Eastern Allergy Conference

Treatment for Non-T2 severe asthma – Personalized Medicine

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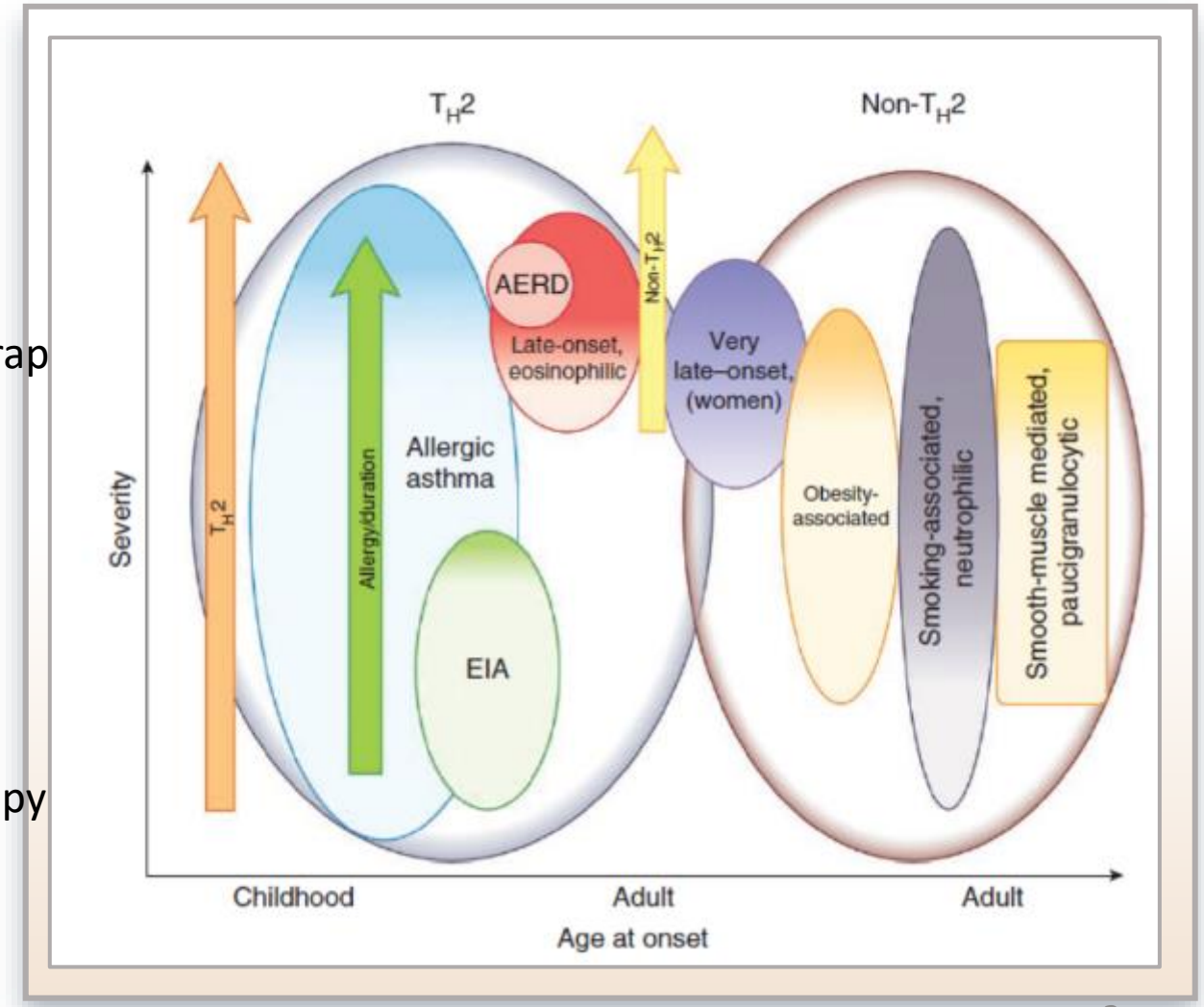
Objectives

1. Assess new phenotypes in severe asthma
2. Discuss available therapies for severe T2 asthma
3. Characterize the use of six biologics currently approved for treatment of severe asthma
4. Review criteria for selection of patients that will benefit from asthma biologics

Asthma Phenotypes According to Type 2-High and Type 2-Low

- Type 2-High Asthma[1-3]:
  - Eosinophilia
  - Early age of onset
  - Atopic/allergic component
  - More likely to respond to corticosteroid therap
- Type 2-Low Asthma[1-3]:
  - Lower levels of eosinophilia
  - Generally adult onset
  - May be linked to obesity, neutrophilia, smoking
  - Less likely to respond to corticosteroid therapy



Reprinted with permissions from *Nat Med*. 2012;18(5):716-725.

1. Wenzel SE. *Nat Med*. 2012;18(5):716-725.
2. Fahy JV. *Nat Rev Immunol*. 2015;15(2):57-65.
3. Woodruff PG et al. *Am J Respir Crit Care Med*. 2009;180(5):388-395.

Inflammation in Asthma Is Complex and Heterogeneous

Type 2 — **Spectrum of Inflammation** — **Non-Type 2**

- FeNO=fractional exhaled nitric oxide; IgE=immunoglobulin E; IL=interleukin.

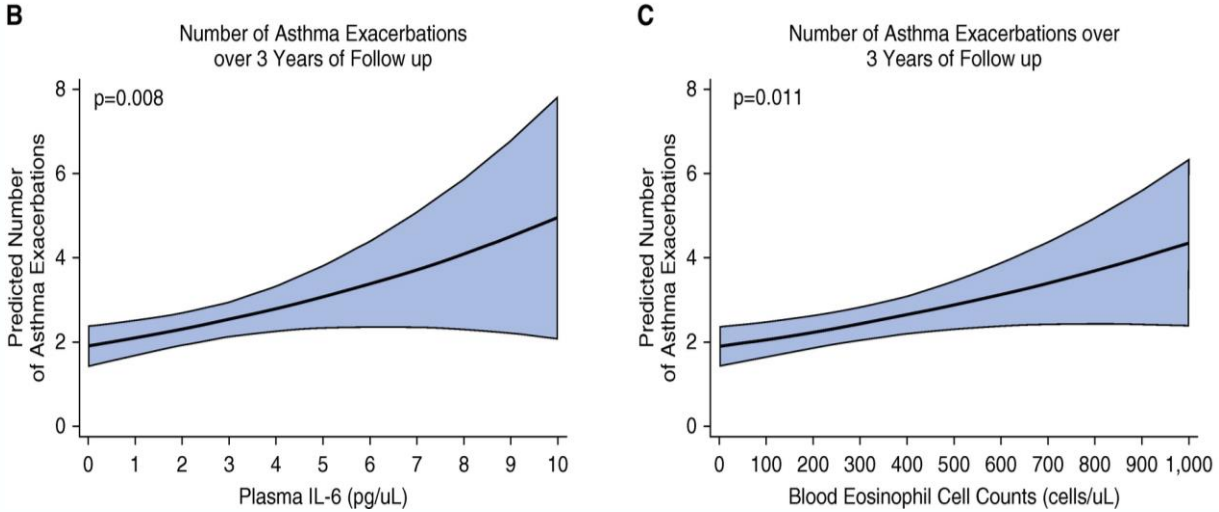
Type 2 (Type 2 High)	**Non-Type 2** (Type 2 Low)
More severe	Less severe
Blood eosinophilia	Airway neutrophilia
Elevated tissue eosinophilia	Pauci-granulocytes
Elevated serum IgE	Poor response to corticosteroids
Elevated FeNO	Obesity associated
Variable response to corticosteroids	Lack response to targets of type 2 inflammation
Targets type 2 inflammation	
Type 2 comorbidities	
Most common cytokines: IL-4, IL-13, and IL-5	

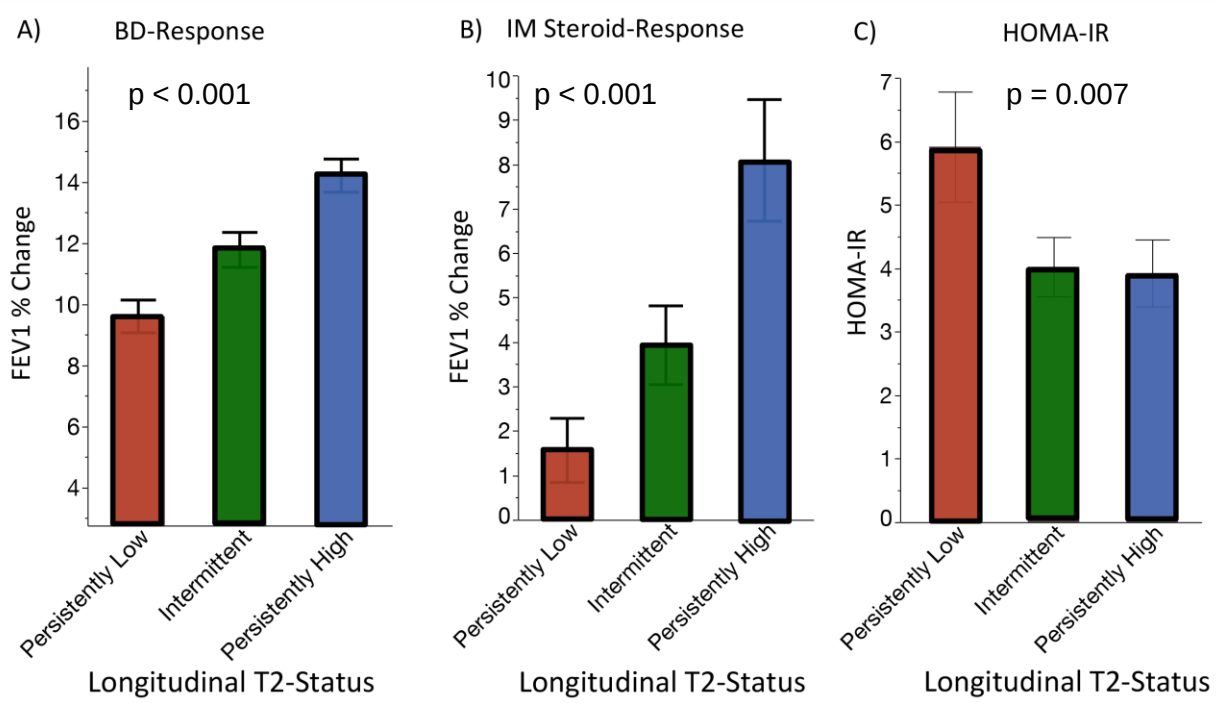
GINA Guidelines recognize the need to assess the inflammatory phenotype, type 2 or non-type 2, in patients with severe asthma[5]

IL-6 and Blood Eos predict Future Exacerbations

T2 Low Subjects Are Less Responsive to Therapy & Demonstrate Metabolic Dysfunction

Each 1-pg/ml increase in baseline plasma IL-6 levels increased the incident rate ratio (IRR) of asthma exacerbations by 10% over 3 years!



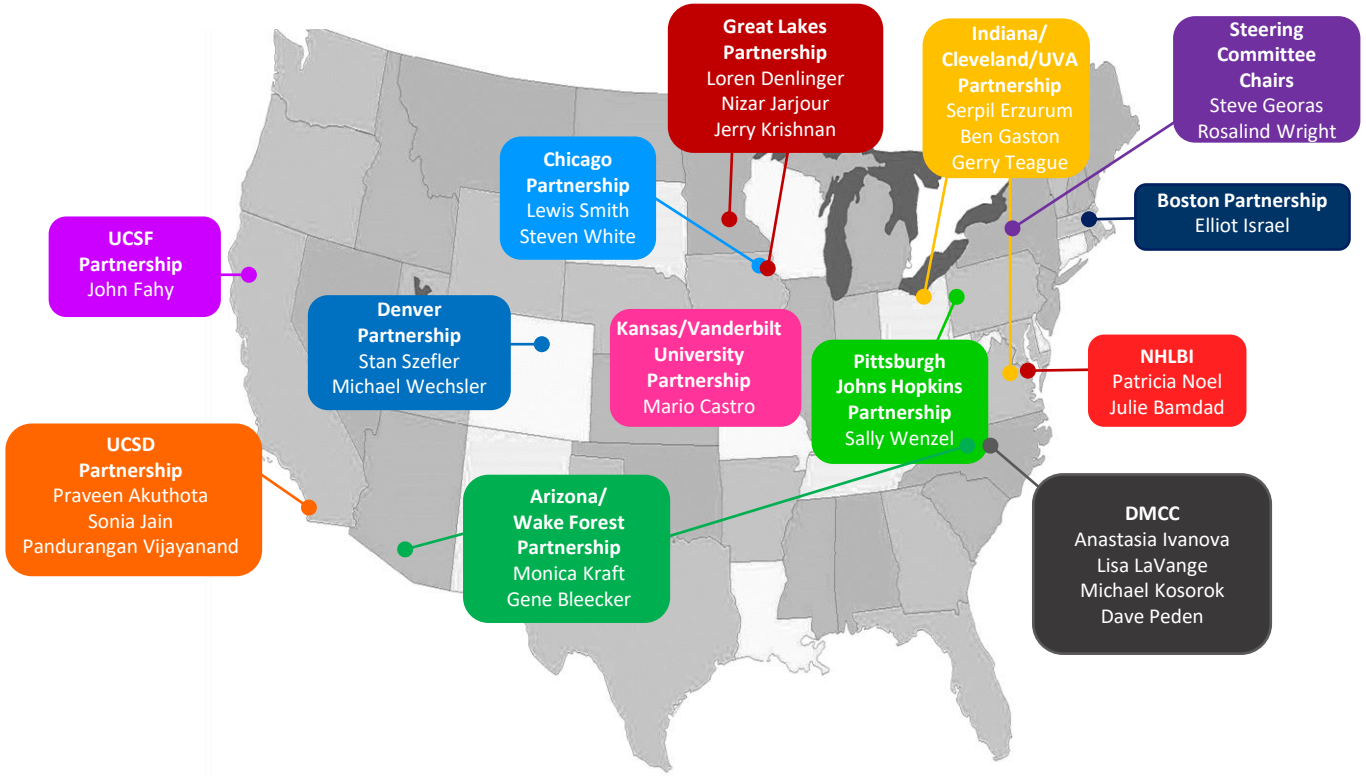


Marginal effect of primary predictor variables of (*B*) plasma IL-6 and (*C*) blood eosinophil cell counts are controlled for BMI, age, and history of depression. Marginal effect of plasma IL-6 and blood eosinophils are also controlled for each other.

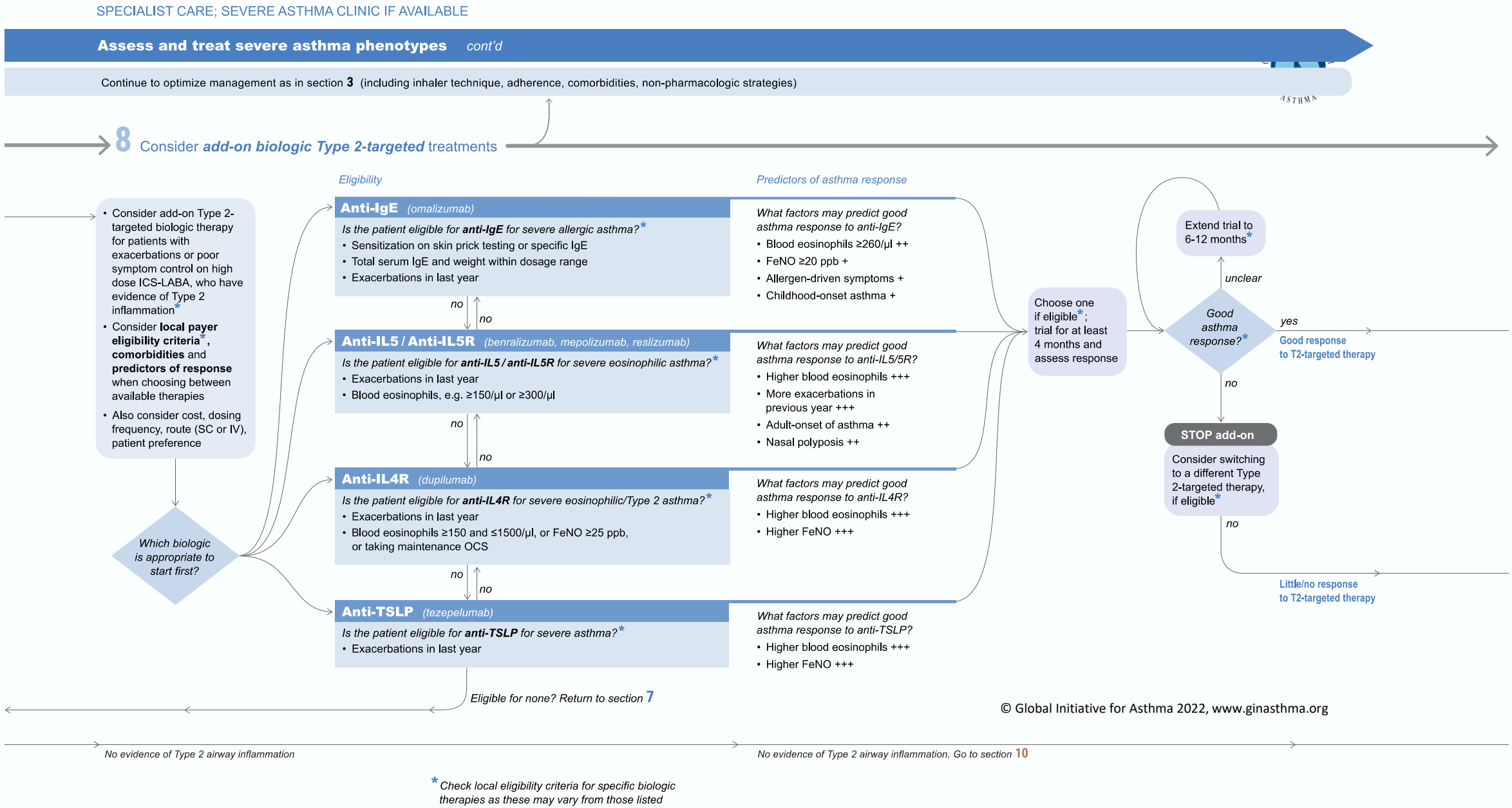
Peters MC et al Am J Respir Crit Care Med, 2020

PrecISE
PRECISION INTERVENTIONS FOR SEVERE ASTHMA

PrecISE Network: the partnerships



GINA: Identifying Patients and Selecting Biologic



Macrolide therapy - Potential for NonT2 Asthma

- 420 patients were randomly assigned (213 in the azithromycin group and 207 in the placebo group
- Azithromycin reduced asthma exacerbations (1·07 per patient-year [95% CI 0·85-1·29]) compared with placebo (1·86 per patient-year [1·54-2·18]; incidence rate ratio [IRR] 0·59 [95% CI 0·47-0·74]; p<0·0001).
- Azithromycin significantly improved asthma-related quality of life (adjusted mean difference, 0·36 [95% CI 0·21-0·52]; p=0·001).
- Diarrhoea was more common in azithromycin-treated patients (72 [34%] vs 39 [19%]; p=0·001).

Gibson, P et al Lancet. 2017 Aug 12;390(10095):659-668.

Macrolides In suboptimally Asthma (MIA) Study

4 week run-in → **Biopsy** → **16 week treatment**

n=253

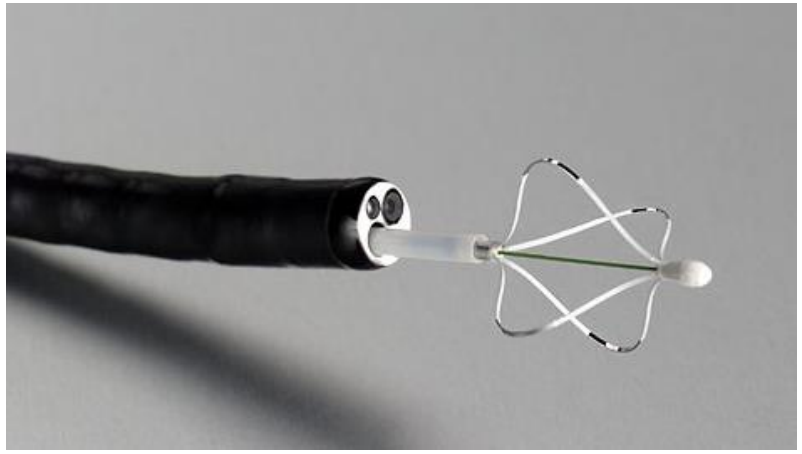
Group	Within-PCR group change (SE)	Within-PCR, between-treatment group change (SE)	p
PCR –, Clari/FP (n=41)	-0.4 (0.1)	-0.2 (0.2)	0.3
PCR –, Placebo/FP (n=39)	-0.2 (0.1)		
PCR+, Clari/FP (n=6)	-0.4 (0.4)	-0.3 (0.5)	0.6
PCR +, Placebo/FP (n=6)	-0.1 (0.3)		

n=41; Clarithromycin + FP

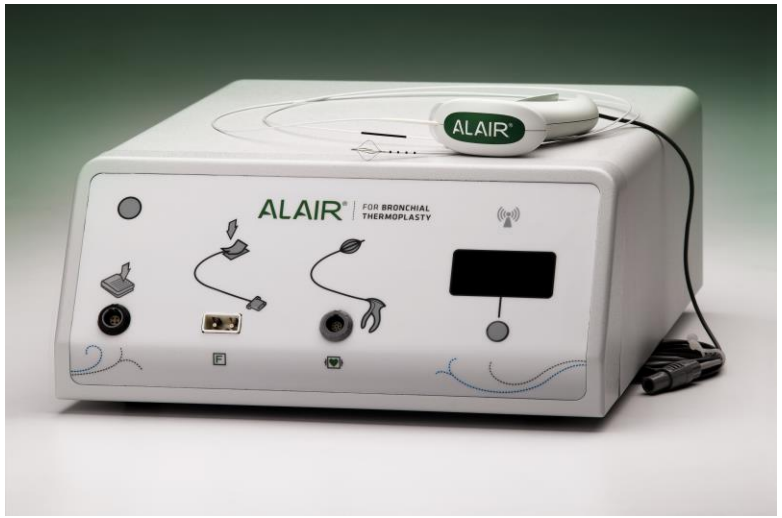
Sutherland, ER et al J Allergy Clin Immunol 2010;126:747-53.

Bronchial Thermoplasty

The catheter is a flexible tube with an expandable wire array at the tip



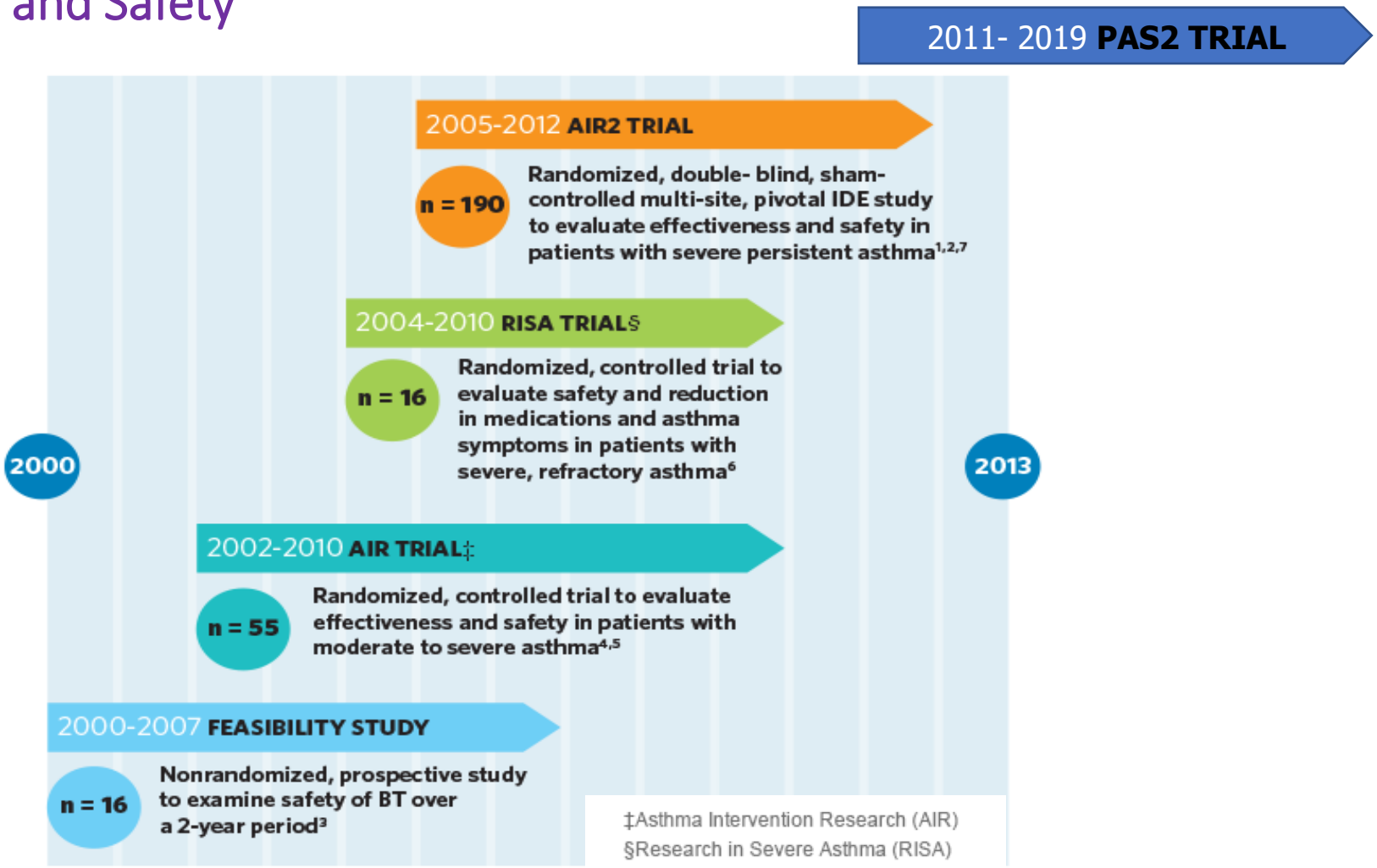
The Radiofrequency Controller supplies energy that is converted to heat in the airway wall



- Monopolar radiofrequency (RF) energy
- Temperature controlled: 65 °C
- 10 seconds
- Multiple safety algorithms to ensure controlled energy delivery

BT Clinical Studies

Effectiveness and Safety



5 clinical studies in patients with asthma, all with 5 years of follow-up

3 randomized, controlled, clinical studies , with 1 sham-controlled

Evidence: Bronchial Thermoplasty (BT)

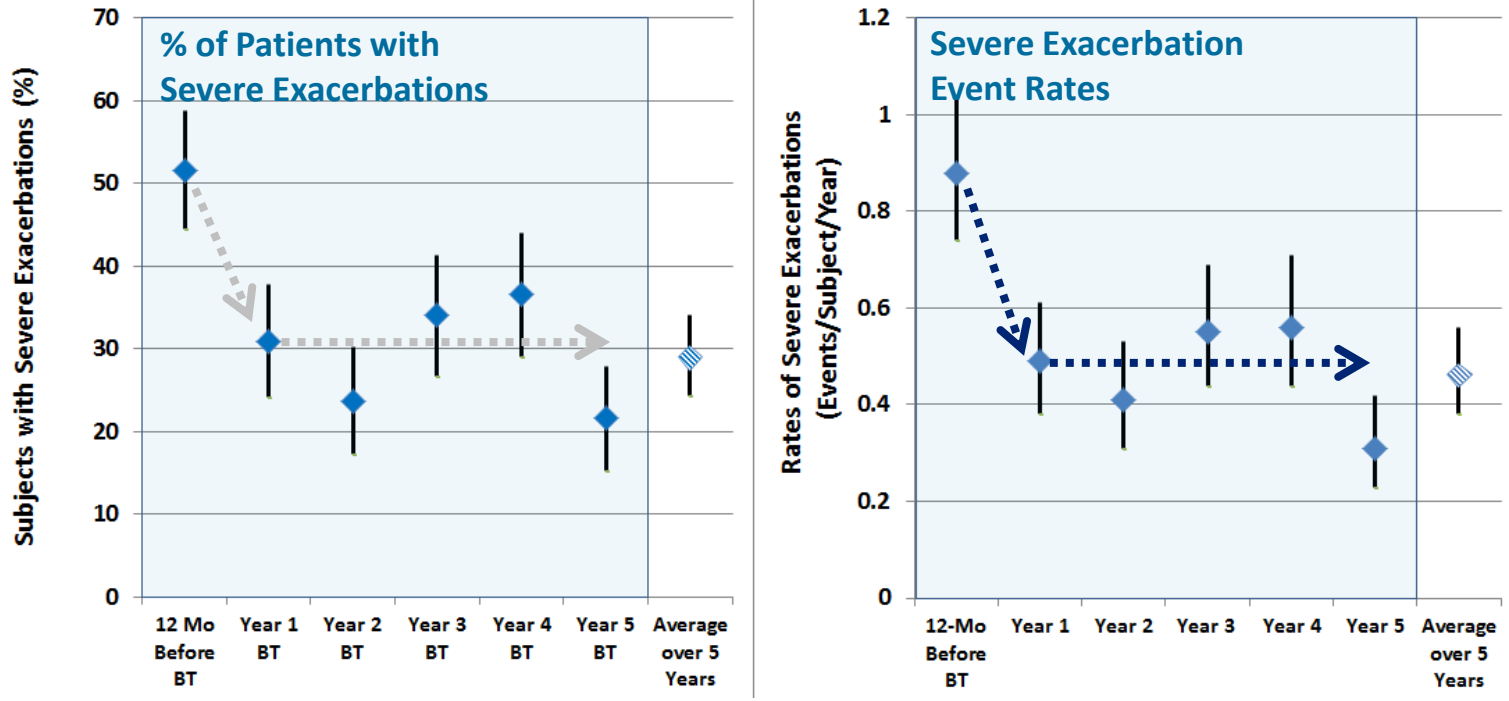
- One-time treatment lasting for 5 years[1]
  - Patients (N=288, AIR2) ICS 1,000 µg/d beclomethasone or equivalent and LABA >100 µg/d salmeterol or equivalent, other meds including leukotriene modifiers, OmAb (if used for ≥1 year prior), and ≤10 mg/d OCS
- 32% decrease in severe exacerbations (requiring systemic CS) vs no treatment[2]
  - Reduction in exacerbations at 1 year maintained for ≥5 years[1]
- 84% reduction in ED visits for respiratory symptoms at 1 year vs no treatment[2]
  - Reduction in ED visits at 1 year maintained for ≥5 years[1]

CS, costicosteroid; ED, Emergency department; OmAb, Omalizumab; OCS, oral corticosteroid

1. Wechsler M, et al. *J Allergy Clin Immunol*. 2013;132(6):1295-1302.
2. Castro M, et al. *Am J Respir Crit Care Med*. 2010;181(2):116-124.

Bronchial Thermoplasty
- Severe Exacerbations over 5 yrs

- The reduction in severe exacerbations requiring systemic corticosteroids at 1 year (vs. sham-treated patients) was maintained out to at least 5 years.

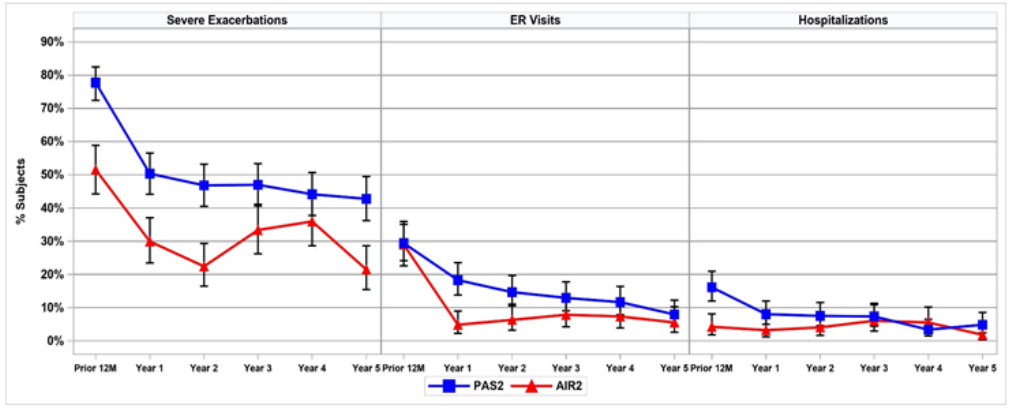


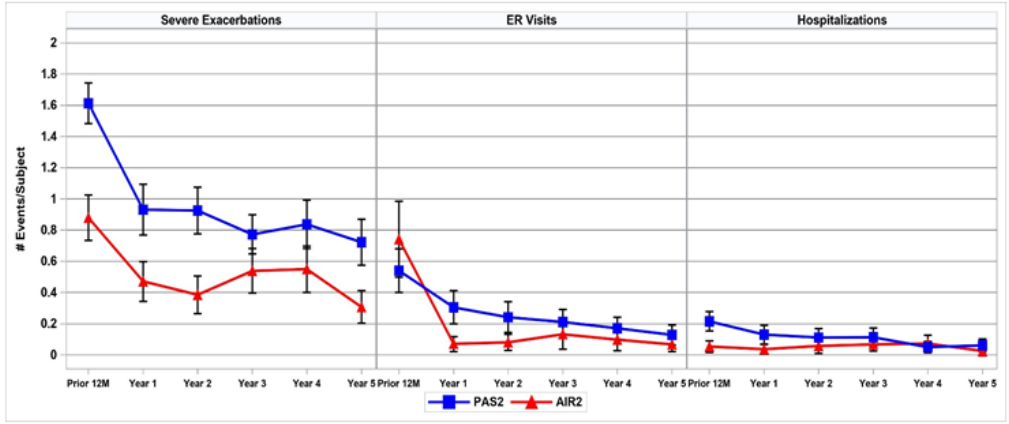
Compared with 1 year prior to BT treatment (baseline):

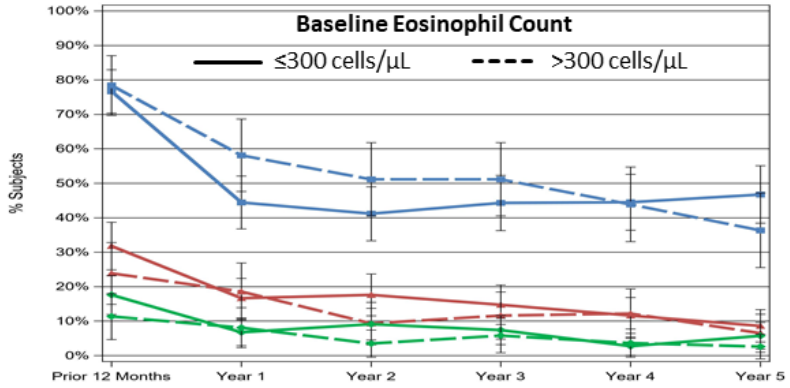
- 44% average decrease in percentage of patients having severe exacerbations
- 48% average decrease in severe exacerbation event rates

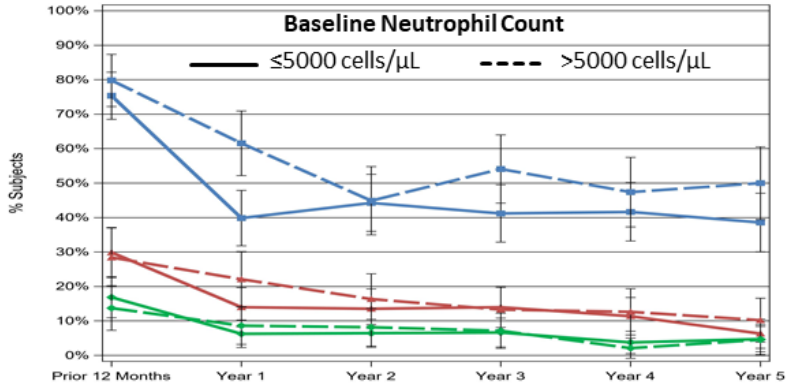
Wechsler ME et al *J Allergy Clin Immunol.* 2013

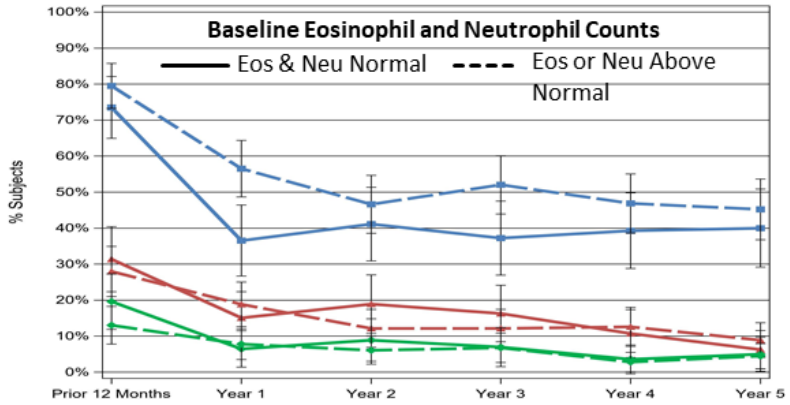
PAS2, 5 Year Data











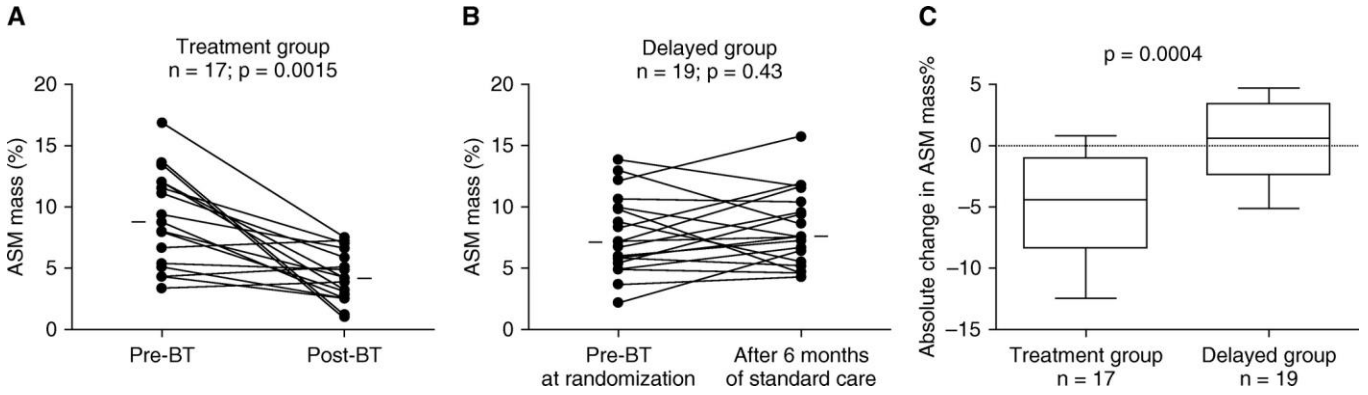
Severe Exacerbations ER Visits Hospitalizations

TASMA trial

- 40 patients with severe asthma randomized to immediate BT or delayed
- Median ASM mass decreased by >50% in immediate BT ($n = 17$) versus no change in the delayed controls ($n = 19$) ($P = 0.0004$).
- In immediate BT, Asthma Control Questionnaire scores improved with −0.79 ([IQR], −1.61 to 0.02) compared with 0.09 (IQR, −0.25 to 1.17) in delayed ($P = 0.006$).
- Treatment response in the total group ($n = 35$) was **positively associated with serum IgE and eosinophils** but not with baseline ASM mass.

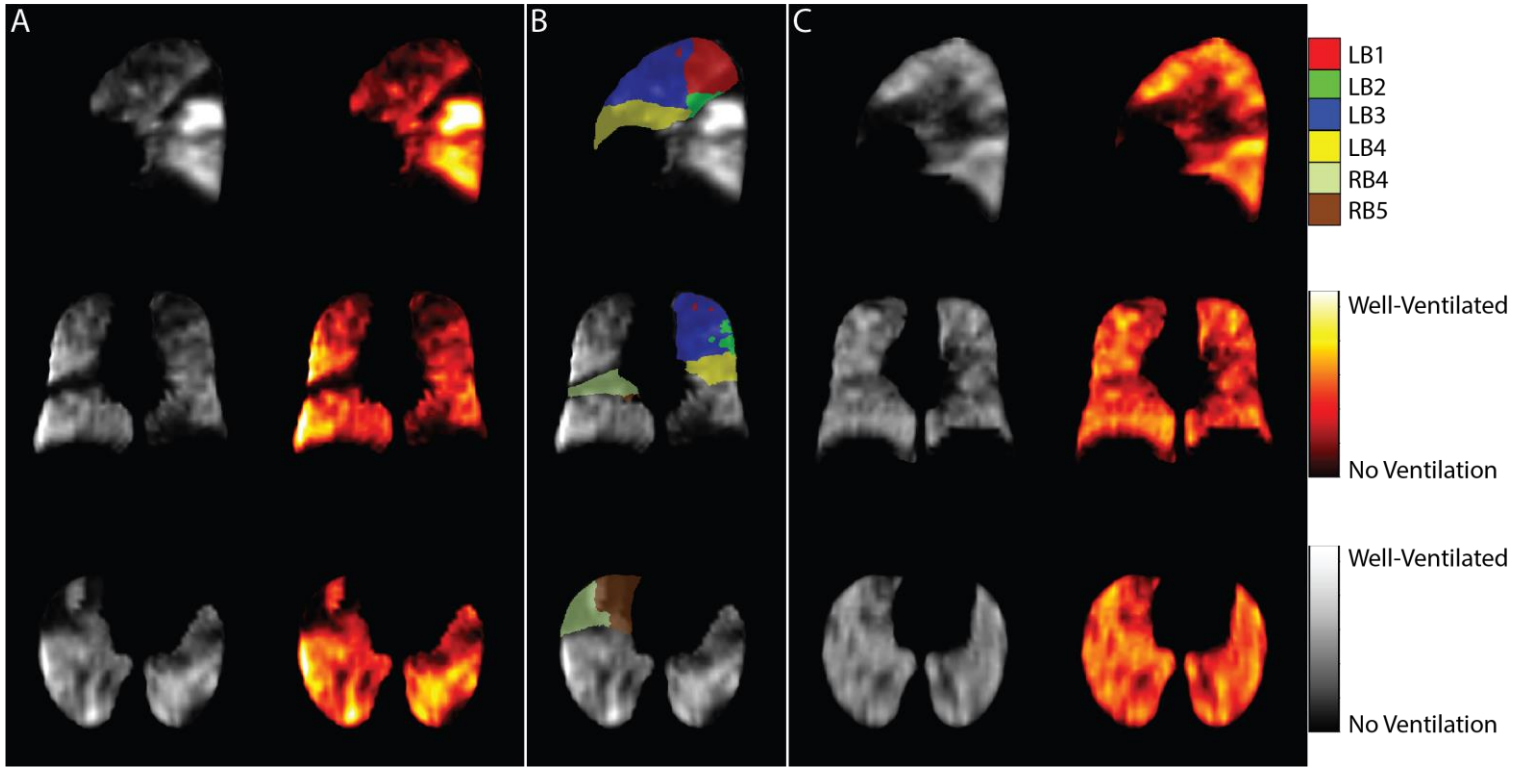
Table 3. Clinical Characteristics before and after BT in the Total Group ($n = 35$)

Characteristics	Before BT	After BT	Median Difference (95% CI)	*P* Value
ACQ-6 score	2.67 ± 0.64	2.00 ± 1.05	−0.67 (−0.17 to −1.17)	0.0005*
AQLQ score	3.99 ± 1.00	4.73 ± 1.24	0.85 (0.19 to 1.41)	0.0023*
Exacerbation rate/6 mo	1.5 (1.0 to 3.0)	0 (0 to 1)	−1.0 (−0.50 to −1.50)	<0.0001*
Pre–short-acting bronchodilator FEV_1, % predicted†	83 ± 25	87 ± 24	4.00 (−10.00 to 16.00)	0.14
Reversibility FEV_1, %†	10.5 (4 to 16)	3.5 (2 to 14)	−5.00 (-6.61×10^{-6} to −8.00)	0.03*
PC_{20}, mg/ml‡	0.25 (0.03 to 2.42)	0.42 (0.04 to 4.0)	0.02 (−0.18 to 1.12)	0.11
ASM mass desmin, %§	8.6 (5.3 to 11.6)	4.0 (2.7 to 5.8)	−4.07 (−2.49 to −5.78)	<0.0001*
ASM mass α-SMA, %§	19.5 (15.9 to 23.9)	11.8 (8.9 to 13.9)	−7.54 (−5.07 to −10.09)	<0.0001*



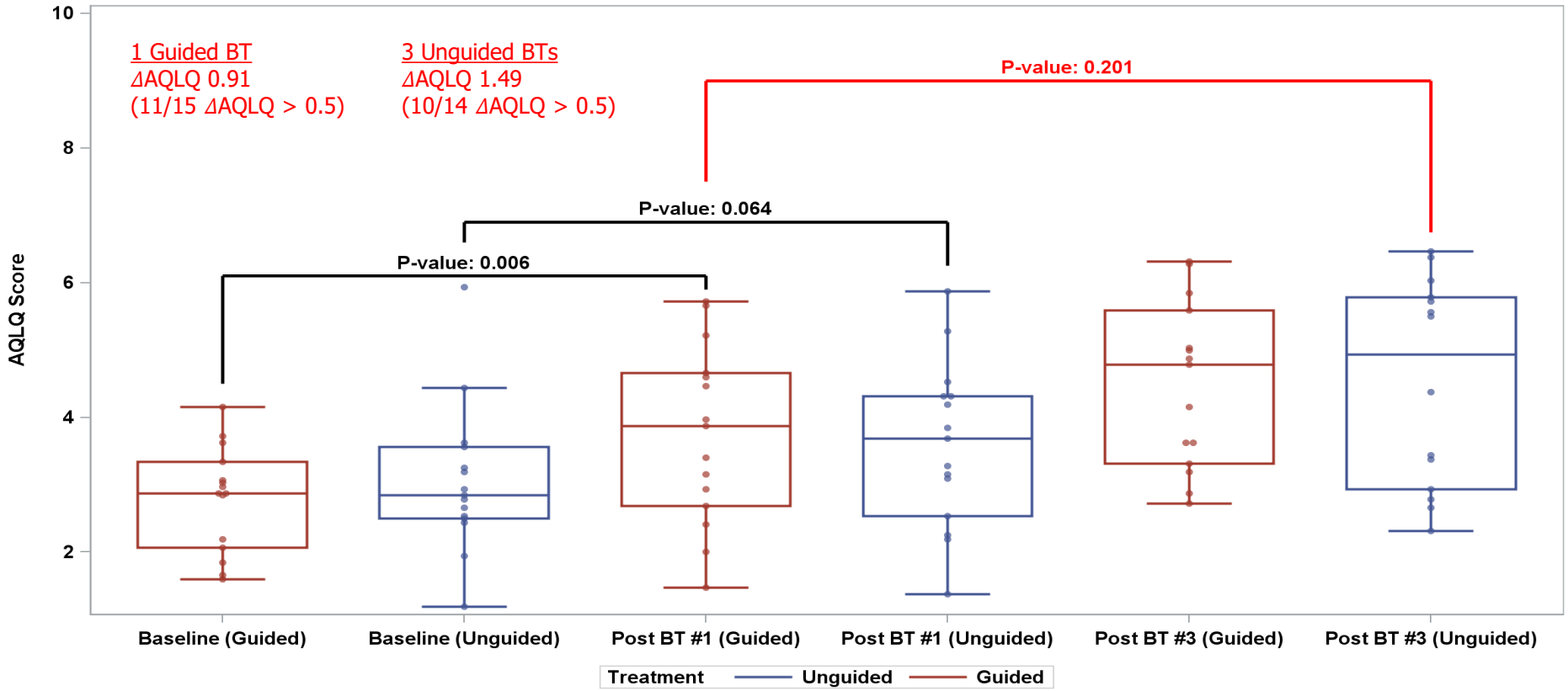
Goorsenberg, AWM et al AJRCCM 2021; 203: 175

Guided XeMRI BT



Hall CS, et al. Am J Respir Crit Care Med. 2020;202:524-534.

Guided versus Conventional BT -Primary Endpoint



Single BT treatment guided by ^{129}Xe MRI provided similar quality of life improvement as standard three-session BT

Hall CS, et al. Am J Respir Crit Care Med. 2020;202:524-534.

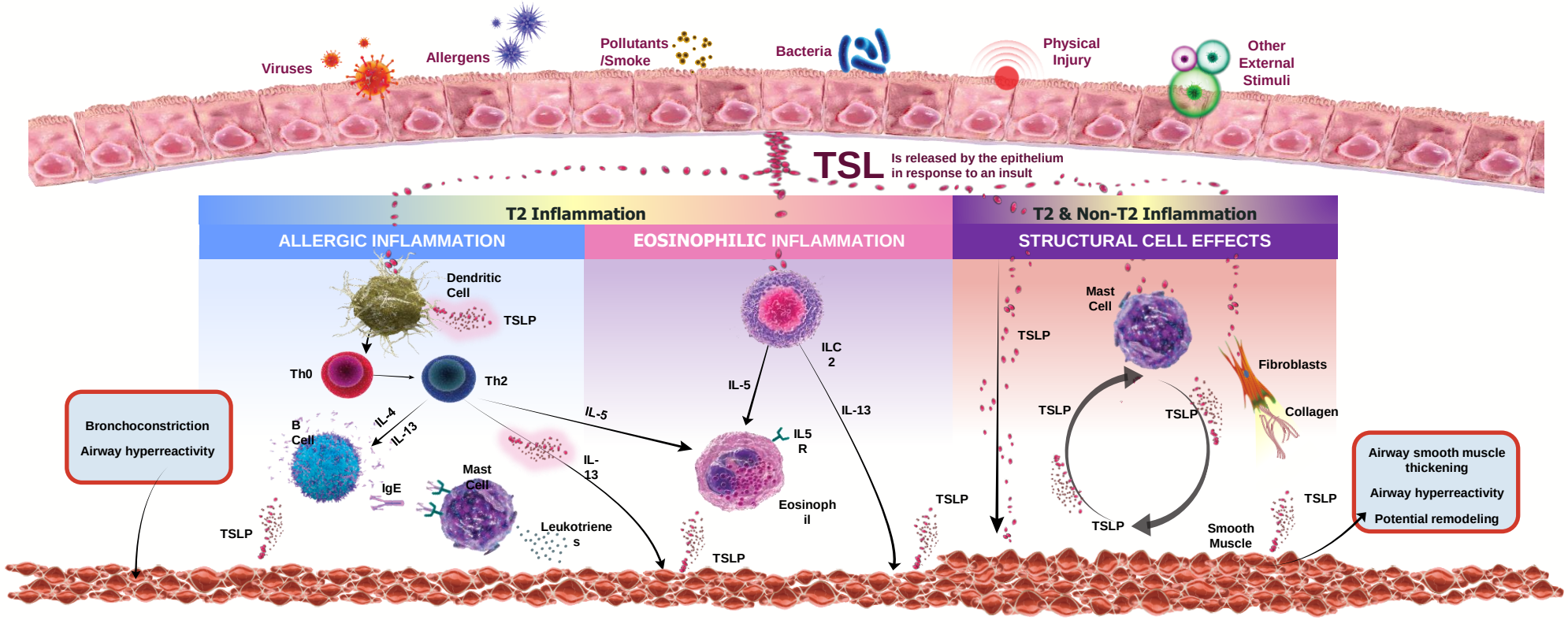
Guided versus Conventional BT
- Adverse Events within 3 Weeks of BT

	Asthma Exacerbations	Guided BT	Unguided BT
BT 1	AE	4/15 (26.7%)	7/15 (46.7%)
	SAE	1/15 (6.7%)	2/15 (13.3%)
BT 2	AE	1/15 (6.7%)	5/15 (33.3%)
	SAE	1/15 (6.7%)	1/15 (6.7%)
BT 3	AE	4/15 (26.7%)	5/14 (35.7%)
	SAE	2/15 (13.3%)	3/14 (21.4%)
	Total Events	**13 Events**	**23 Events**
	1 Guided vs 3 Unguided	**4 AE / 1 SAE (33%)**	**17 AE / 6 SAE (73%)**

Single BT guided by ^{129}Xe MRI is associated with fewer peri-procedure adverse events than standard 3-session BT

Hall CS, et al. Am J Respir Crit Care Med. 2020;202:524-534.

TSLP Is Also Released by Multiple Downstream Cells, Perpetuating Inflammation

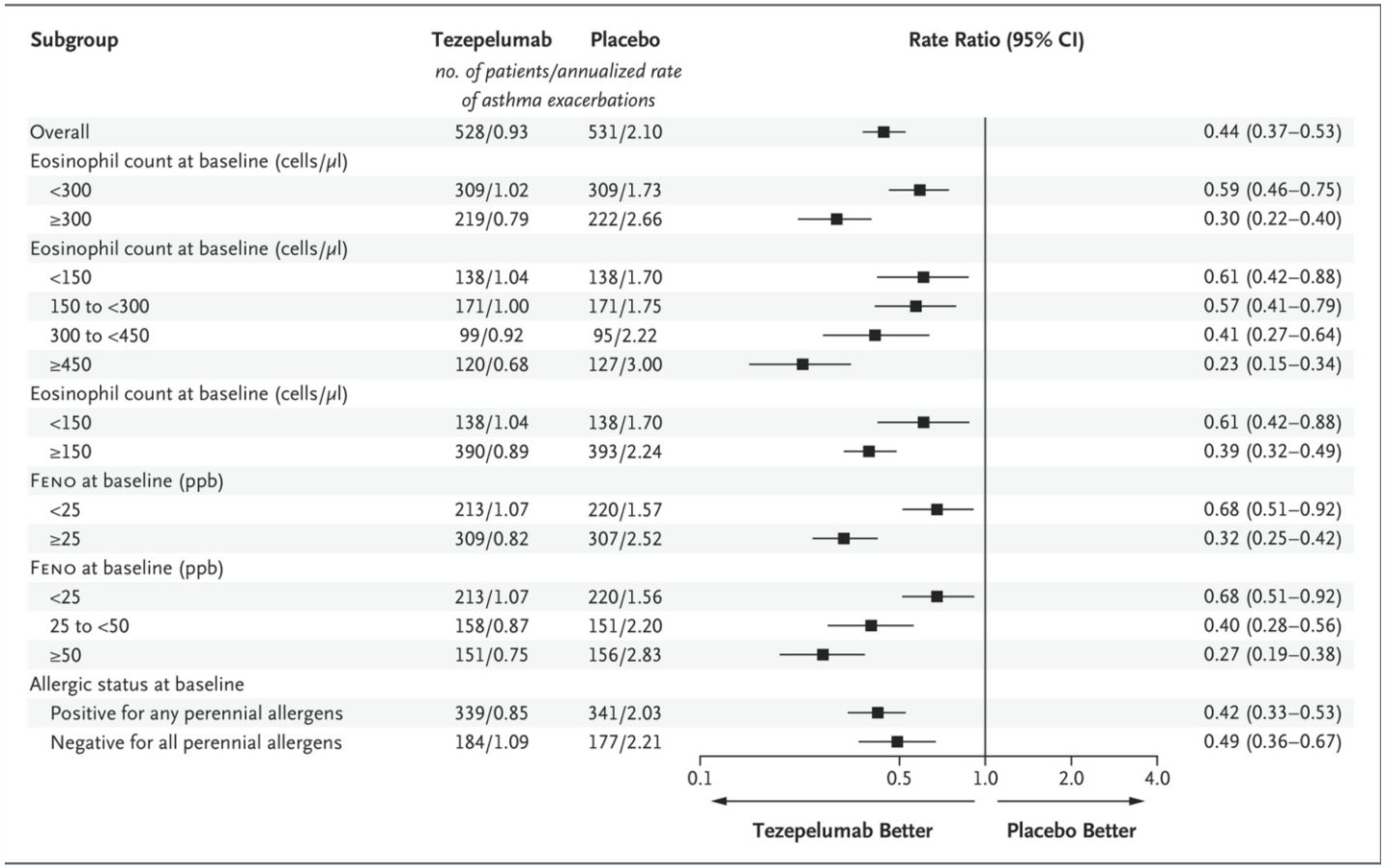


Shan L, et al. *J Immunol.* 2010;184(12):7134-7143. 9. Pasha MA, et al. *Allergy Asthma Proc.* 2019;40(3):138-145. IgE = immunoglobulin E; IL = interleukin; ILC2 = innate lymphoid cell 2; R = receptor; Th = T helper; TSLP = thymic stromal lymphopoietin.

1. Redhu NS, Gounni AS. *Clin Exp Allergy.* 2012;42(7):994-1005. 2. Sebastian K, et al. *Cell Commun Signal.* 2008;6:5. doi:10.1186/1478-811X-6-5. 3. Kaur D, et al. *Chest.* 2012;142(1):76-85. 4. Allakhverdi Z, et al. *J Allergy Clin Immunol.* 2009;123(4):958-960.e2. 5. Brusselle G, Bracke K. *Ann Am Thorac Soc.* 2014;11(suppl 5):S322-S328. 6. Cao L, et al. *Exp Lung Res.* 2018;44(6):288-301. 7. Wu J, et al. *Cell Biochem Funct.* 2013;31(6):496-503. 8. 10. Brusselle G, et al. *Nat Med.* 2013;19:977-979. 11. Pelaia G, et al. *Nat Rev Drug Discov*. 2012;11:958-997.

Tezepelumab: Efficacy in Reducing Asthma Exacerbations

- 1,061 patients ages 12+ y with uncontrolled asthma (2 exacerbations prior yr) randomized to placebo or tezepelumab (210 mg SQ q 4 wks)
- Improved preBD FEV_1 (Tezepelumab 0.23 vs. placebo 0.09 liters; difference, 0.13 liters; 95% CI, 0.08 to 0.18; P<0.001)
- Adverse events were similar across groups

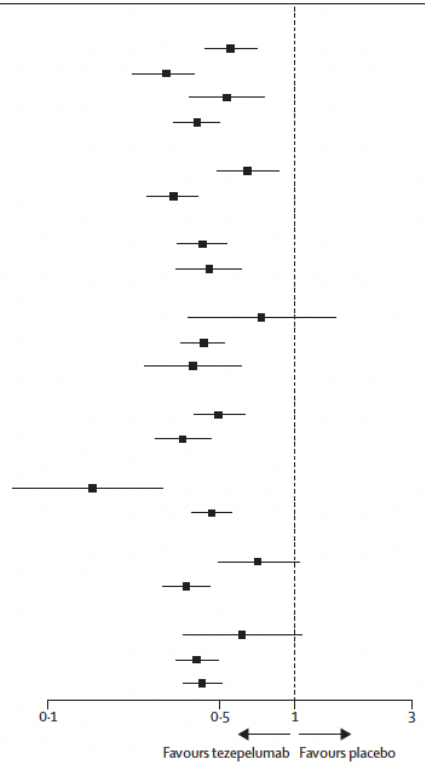


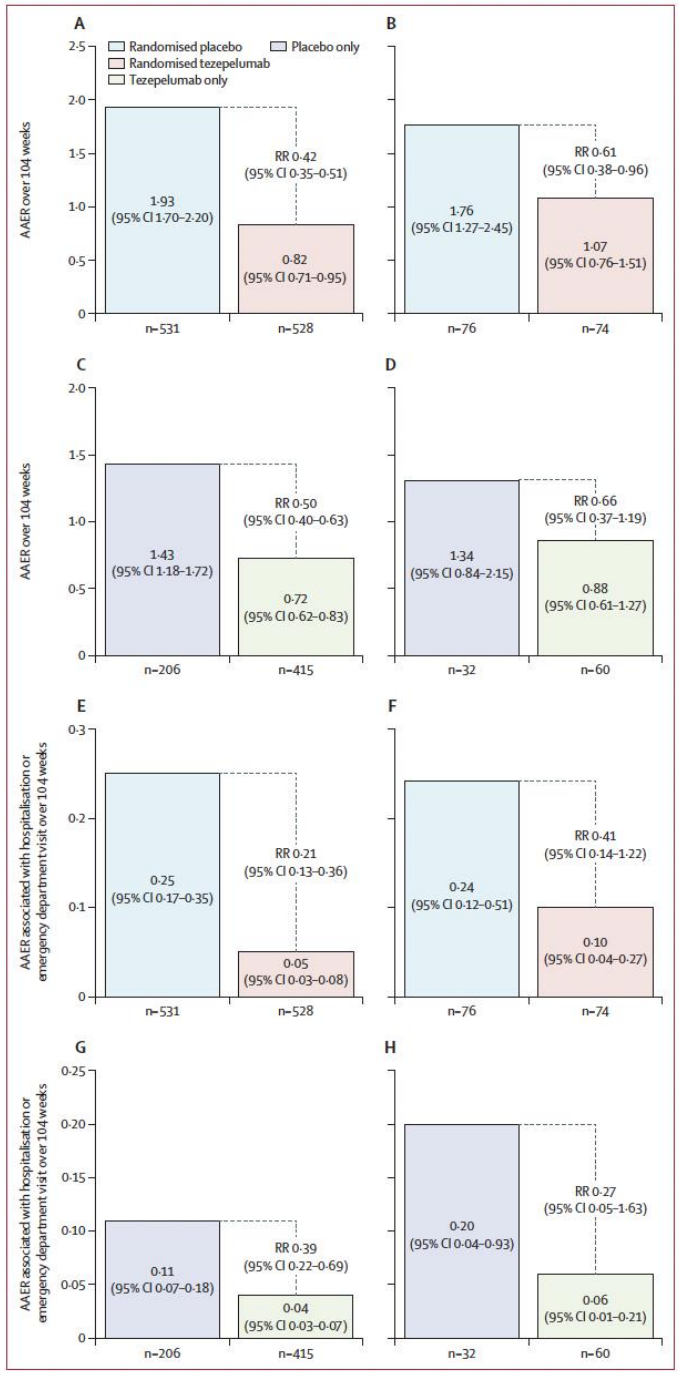
*Now approved for severe asthma 12 yrs and older without phenotypic or biomarkers

Menzies-Gow A, et al. *N Engl J Med* 2021;384:1800-9.

Long term efficacy of Tezepelumab - DESTINATION

	Randomised tezepelumab n/estimate	Randomised placebo n/estimate	Rate ratio (95% CI)
Baseline blood eosinophil count			
<300 cells per µL	309/0·88	309/1·60	0·55 (0·44–0·70)
≥300 cells per µL	219/0·73	222/2·46	0·30 (0·22–0·39)
<150 cells per µL	138/0·82	138/1·55	0·53 (0·37–0·76)
≥150 cells per µL	390/0·82	393/2·08	0·40 (0·32–0·49)
Baseline FeNO level			
<25 ppb	213/0·90	220/1·40	0·64 (0·48–0·86)
≥25 ppb	309/0·75	307/2·37	0·32 (0·25–0·40)
Allergy status			
FEIA positive for any perennial aeroallergen	339/0·77	341/1·84	0·42 (0·33–0·53)
FEIA negative for all perennial aeroallergens	184/0·94	177/2·09	0·45 (0·33–0·61)
Age at study entry			
Adolescent (≥12 to <18 years)	41/0·56	41/0·78	0·72 (0·36–1·45)
Adult (≥18 to <65 years)	391/0·88	416/2·11	0·42 (0·34–0·51)
Older adult (≥65 years)	96/0·65	74/1·73	0·38 (0·24–0·60)
Number of asthma exacerbations in the year before study entry			
≤2	310/0·61	325/1·23	0·49 (0·39–0·63)
>2	218/1·10	206/1·11	0·35 (0·27–0·46)
Nasal polyps in the 2 years before randomisation			
Yes	42/0·39	41/2·65	0·15 (0·07–0·29)
No	486/0·86	490/1·88	0·46 (0·38–0·55)
Inhaled corticosteroid dose group			
Medium	131/0·85	132/1·18	0·71 (0·49–1·04)
High	397/0·81	398/2·22	0·36 (0·29–0·45)
Maintenance oral corticosteroid use			
Yes	49/1·85	51/3·01	0·61 (0·35–1·07)
No	479/0·73	480/1·82	0·40 (0·33–0·49)
Overall	**528/0·82**	**531/1·93**	**0·42 (0·35–0·51)**

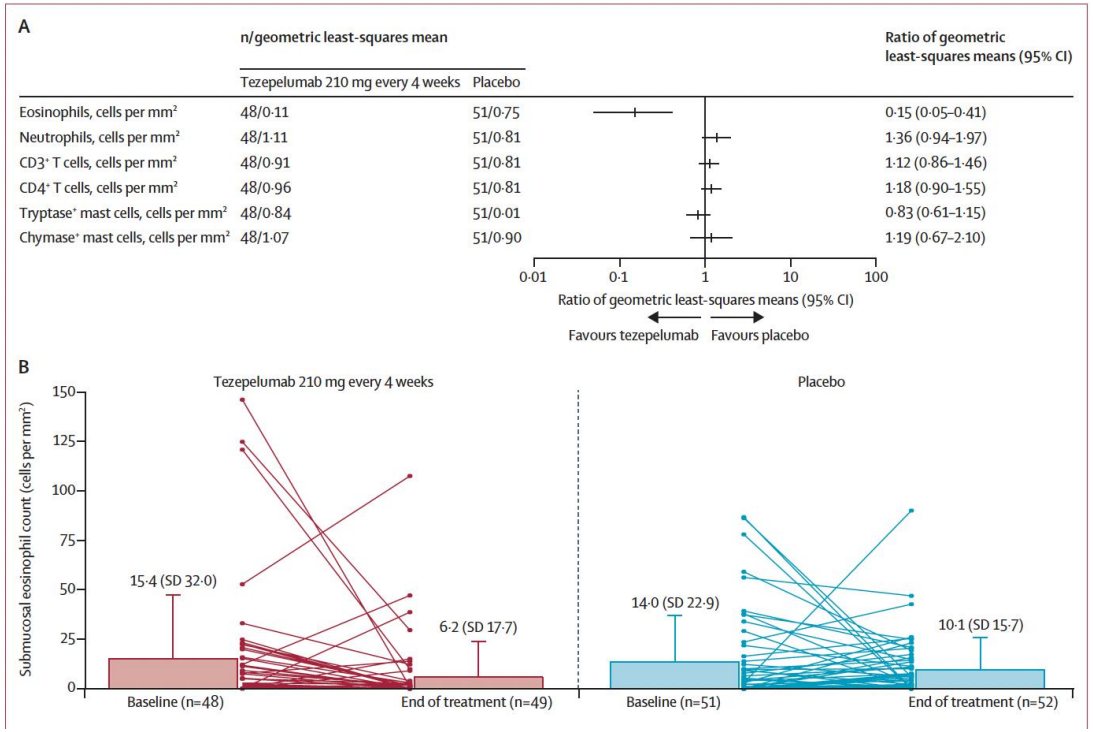


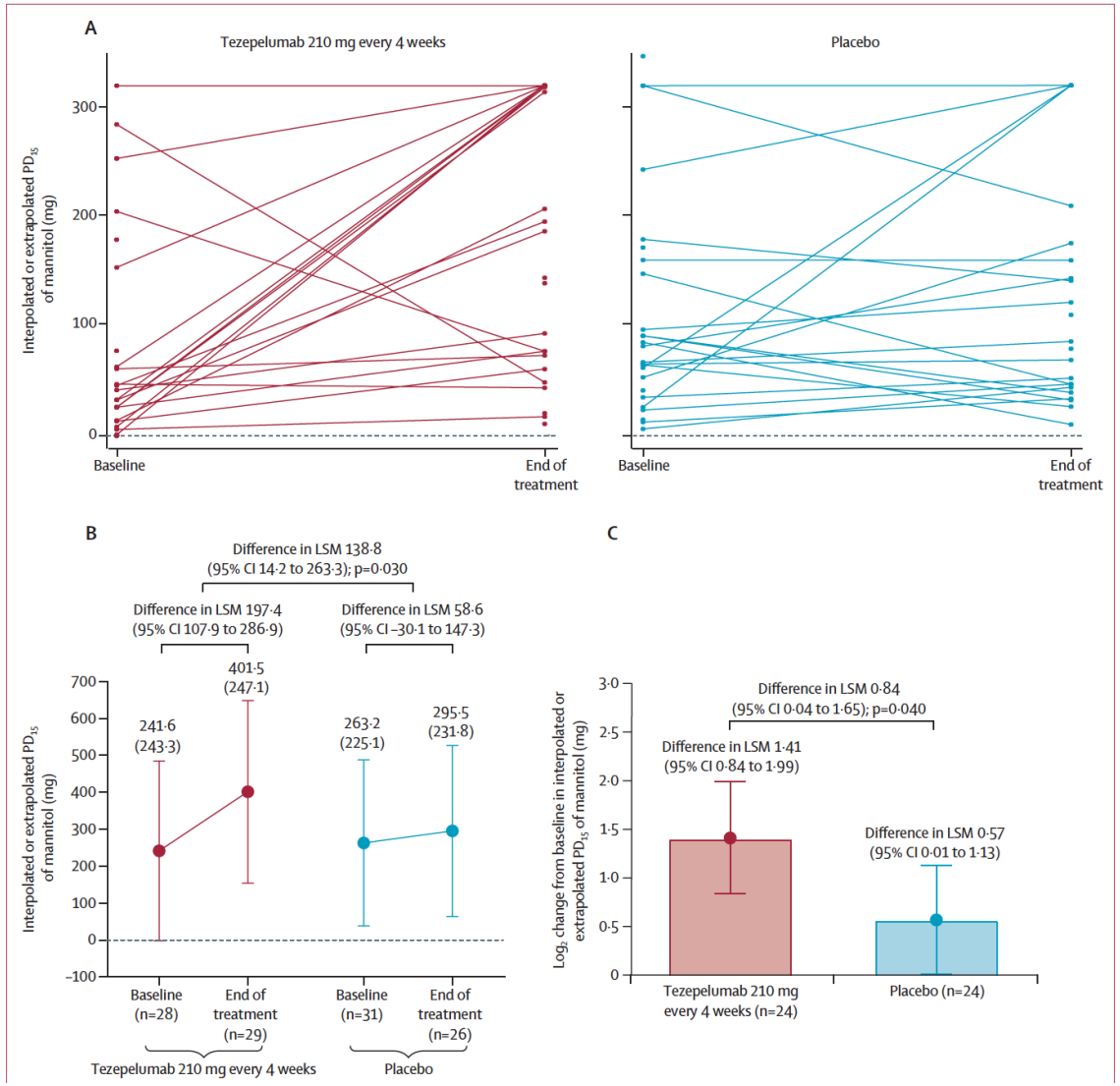


Safety concern: higher incidence of cardiac disorder serious adverse events in participants receiving tezepelumab than in those receiving placebo (unexpected low rate in placebo group)

Menzies-Gow, A et al. Lancet Respir Med. 2023 Jan 23

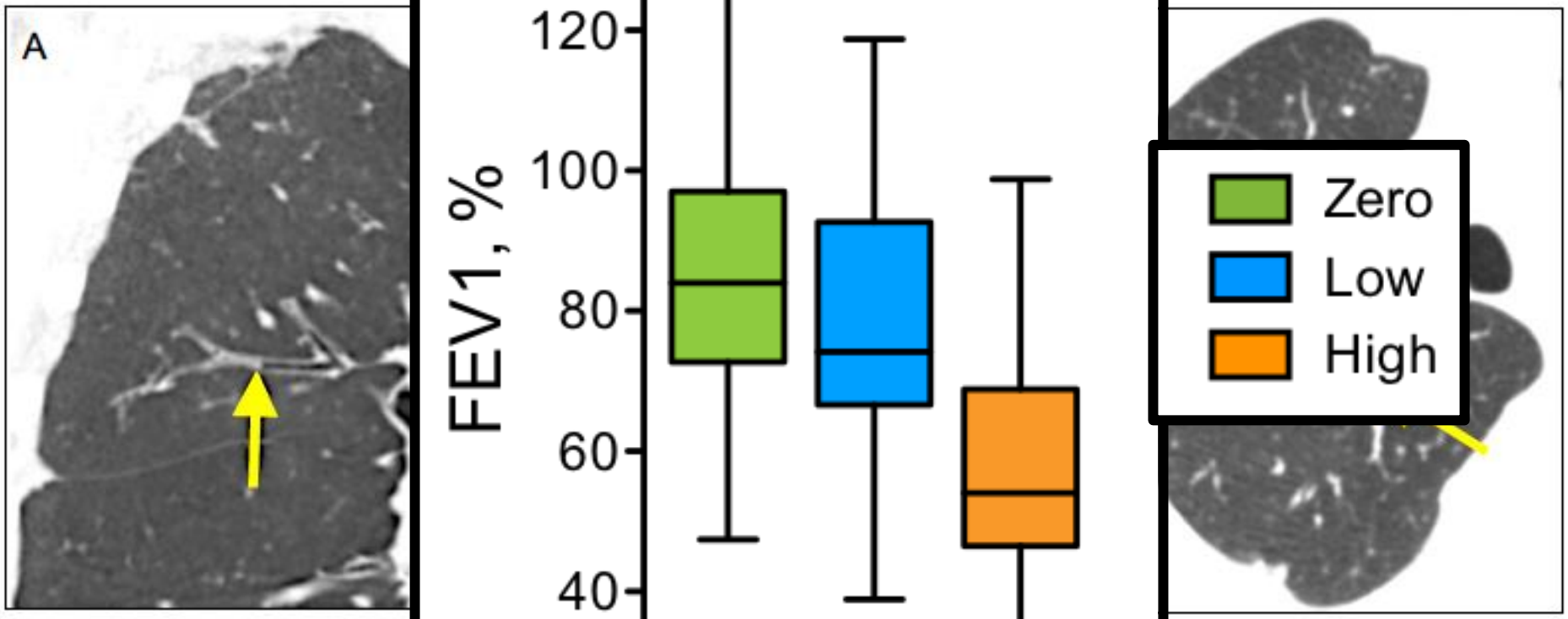
Effect of Tezepelumab on Inflammatory Cells – CASCADE study





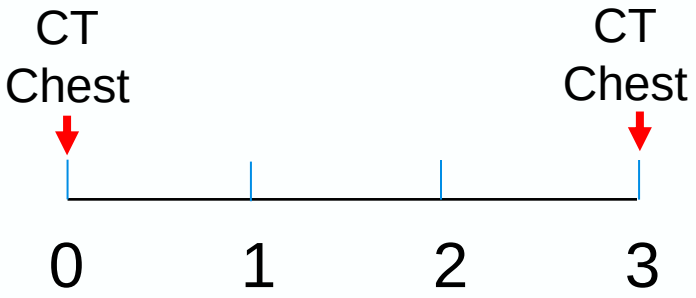
No significant differences between treatment groups in the other cell types evaluated: neutrophils, CD3+ or CD4+ T cells, tryptase+ or chymase+ mast cells

Radiograp ucus Plugs

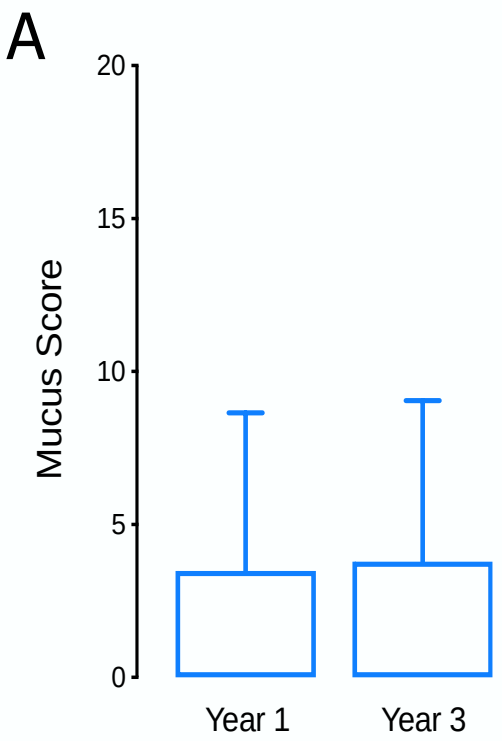


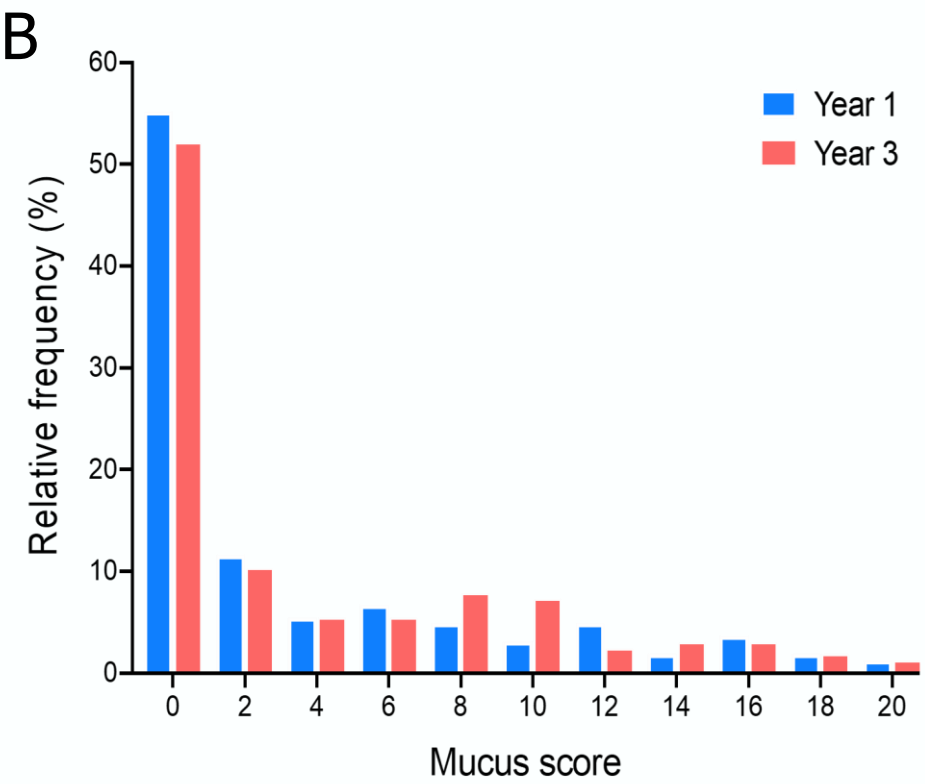
Dunican E & SARP. J Clin Invest 2018

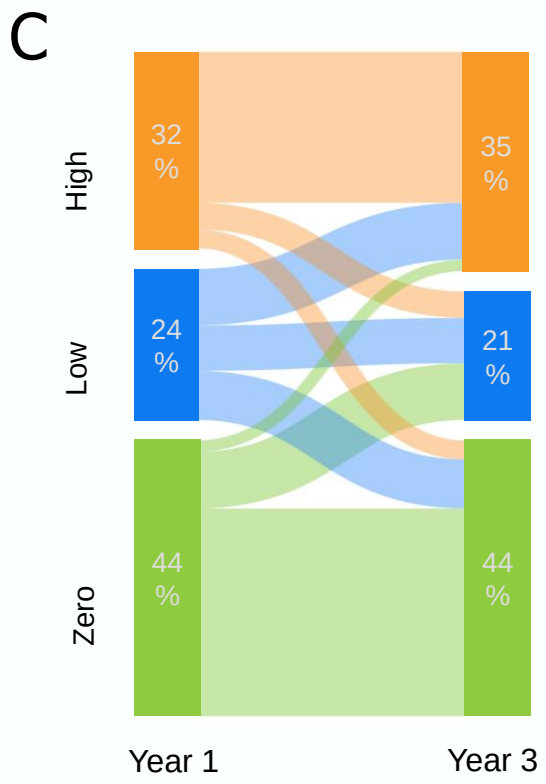
Persistent Airway Mucus Plugs in Severe Asthma



168 subjects with Year 1 and Year 3 CT scans

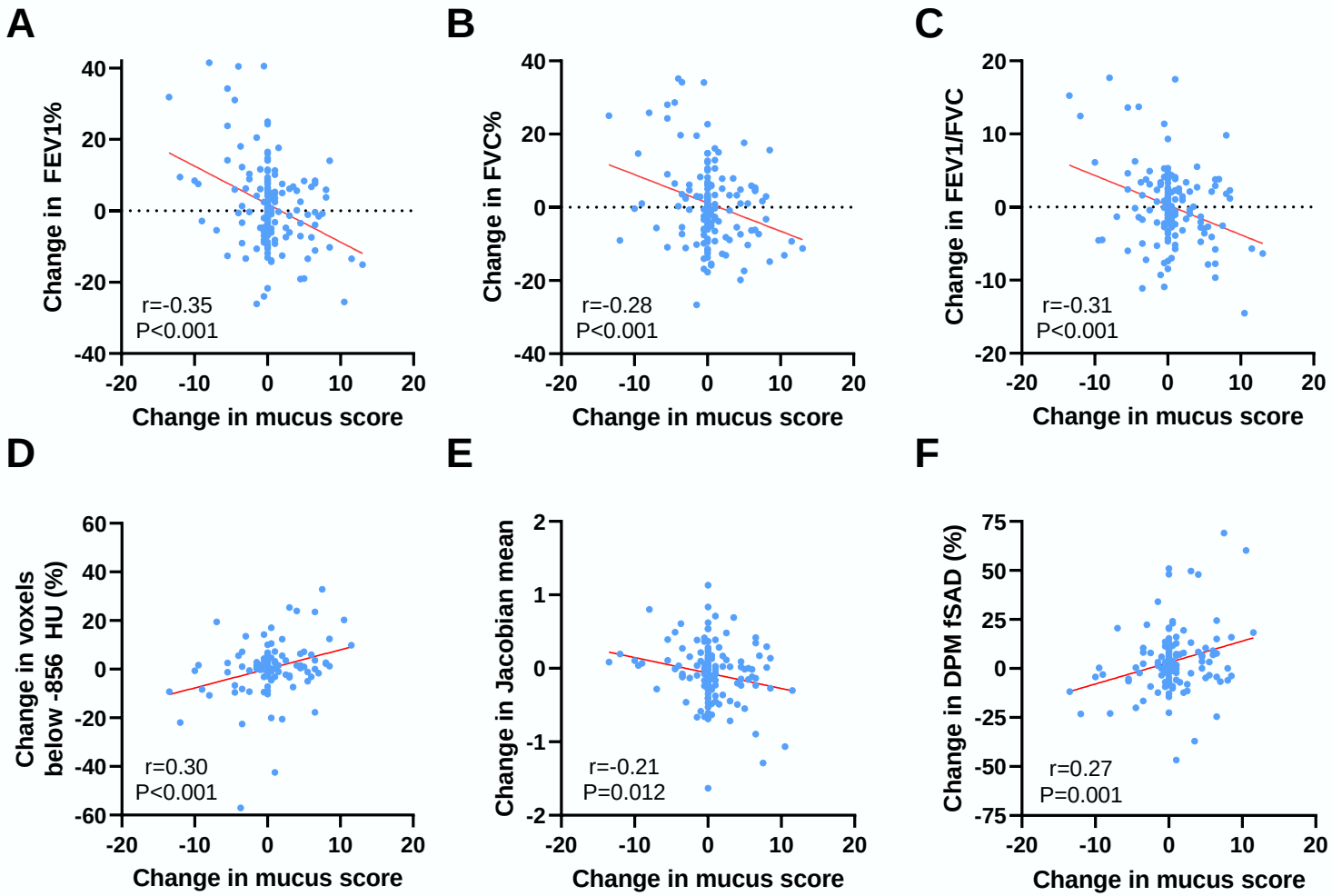




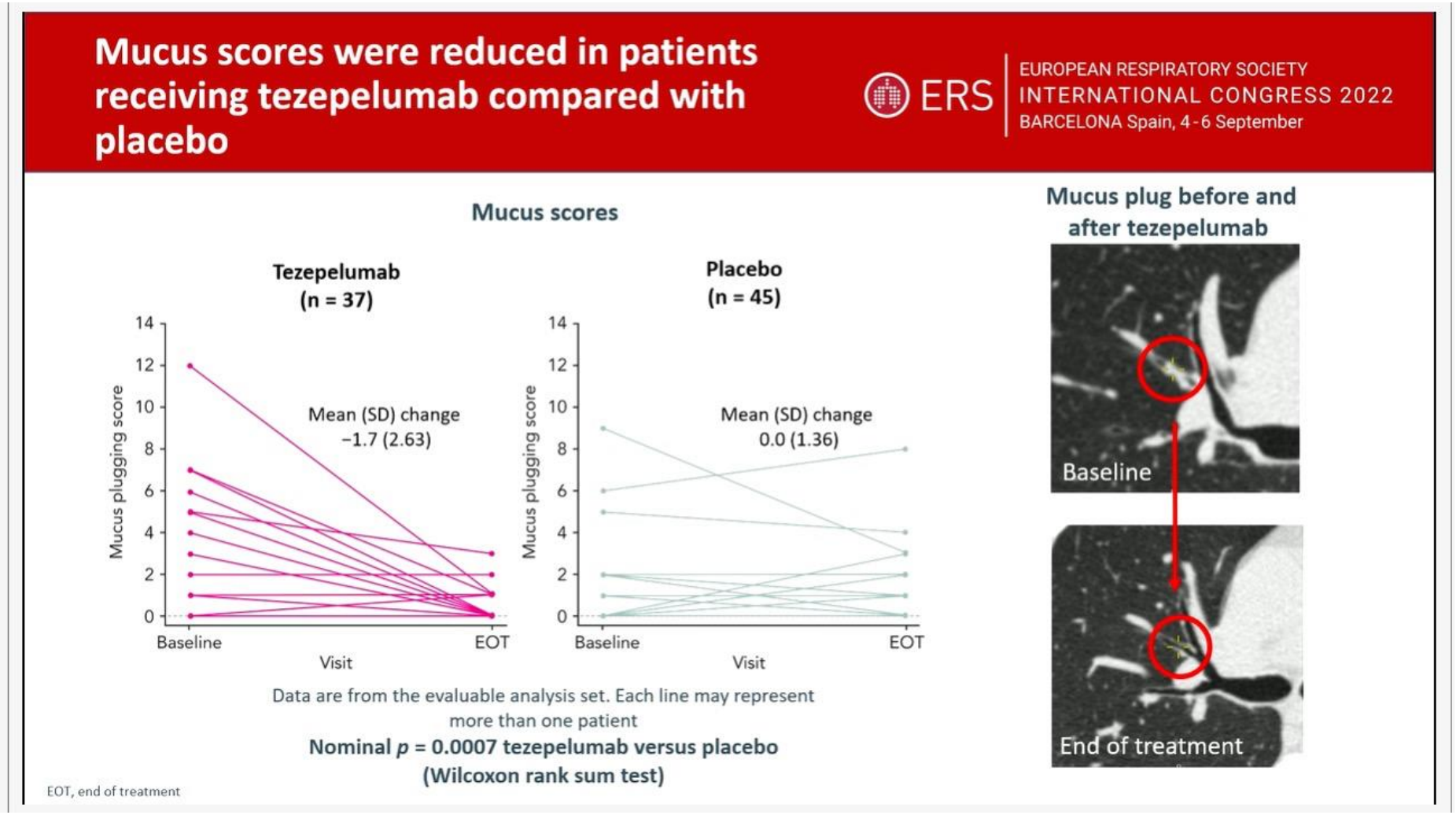


Tang M & SARP. AJRCCM 2022

Mucus plug relation to airflow over time



Tang M & SARP. AJRCCM 2022



- 116 pts randomized to Tezepelumab (anti-TSLP) mAb or placebo for 28 wks in the CASCADE Phase 2 study; 82 patients scored for MP with paired CT scans over treatment period
- Change in FEV1 correlated with change in mucus score r=-0.505, p=0.0001

Brightling, C et al CASCADE Phase 2. ERS Sept 2022

Non-T2 therapies for asthma

- Severe asthma is quite heterogenous with different phenotypes: exacerbation-prone, airway inflammation, mucus plugs, and airway and parenchymal remodeling
- New biomarkers are needed for Non-T2 asthma
  - Exacerbation prone asthma is characterized by lower FEV1, obesity, HTN, DM and higher IL-6 levels
- Macrolide therapy (azithromycin) may add benefit though this has not been replicated (low evidence)
- Bronchial thermoplasty offers benefit to those with uncontrolled asthma with an acceptable safety profile in selected patients
  - It has not been specifically tested in non-T2 asthma (low evidence)
- Tezepelumab blocks TSLP, an epithelial alarmin
  - Reduces exacerbations even in the low eosinophil severe uncontrolled asthma patient
  - Sustained effects on exacerbations (~0.4-0.6/yr) and lung function (FEV1 ~200 ml) over two years
  - Significant reduction in submousal eosinophils (though no other cells) with significant reduction in T2 inflammatory markers and airway hyperresponsiveness to mannitol

Options for Non-T2 asthma are expanding … can we get to therapies for nearly all endotypes??

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