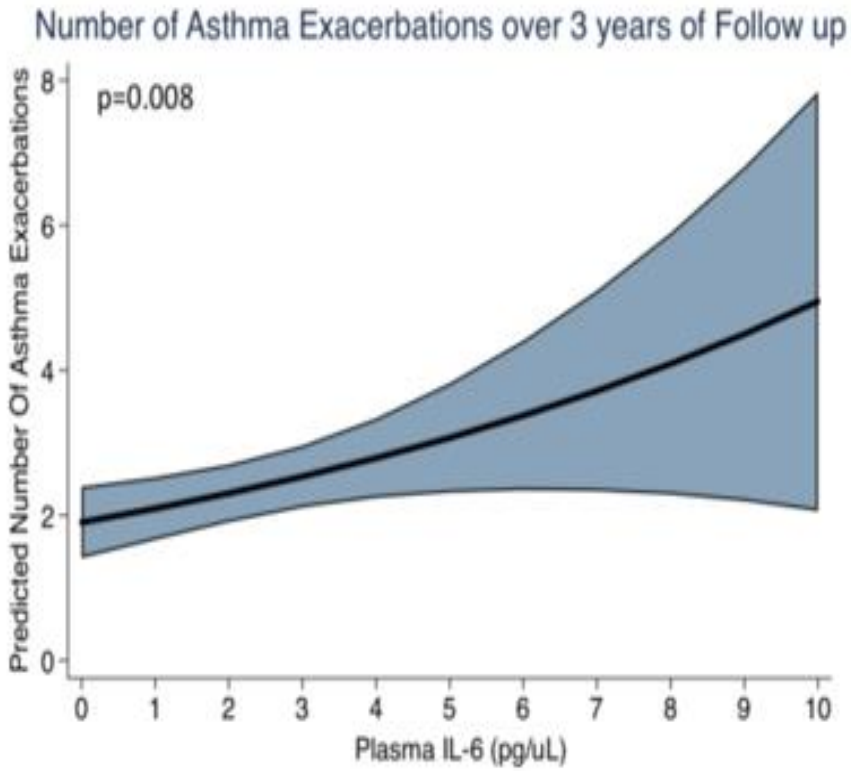


Xie, Abel, Casale, Tu. JACI, 2022

Rationale For Anti-IL-6 Blockade In Severe Asthma







Testing Anti-IL6 Blockade with Clazakizumab in NHLBI-PRECISE Study On Severe Asthma

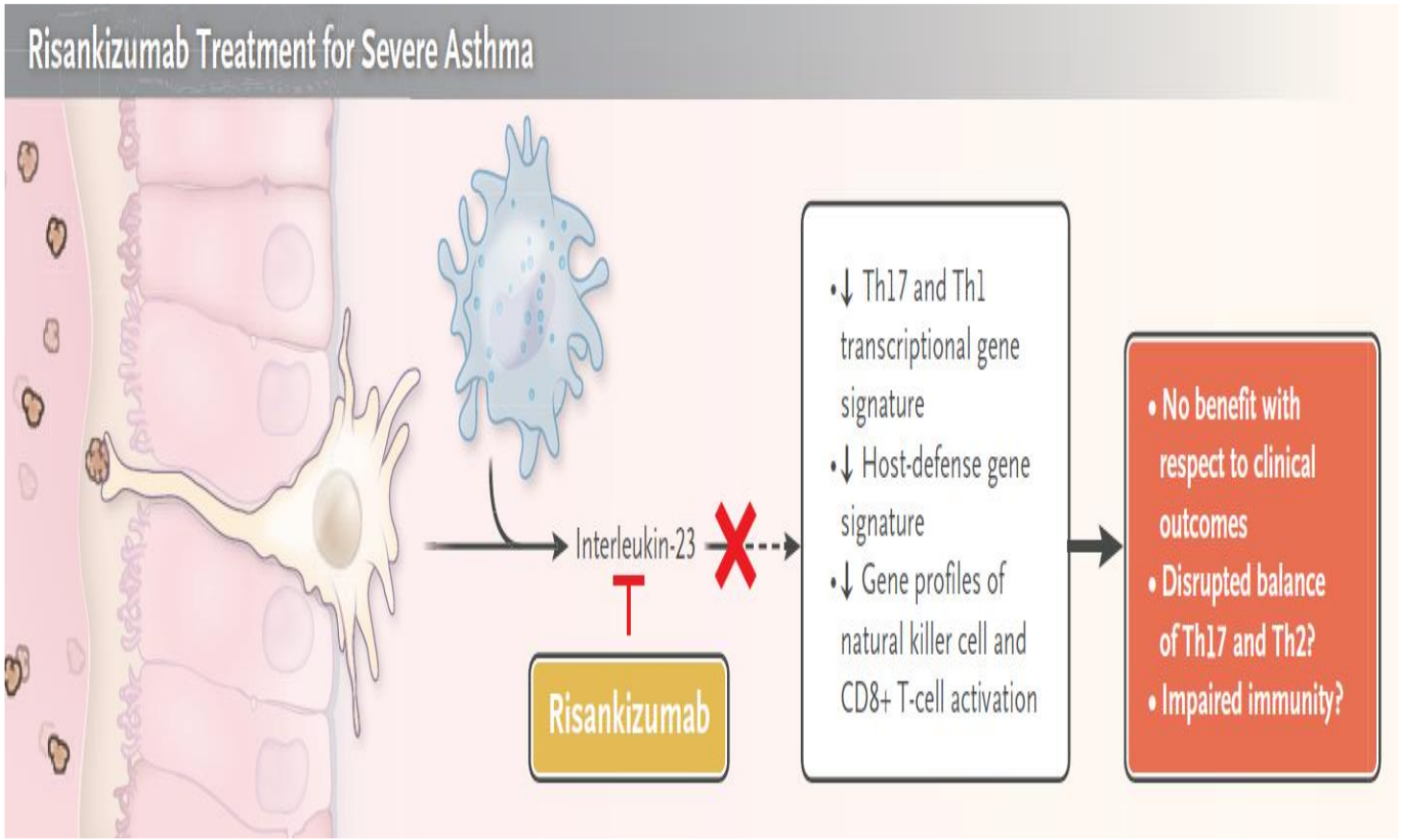
Peters et al Lancet Respir 2016, AJRCCM 2020

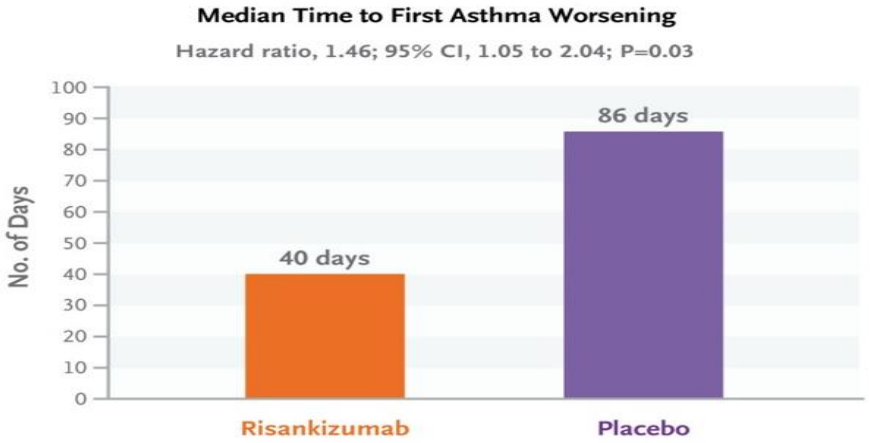
RESEARCH SUMMARY

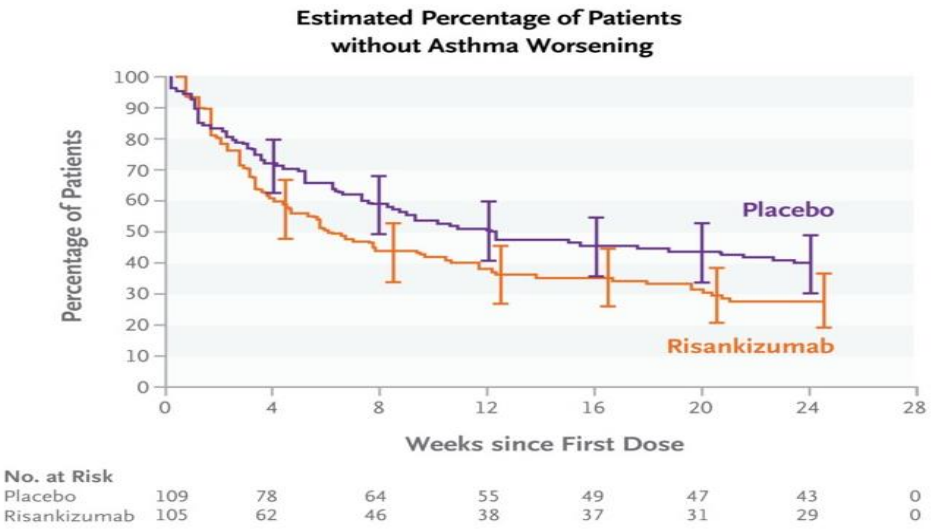
Risankizumab in Severe Asthma — A Phase 2a, Placebo-Controlled Trial

Brightling CE et al. DOI: 10.1056/NEJMoa2030880

Brightling CE et al. N Engl J Med 2021;385:1669-1679





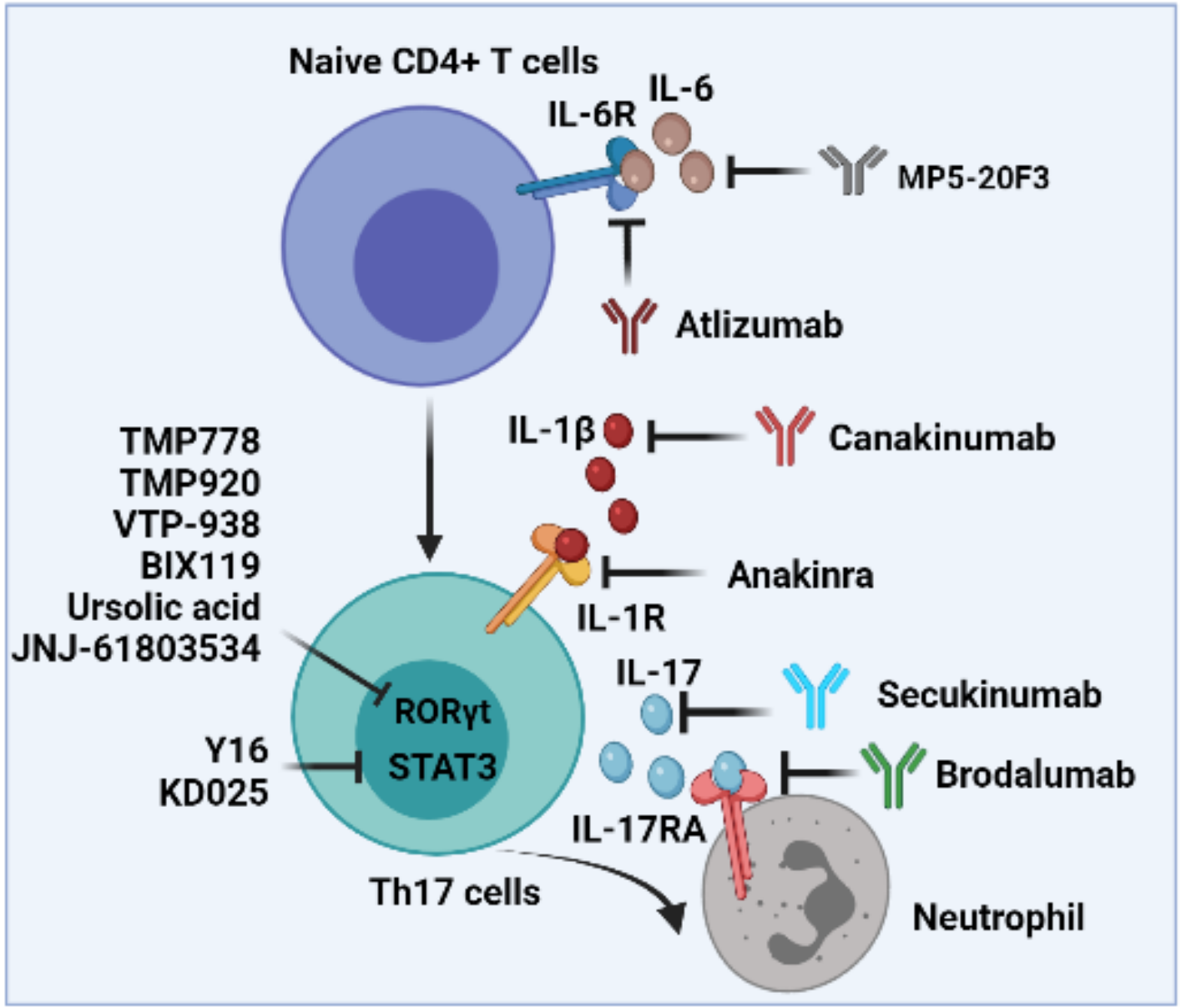


CONCLUSIONS

Treatment with the monoclonal antibody risankizumab was not beneficial in severe asthma and resulted in worse outcomes than placebo.

Bardin and Foster. n engl j med 385;18, October 28, 2021

Therapeutic Agents Targeting Th17 Cell Responses



Xie, Abel, Casale, Tu. JACI, 2022

Neutrophils and IL-17

- **Cutoff of 76% neutrophils in sputum proposed, but….**
  - **Neutrophilia does not always predict neutrophilic bronchial inflammation.**
  - **Neutrophilia can coexist with eosinophilia.**

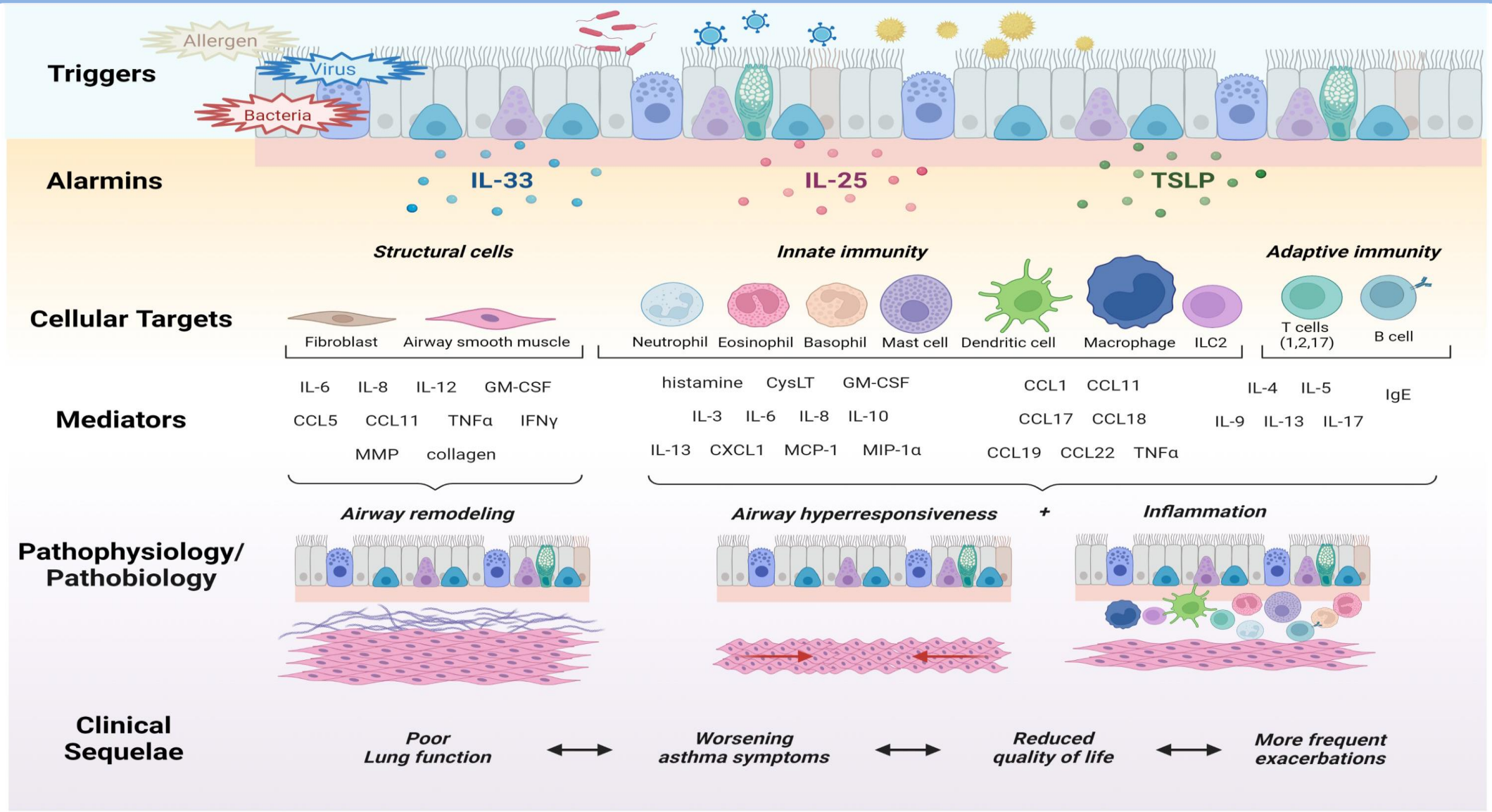
- **IL-17A levels elevated in bronchial tissues, PBMCs, and serum in asthma and assoc with incr AHR and asthma severity.**

- **IL-17F level also increased in asthma and correlated with airway neutrophils and more severe disease.**

- **2 clinical trials of humanized anti–IL-17A mAbs, secukinumab (AIN457) and CJM112, and 1 trial of brodalumab (AMG-827), mAb that binds to IL-17RA, *FAILED!***

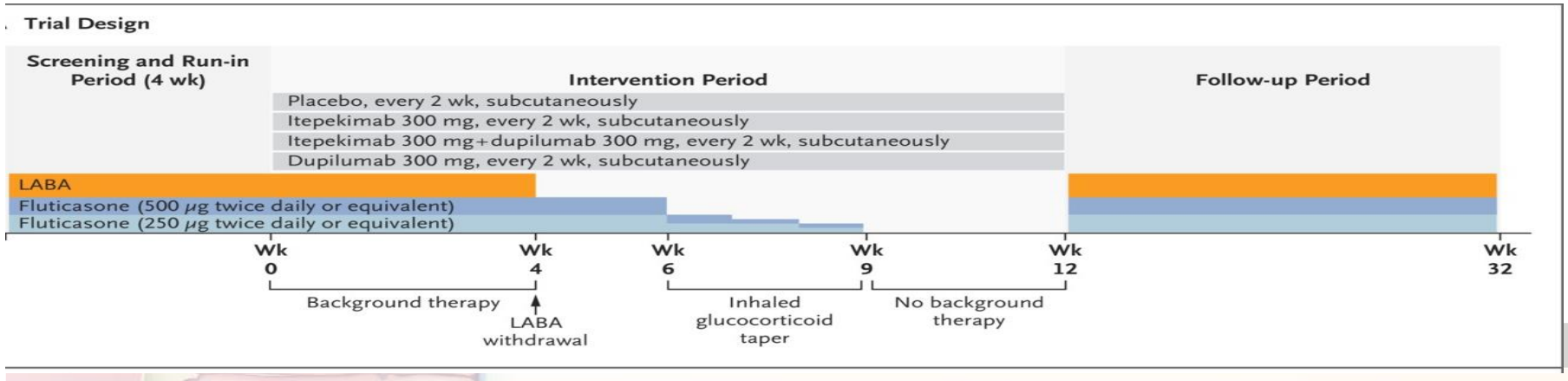
Xie, Abel, Casale, Tu. JACI, 2022

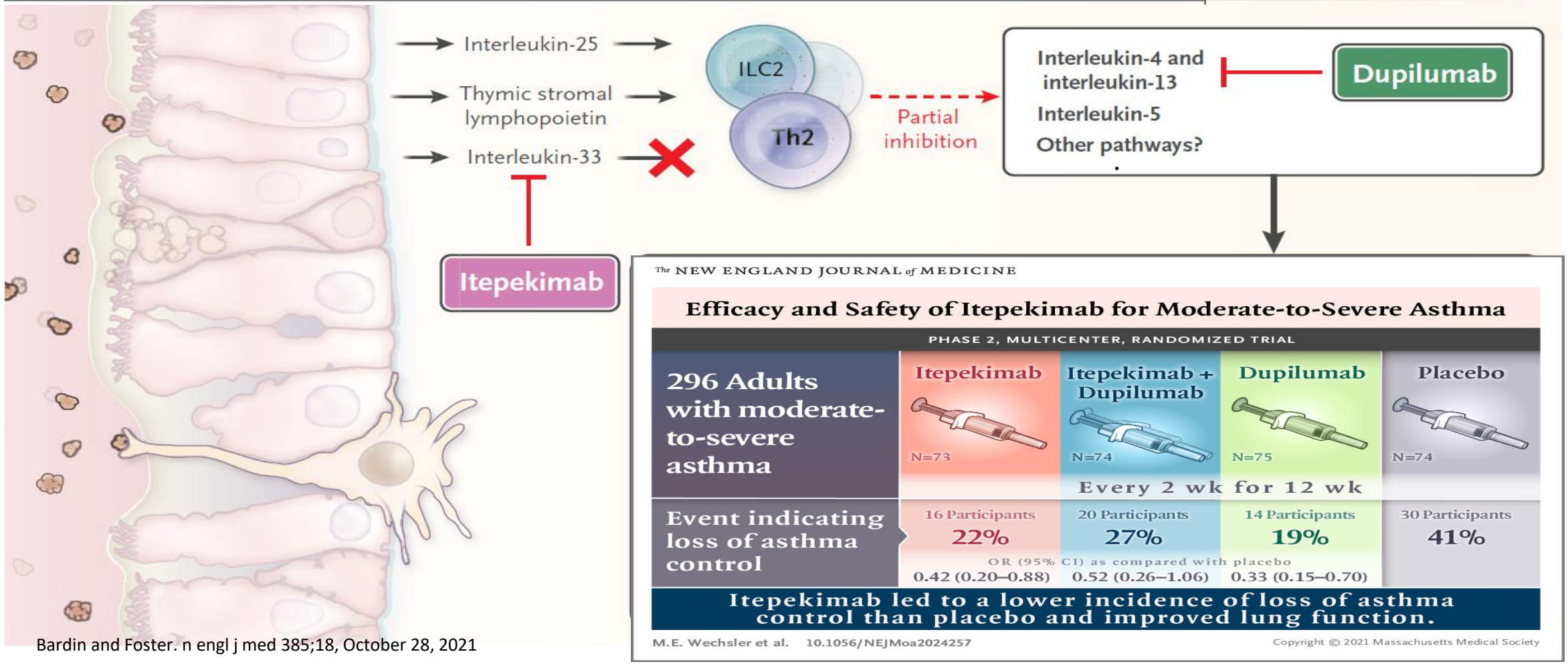
Overview Of The Pathobiology/Pathophysiology Of Alarmins In Asthmatic Airways Leading To Clinical Sequelae



Allergy. 2023;78:402–417

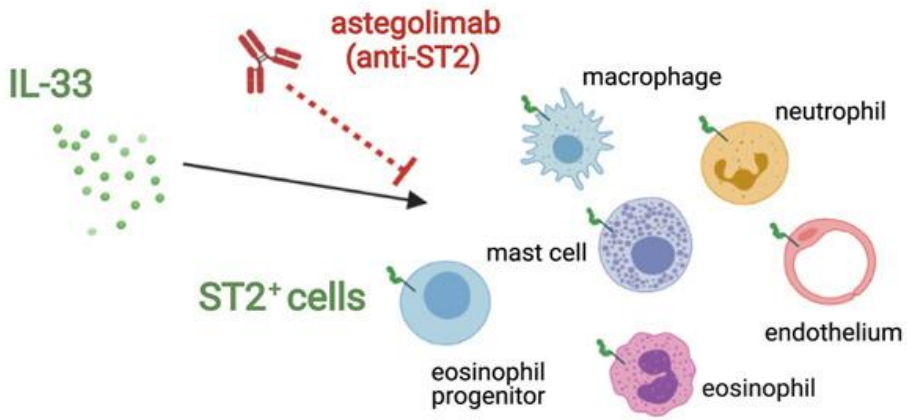
Anti-IL-33 +/- Dupilumab



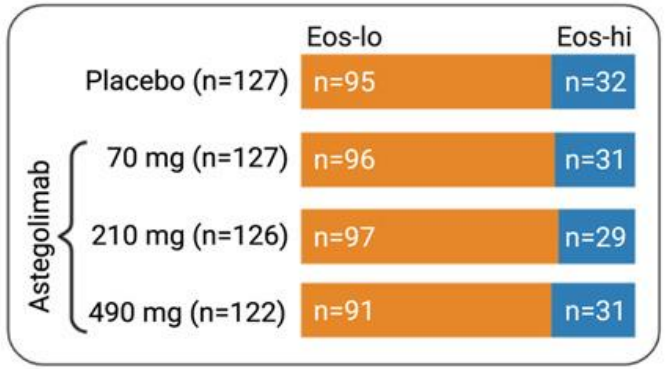


Bardin and Foster. n engl j med 385;18, October 28, 2021

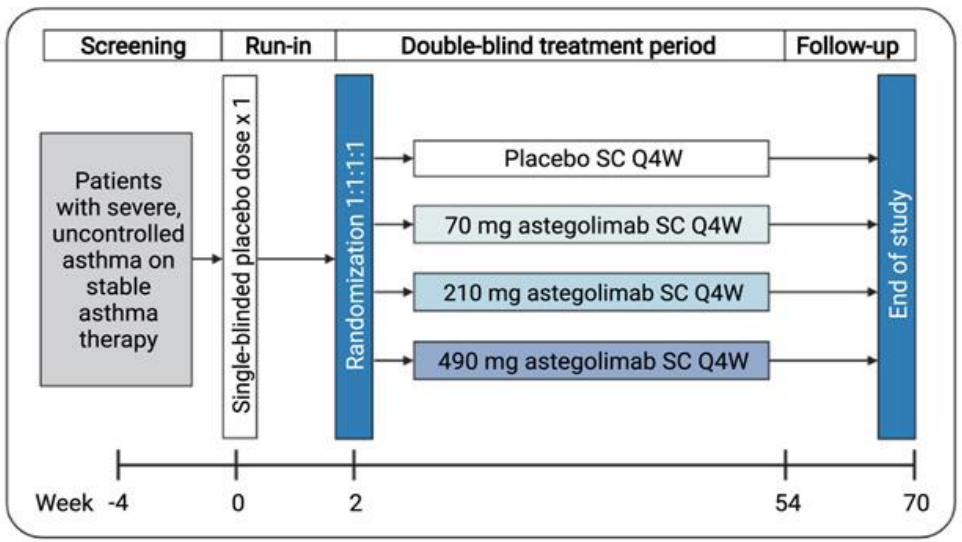
Astegolimab (anti-ST2) efficacy and safety in adults with severe asthma, including patients with low eosinophils



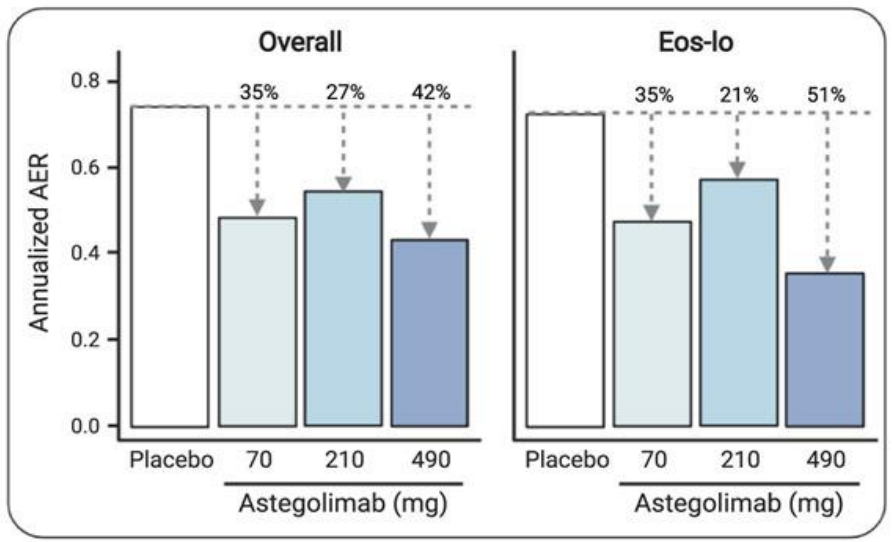
Patients enrolled



Study design



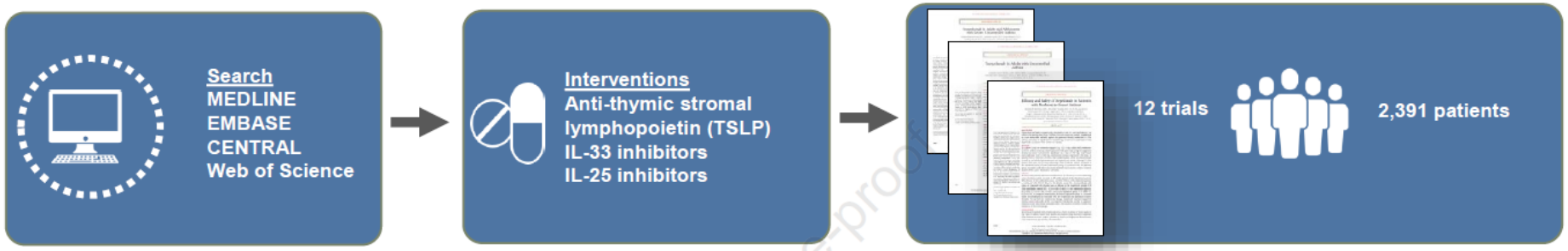
Primary endpoint: annualized asthma exacerbation rate



AER, asthma exacerbation rate; Eos-lo, <300 eosinophils/μL; Eos-hi, ≥300 eosinophils/μL; IL, interleukin; Q4W, every 4 weeks; SC, subcutaneous

Journal Pre-proof

Anti-epithelial derived cytokines for severe asthma: a systematic review and meta-analysis



Outcomes	Number of participants (studies)	Certainty of the evidence (GRADE)	Risk difference with usual care
Exacerbations (≥300 cell/uL)	921 (4 RCTs)	⊕⊕⊕◯ Moderate	**301 fewer per 1,000** (352 fewer to 230 fewer)
Exacerbations (<300 cells uL)	1338 (4 RCTs)	⊕⊕◯◯ Low	**165 fewer per 1,000** (259 fewer to 24 fewer)
Change in FEV1 (≥ 300 cells/uL)	758 (4 RCTs)	⊕⊕⊕⊕ High	MD **218.48 mL higher** (160.25 higher to 276.71 higher)
Change in FEV1 (< 300 cells/uL)	893 (4 RCTs)	⊕⊕⊕◯ Moderate	MD **68.76 mL higher** (22.36 higher to 115.16 higher)
Serious adverse events	2722 (11 RCTs)	⊕⊕⊕◯ Moderate	**3 more per 1,000** (0 fewer to 6 more)

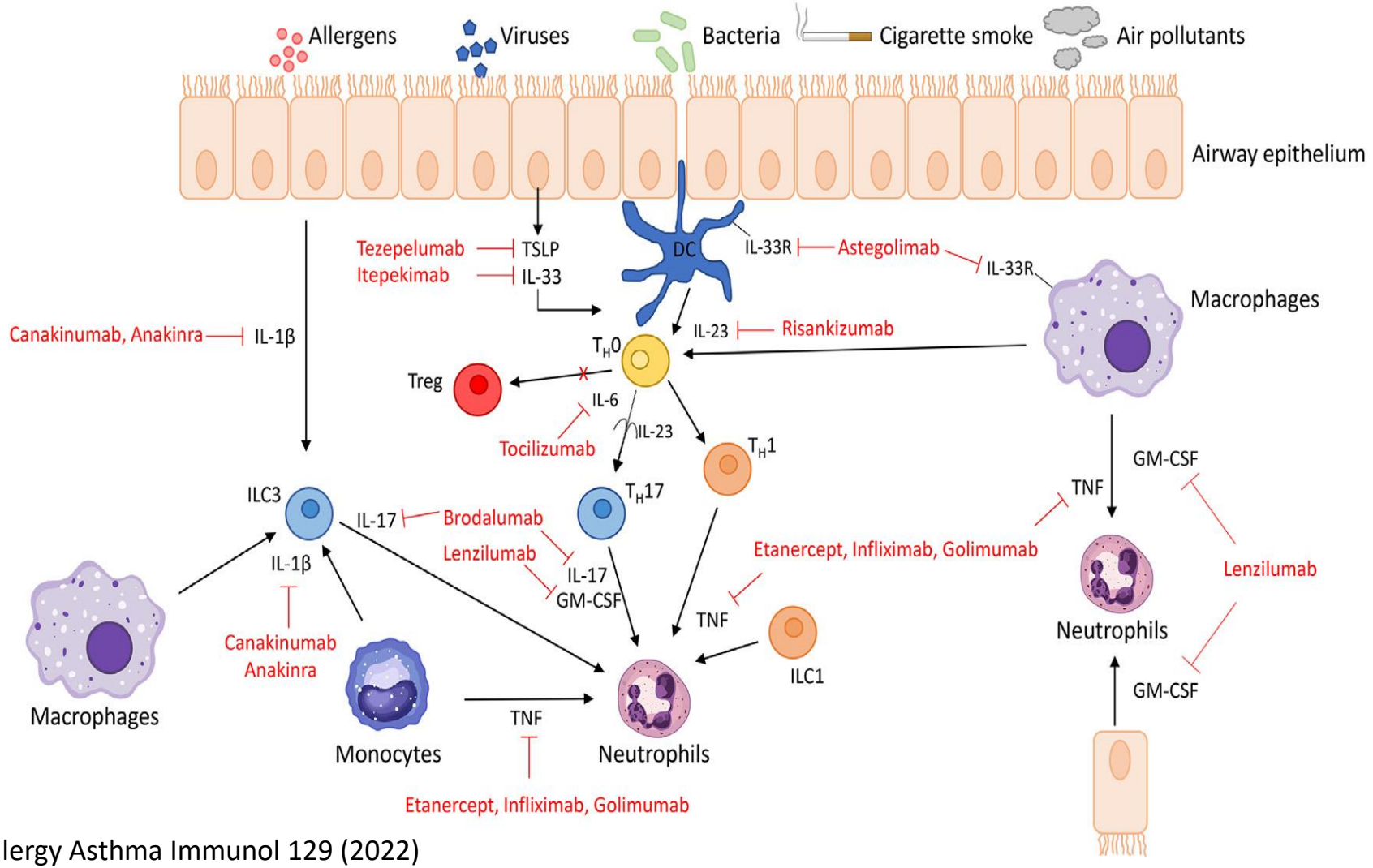
Conclusions: Anti-epithelial derived (type 2) cytokines are effective at improving lung function and probably reduce exacerbations in patients with severe eosinophilic asthma (RR 0.36 [95% CI 0.25 to 0.51]). The effect on patients with low (<300 cell/uL) eosinophils is less certain.

Su et al, JACI, In Press

Non-Eosinophilic/T2lo Asthma

- **Lack of good biomarkers**
- **AIT: Not appropriate**
- **No specific T2lo biologics approved, and concern for AEs**
- **T2hi biologics:**
  - **Omalizumab: small case series of nonallergic asthma and ACO**
  - **Dupilumab: works poorly in eosinophil and/or FeNO low patients**
  - **IL-5 blockers: work poorly in eosinophil low patients**
- **Alarmin blockers:**
  - **Tezepelumab**
  - **Astegolimab (anti-ST2)**

Putative Therapeutic Targets for T2lo Asthma



N.M. Niessen et al. / Ann Allergy Asthma Immunol 129 (2022)

Non-Eosinophilic/T2lo Asthma
Points to Consider

- Are we doomed to failure without POC biomarkers that allow patient enrichment for clinical trials?
- Important to recognize that no phenotype or endotype is pure!
- What are the consequences of inhibiting the action of neutrophils in the lung?

Precision Medicine:
The next Generation Cure?!

Try to find something that works like steroids
But costs much more!