

Managing Severe Asthma in Children

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Disclosures

- Employment
 - University of Wisconsin SMPH
- Financial Interests
 - Consultant: Areteia, GlaxoSmithKline, Sanofi, Regeneron, Apogee, Abbvie
 - DSMB: AstraZeneca, Upstream Bio
- Research Interests
 - NIH: NHLBI, NIAID
 - Regeneron
 - Vifor pharma

Why are Asthma Exacerbations Important?

- Major factor in morbidity and mortality¹
- Significant contributor to cost²
 - Emergency department care
 - Hospitalization
 - Lost time from work/school
- Risk for progressive loss of lung function^{3,4}
- “Exacerbation-prone” patients^{1,5–6}
 - Exacerbations not prevented by ICS/LABA
 - More severe disease
 - “Destabilized” asthma

1. Dougherty, Clinical Exp Allergy 2009

2. Rodrigo, Chest 2004

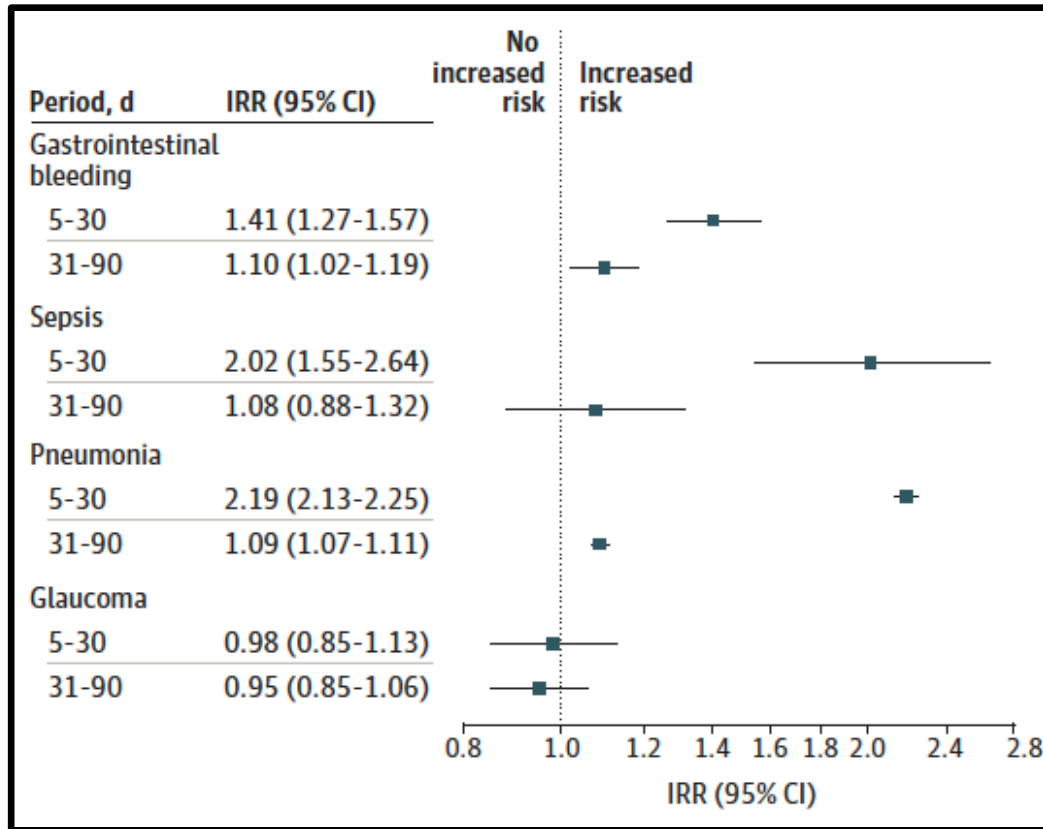
3. O’Byrne, AJRCCM 2009

4. O’Brian, JACI 2012

5. Thomson & Chouduri, BMC Pulm Med 2008

6. Koga, Respiratory Med 2006

OCS Associated with Increased Risk of Fracture, GI bleed, Sepsis & PNA

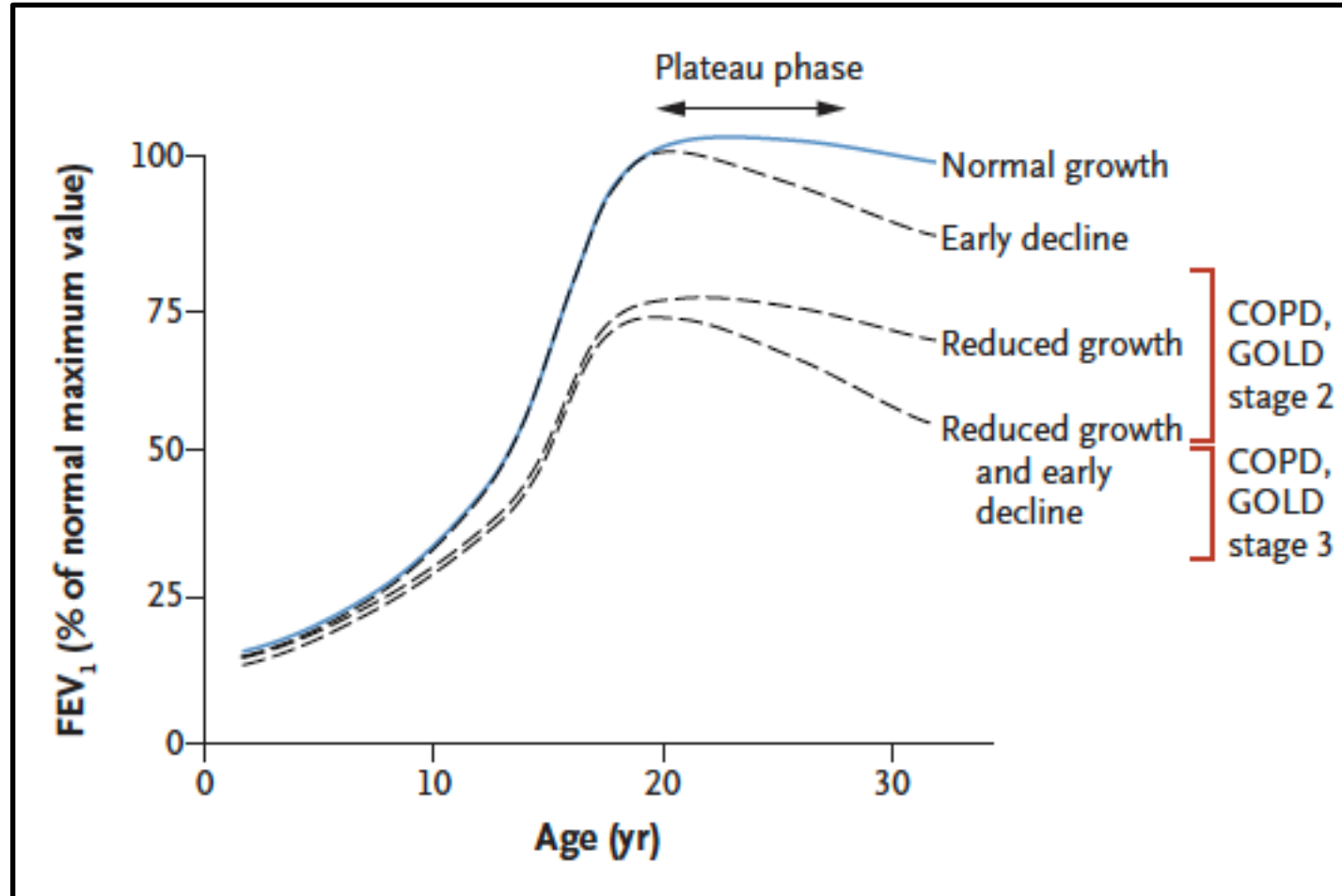


*Increased fracture risk in the year following OCS
RR 1.17 (p=0.01)

Gray et al *JAMA Peds* 2018

Yao et al, *JAMA Peds* 2021

Evidence of Impaired Lung Function Growth & Early Decline in Childhood Asthma

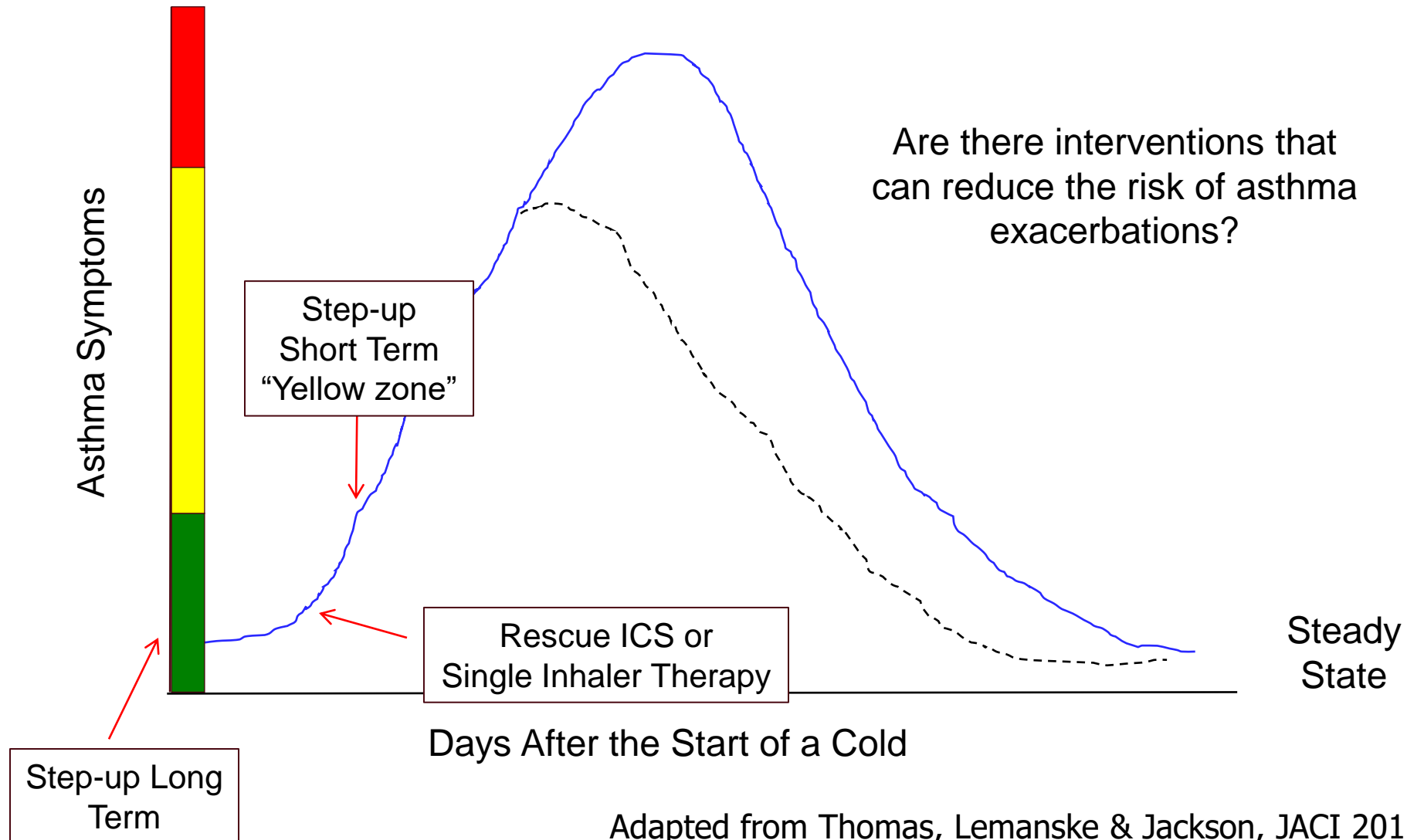


Factors Associated with Impaired Lung Growth in CAMP

- Lower baseline lung function
- Increased BDR
- Increased airway responsiveness to MCh
- Male sex (OR 8)
- Vitamin D <30
- **# of prednisone courses**

**Randomized Treatment (ICS, nedocromil or placebo) NOT associated with lung growth outcomes

Step-Up Approaches to Attempt to Prevent Asthma Exacerbations



Adapted from Thomas, Lemanske & Jackson, JACI 2011

Need for Improved Reliever Strategies

- Adherence to all controller regimens is suboptimal
- All patients with asthma need a reliever
- Inhaled SABA has been 1st line treatment for 50 years
- **SABAs do not treat inflammation and do not prevent exacerbations**
- Greater SABA use associated with annual systemic corticosteroid exposure (Lugogo et al. ATS 2021 Poster; Quint et al. SABINA + *JACI-IP* 2022)

MART with ICS/Formoterol

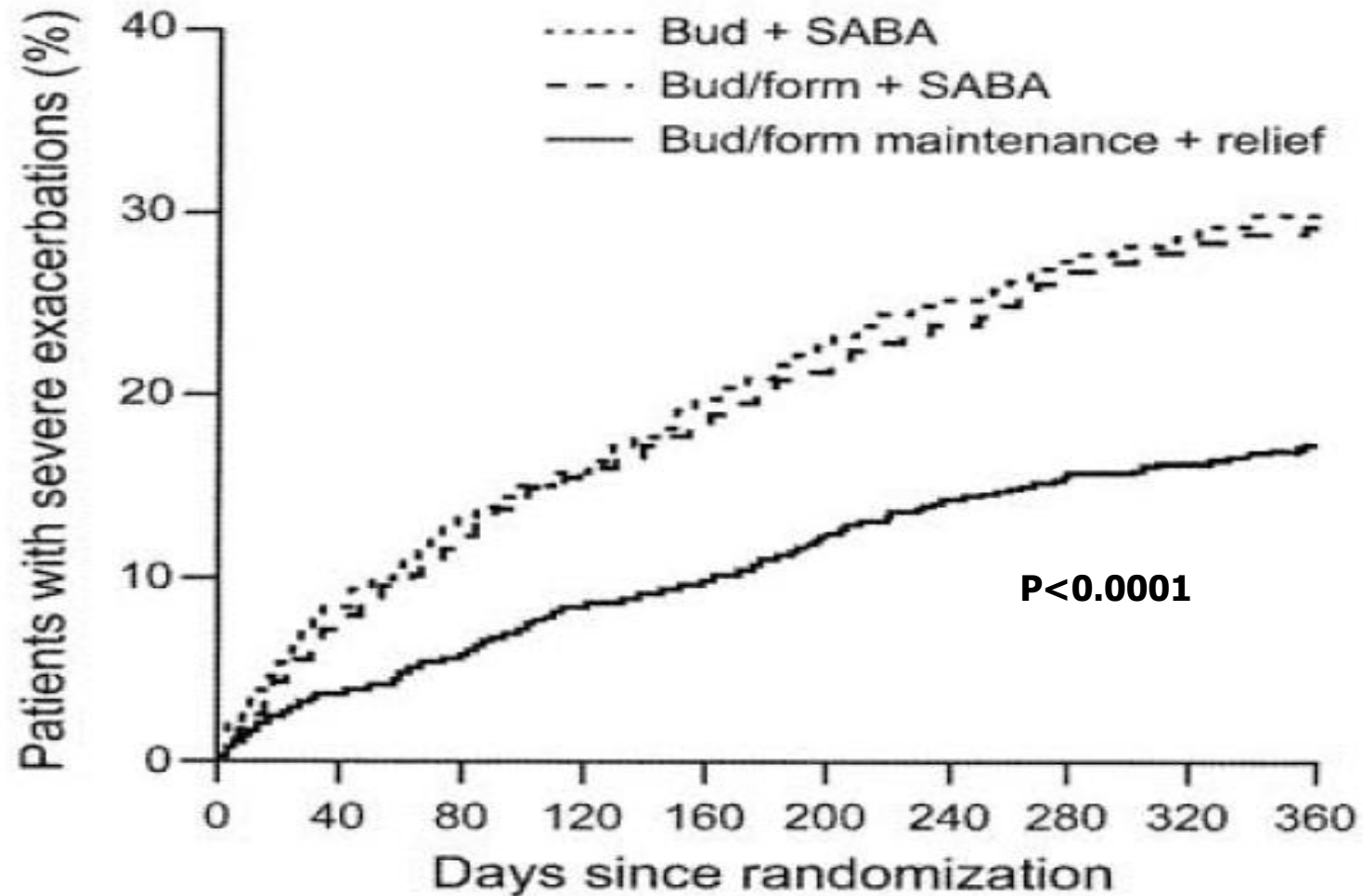
Does ICS/formoterol for Maintenance & Relief Reduce Exacerbations?

2760 patients
4-80 years old
Not well controlled during run-in

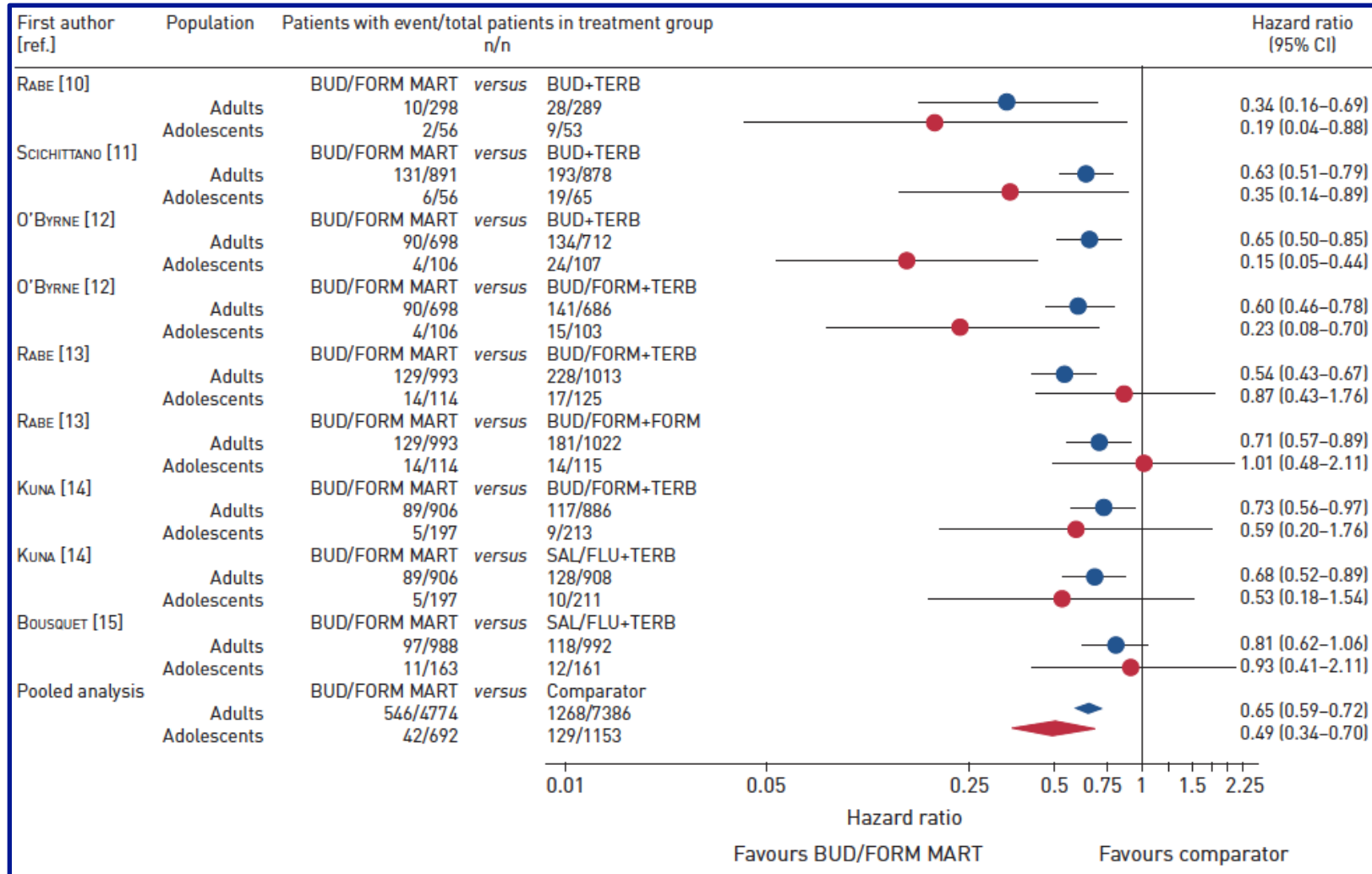
Randomization Groups	Maintenance	Rescue
Budesonide + SABA	Budesonide 320 mcg 2x daily*	Terbutaline
ICS/LABA maintenance	Budesonide/Formoterol 80/4.5 2x daily*	Terbutaline
ICS/LABA maintenance + reliever	Budesonide/Formoterol 80/4.5 2x daily*	Budesonide/Formoterol 80/4.5

***1x daily in 4-11 y/o**

ICS/LABA for Maintenance & Relief Reduces Severe Exacerbations



Adolescents: ICS/formoterol for Maintenance & Relief Significantly Reduced Exacerbations



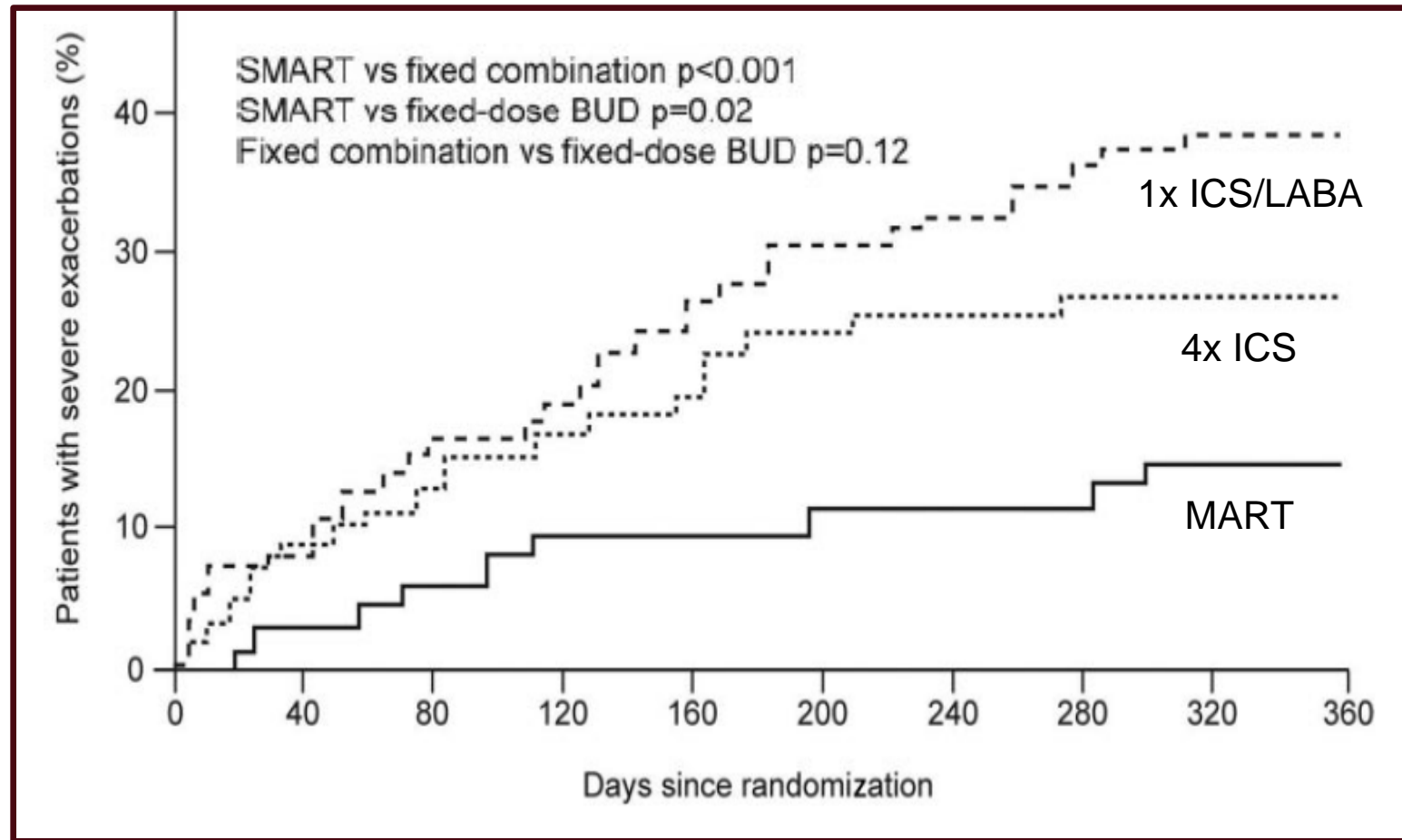
Does ICS/LABA for Maintenance & Relief Reduce Exacerbations in Children?

341 4-11 year old children

*Not well controlled during run-in on 200-500 mcg ICS per day

Randomization Groups	Maintenance	Rescue
Budesonide + SABA	Budesonide 320 mcg 1x daily	Terbutaline
ICS/LABA maintenance	Budesonide/Formoterol 80/4.5 1x daily	Terbutaline
ICS/LABA maintenance + reliever	Budesonide/Formoterol 80/4.5 1x daily	Budesonide/Formoterol 80/4.5

Children: ICS/formoterol for Maintenance & Relief Significantly Reduced Exacerbations



Single Inhaler Therapy - MART

Practical Considerations

- Adherence & Perception of symptoms
- Maintenance & Reliever
 - No FDA approval [package insert and online information not consistent with this approach]
 - Insurance coverage [potentially more than 1 inhaler per month & specific inhaler]
 - Mometasone/formoterol not studied as of yet
 - Side effects at higher doses?
 - Has not been studied in severe disease in children/adolescents

Can Targeted Therapy with Biologics Improve Outcomes in Childhood Asthma?

Biologics Currently with an FDA Indication for Asthma?

Product	Target	Asthma FDA Indication	Other Indications
Omalizumab	IgE	6 years & up	CIU, CRSw/NP, FA*
Mepolizumab	IL-5	6 years & up	EGPA, HES, CRSw/NP
Benralizumab	IL-5R	6 years & up	EGPA
Reslizumab	IL-5	18 years & up	
Dupilumab	IL-4R α	6 years & up	AD [#] , CRSw/NP, EoE, COPD, PN
Tezepelumab	TSLP	12 years & up	

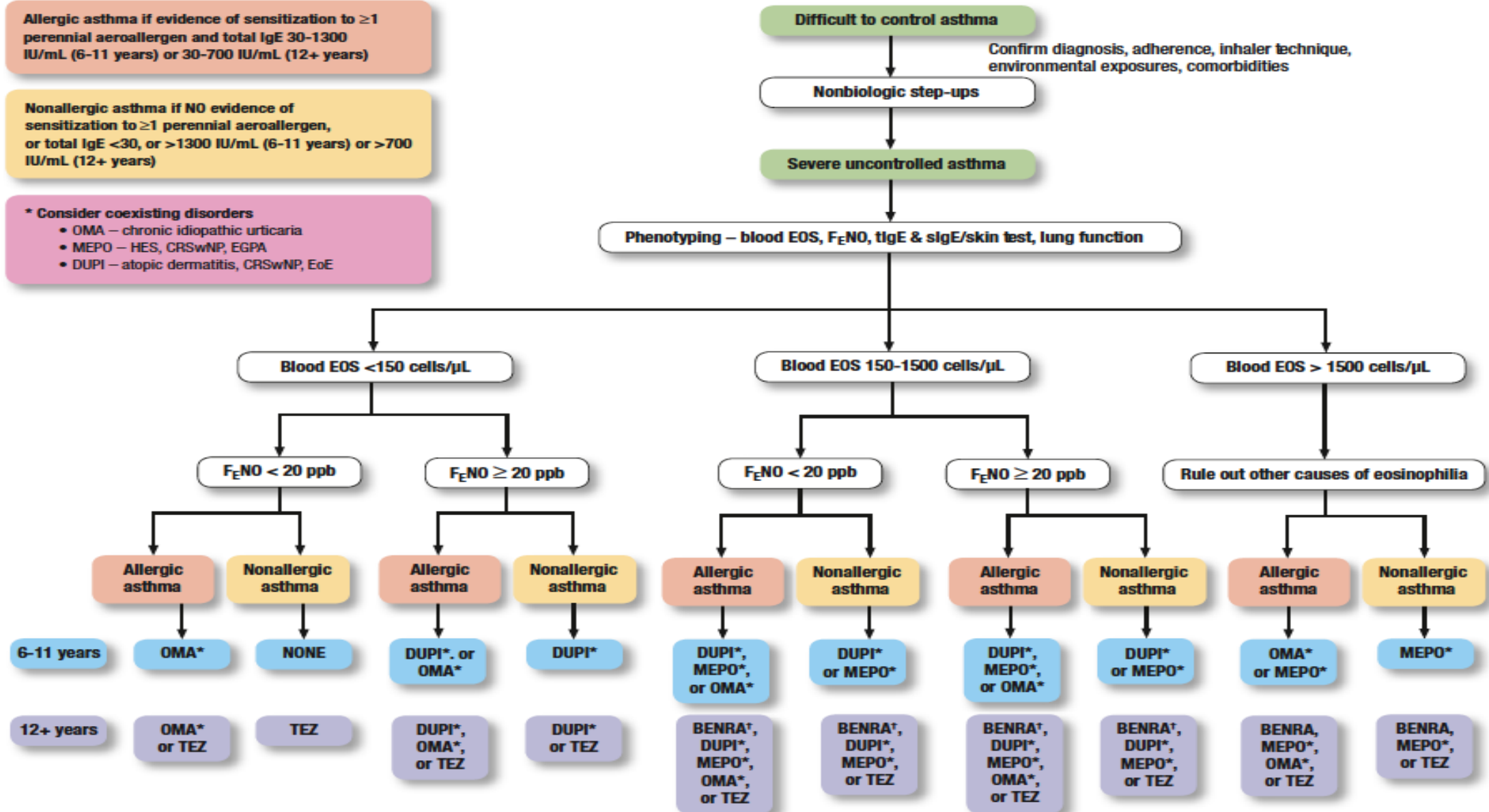
Selecting Biologics in Children & Adolescents

Allergic asthma if evidence of sensitization to ≥ 1 perennial aeroallergen and total IgE 30-1300 IU/mL (6-11 years) or 30-700 IU/mL (12+ years)

Nonallergic asthma if **NO** evidence of sensitization to ≥ 1 perennial aeroallergen, or total IgE < 30 , or > 1300 IU/mL (6-11 years) or > 700 IU/mL (12+ years)

*** Consider coexisting disorders**

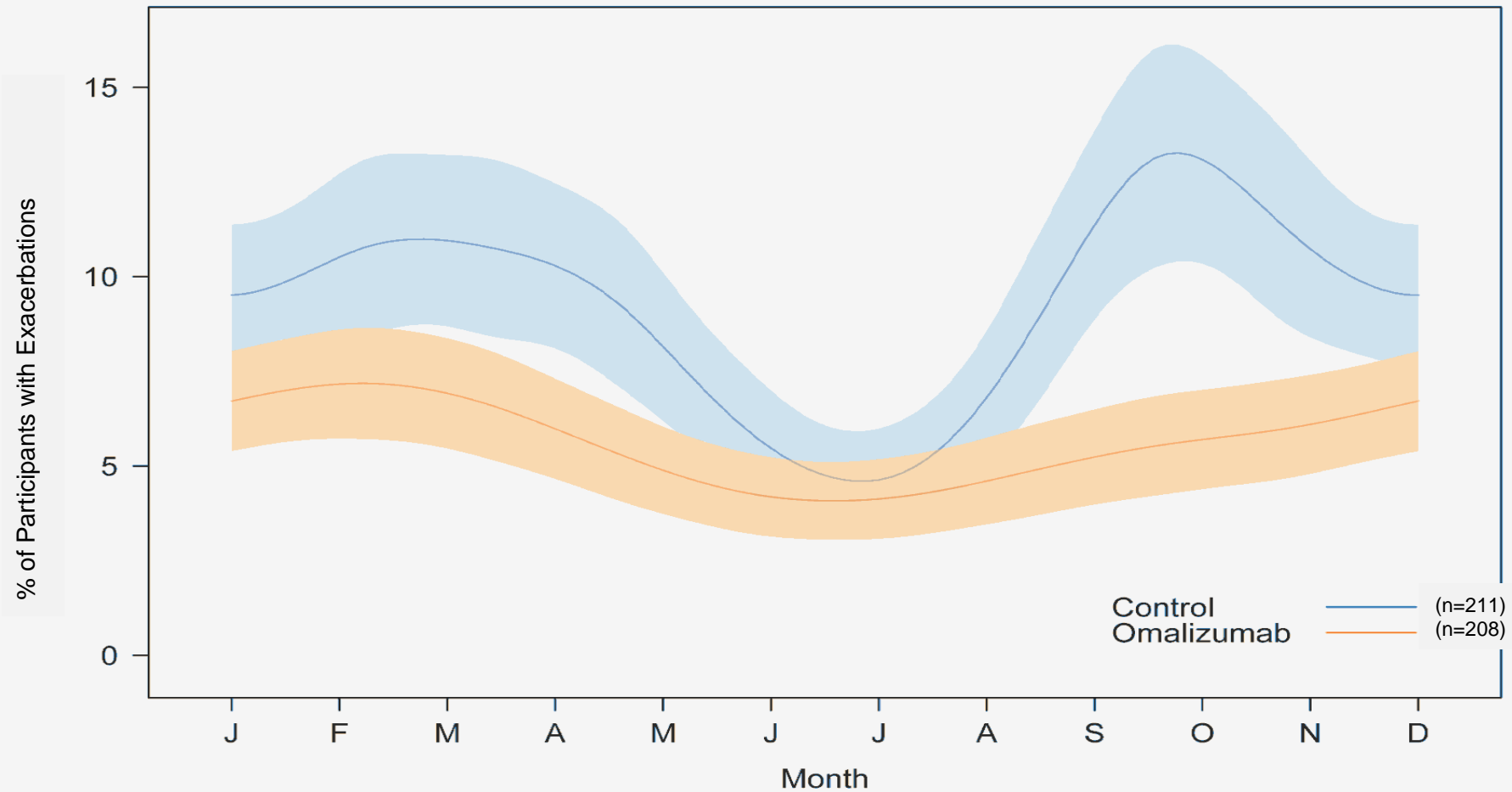
- OMA – chronic idiopathic urticaria
- MEPO – HES, CRSwNP, EGPA
- DUPI – atopic dermatitis, CRSwNP, EoE



Targeting IgE: Omalizumab



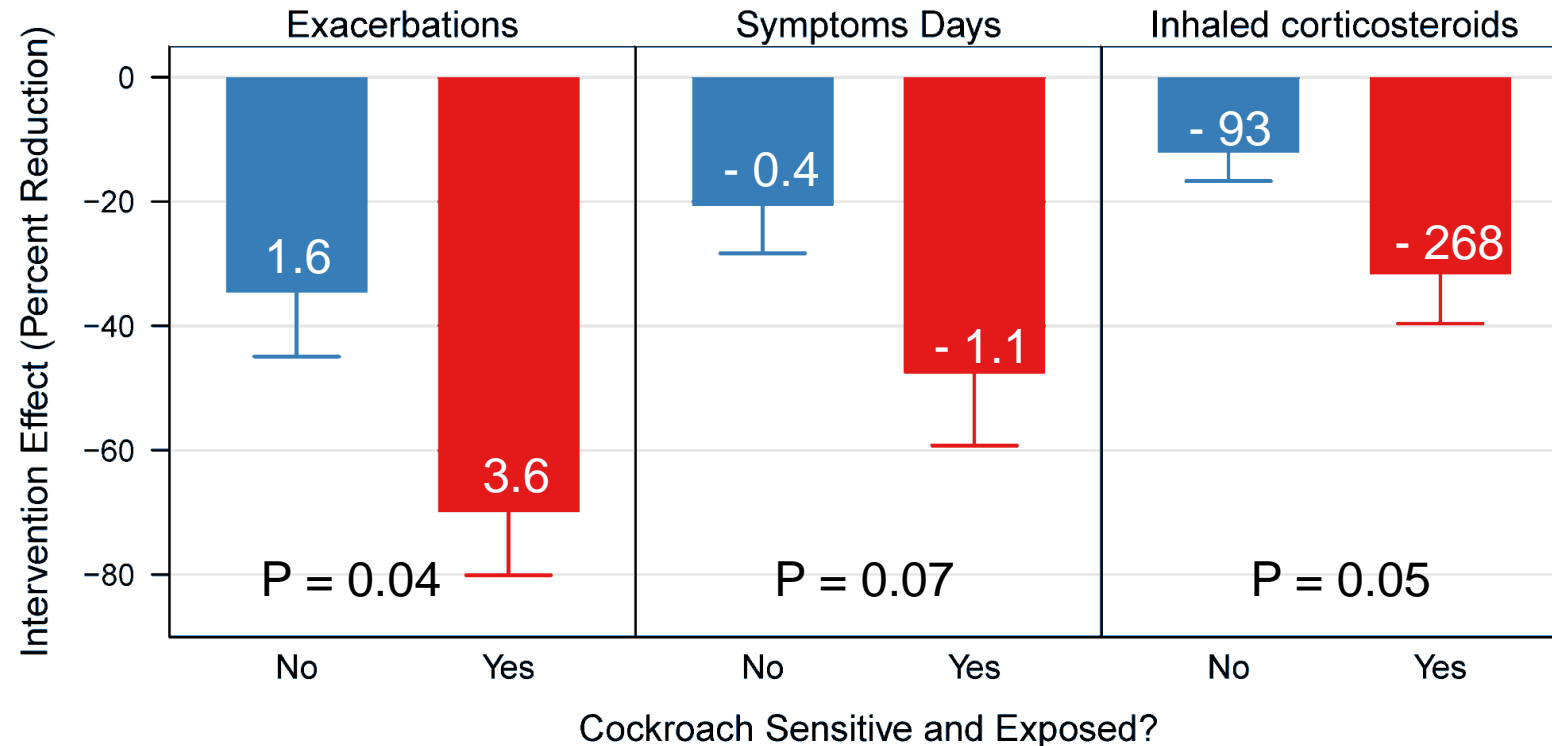
Omalizumab Reduces Severe Exacerbations in Children



Busse et al, *NEJM* 2011

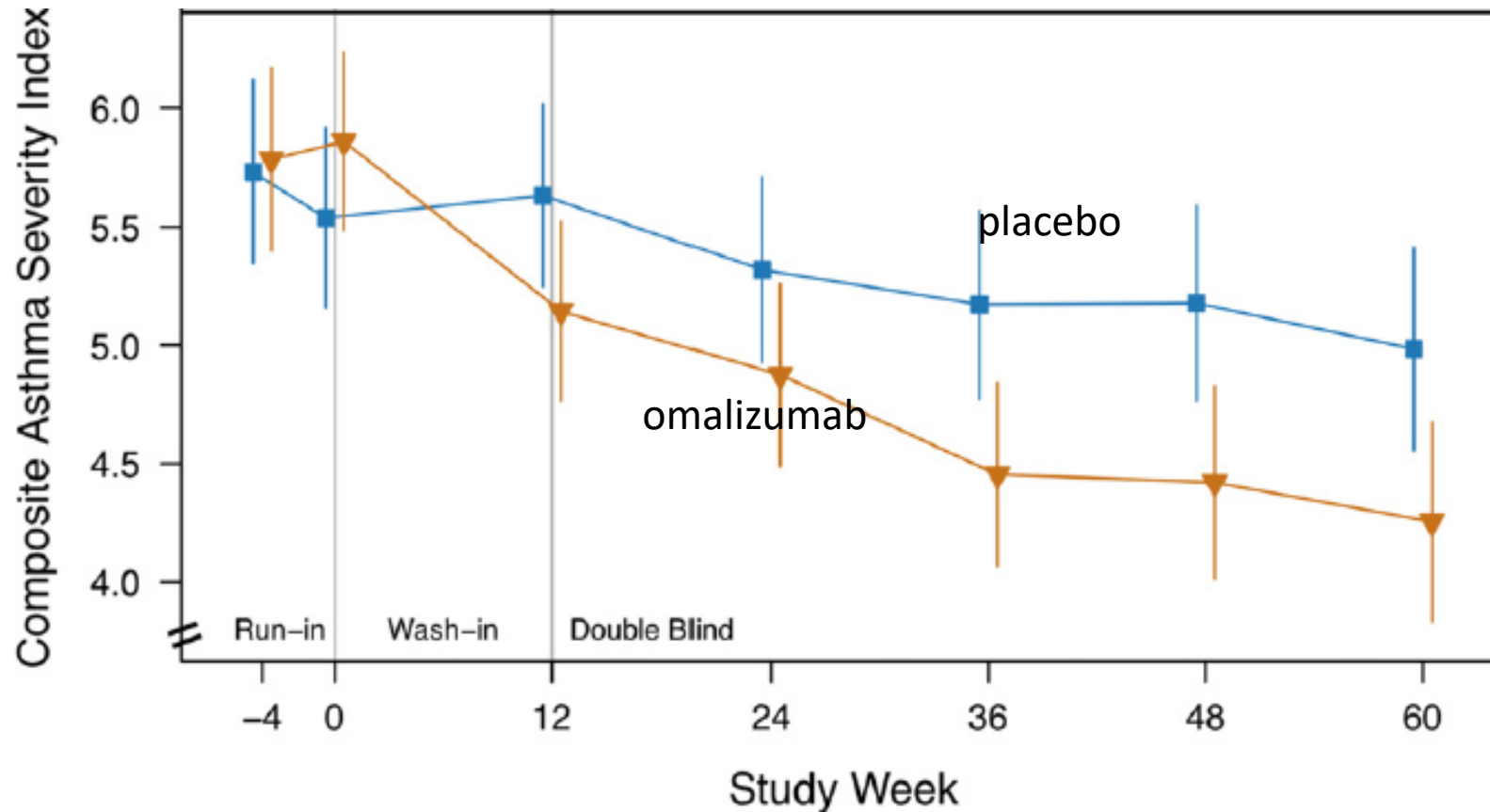


The Effect of Sensitization and Exposure on Omalizumab Efficacy





Omalizumab & Disease Severity: Composite Asthma Severity Index (CASI)



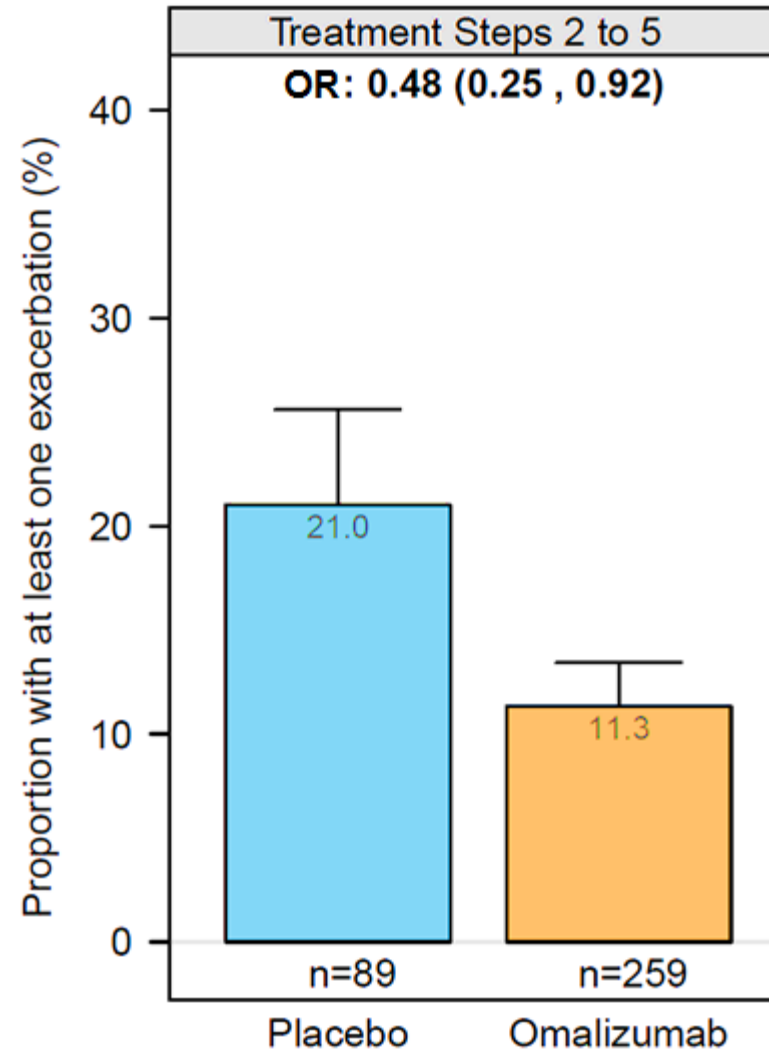
Omalizumab reduced disease severity as measured by CASI

Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations (PROSE)

Can a pre-seasonal intervention with omalizumab, or a boost in ICS, initiated just 4-6 weeks before a return to school, prevent the annual fall spike in asthma exacerbations among inner-city children with persistent allergic asthma and on guideline care?



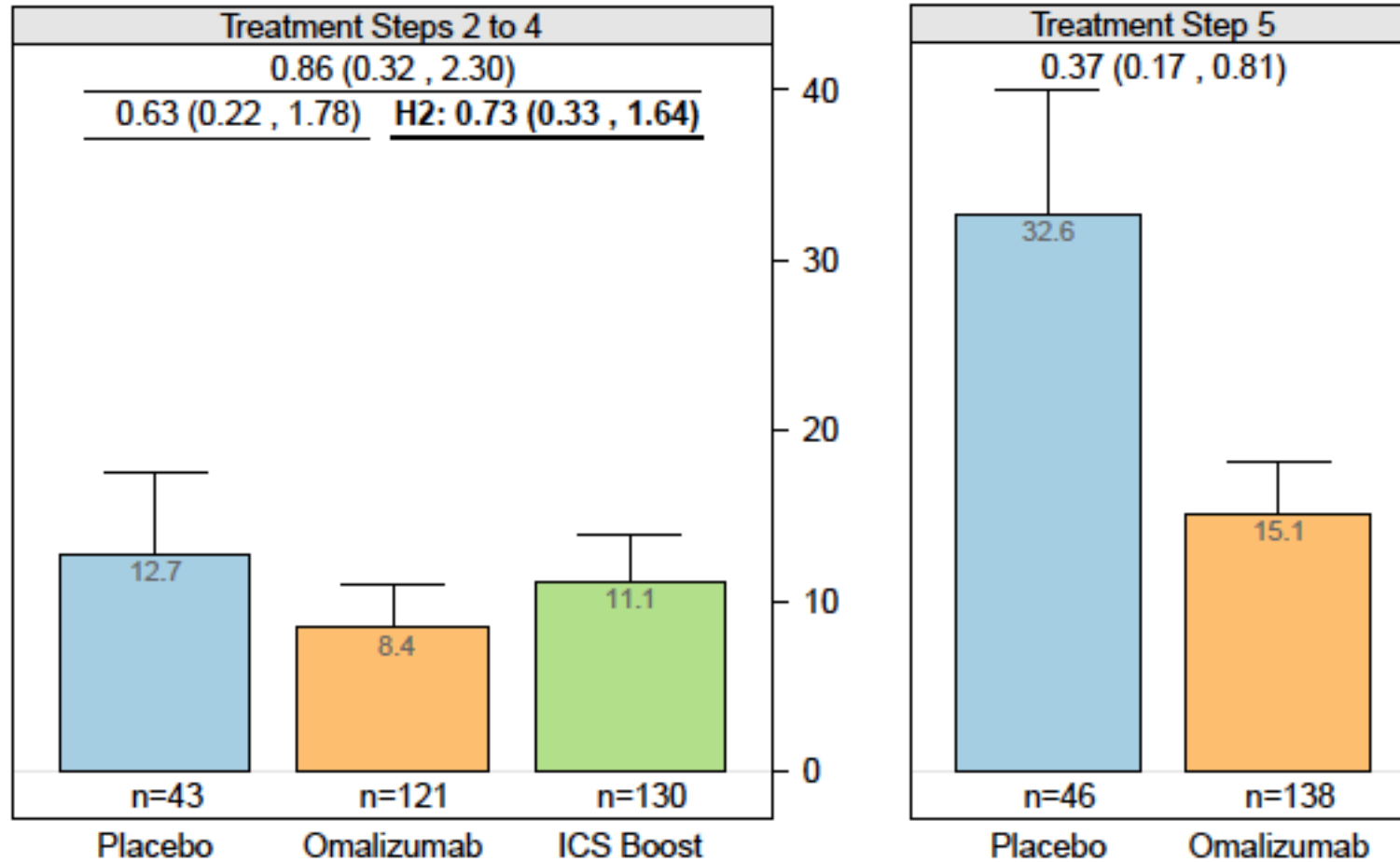
Omalizumab reduced seasonal exacerbations of asthma



*ICS Boost *did not* reduce the exacerbation rate in PROSE



The Benefit was Primarily Observed in Participants with Severe Disease



*ICS Boost *did not* reduce
the exacerbation rate in
PROSE

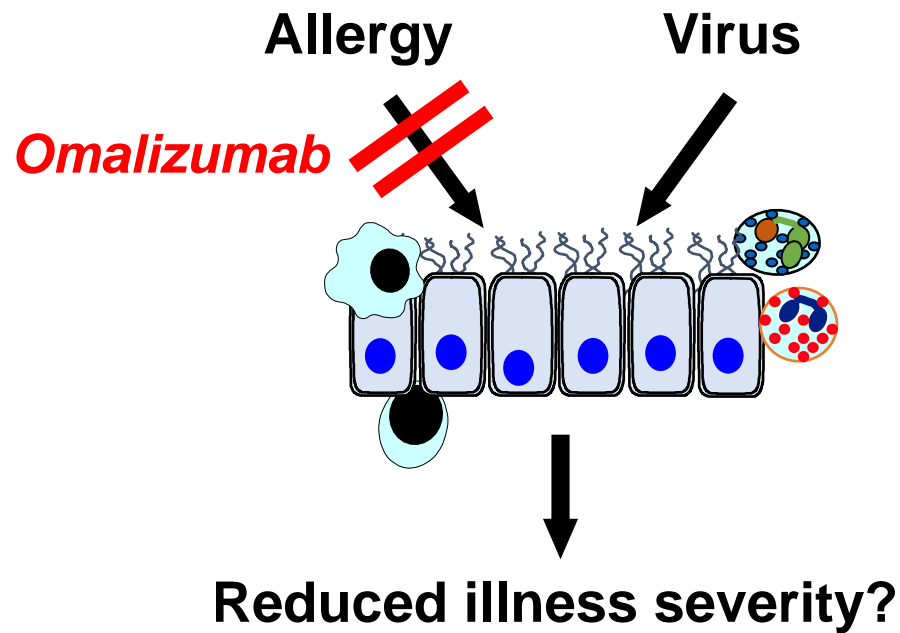


Are T2 Biomarkers Predictive of Omalizumab Response?

Biomarker	Exacerbation Benefit Odds Ratio	P-value	Interaction p-value
FeNO			
<20	1.15 (0.66-1.98)	0.63	0.05
>/= 20	2.57 (1.46-4.54)	<0.01	
Blood Eos			
<2%	0.56 (0.24-1.30)	0.18	<0.01
>/= 2%	2.13 (1.50-3.02)	<0.01	



What are the Mechanisms of Omalizumab Efficacy?



- Fewer Fall exacerbations
 - OR 0.48 (0.25-0.92)
- Fewer RV detection and illnesses
 - RR 0.68 (0.52-0.88)
- Enhanced IFN- α secretion *ex vivo*

Teach S, et al. JACI 2015
Esquivel A et al AJRCCM 2017
Gill MA et al. JACI 2018

- ~50% of exacerbations persisted despite omalizumab highlighting the need to identify pathways that lead to persistent asthma exacerbations

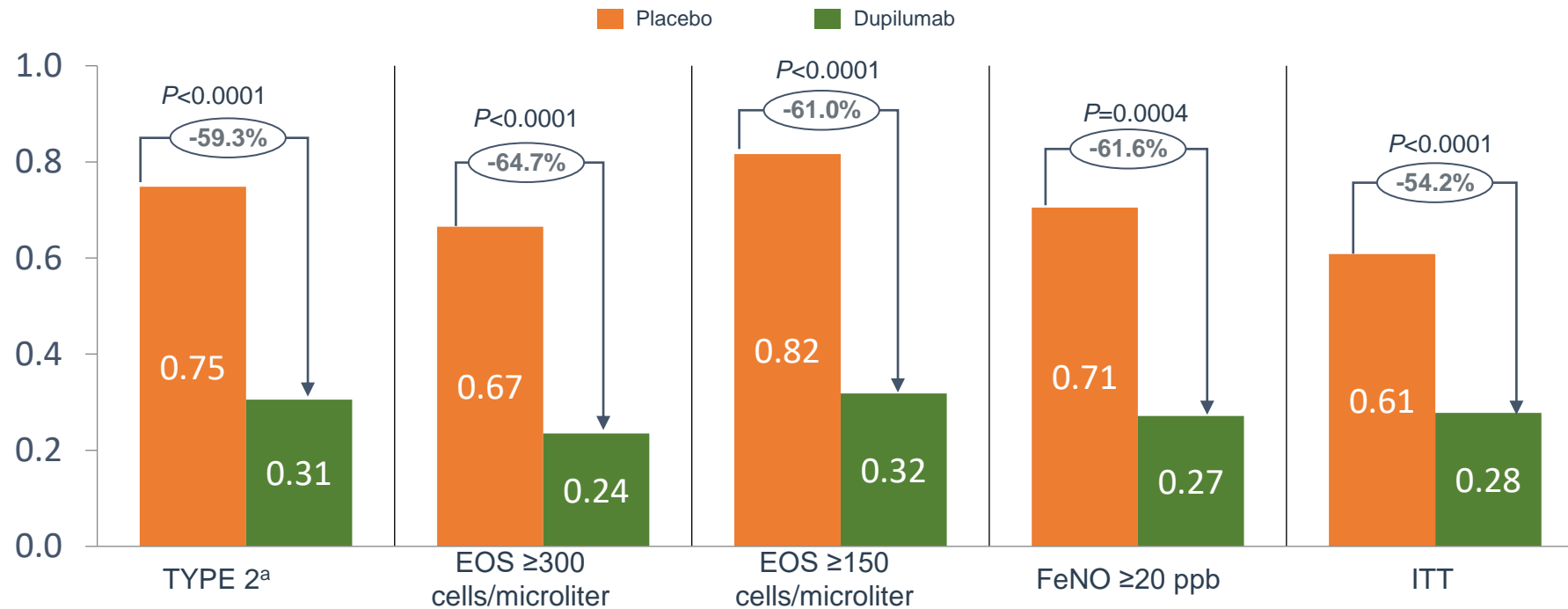
Targeting T2 Inflammation with Anti-IL4/13 Strategies

VOYAGE: Dupilumab in 6-11 y/o children with Moderate-Severe asthma

Dupilumab is a monoclonal antibody directed against the IL-4 receptor α subunit that inhibits both IL-4 and IL-13

Type 2 Population		
	PBO (N=114)	Dupi (N=236)
Age (year), mean (SD)	9.0 (1.6)	8.9 (1.6)
Female, n (%)	36 (31.6%)	84 (35.6%)
Medium ICS, n (%)	64 (56.1%)	131 (55.5%)
High ICS, n (%)	50 (43.9%)	102 (43.2%)
Severe exacerbations/year, mean (SD)	2.18 (1.55)	2.61 (2.58)
Pre-BD FEV ₁ pp, mean (SD)	78.36 (14.51)	77.66 (14.38)
FEV ₁ reversibility, mean (SD)	18.34 (14.89)	23.47 (21.00)

VOYAGE: Dupilumab Reduced Exacerbations

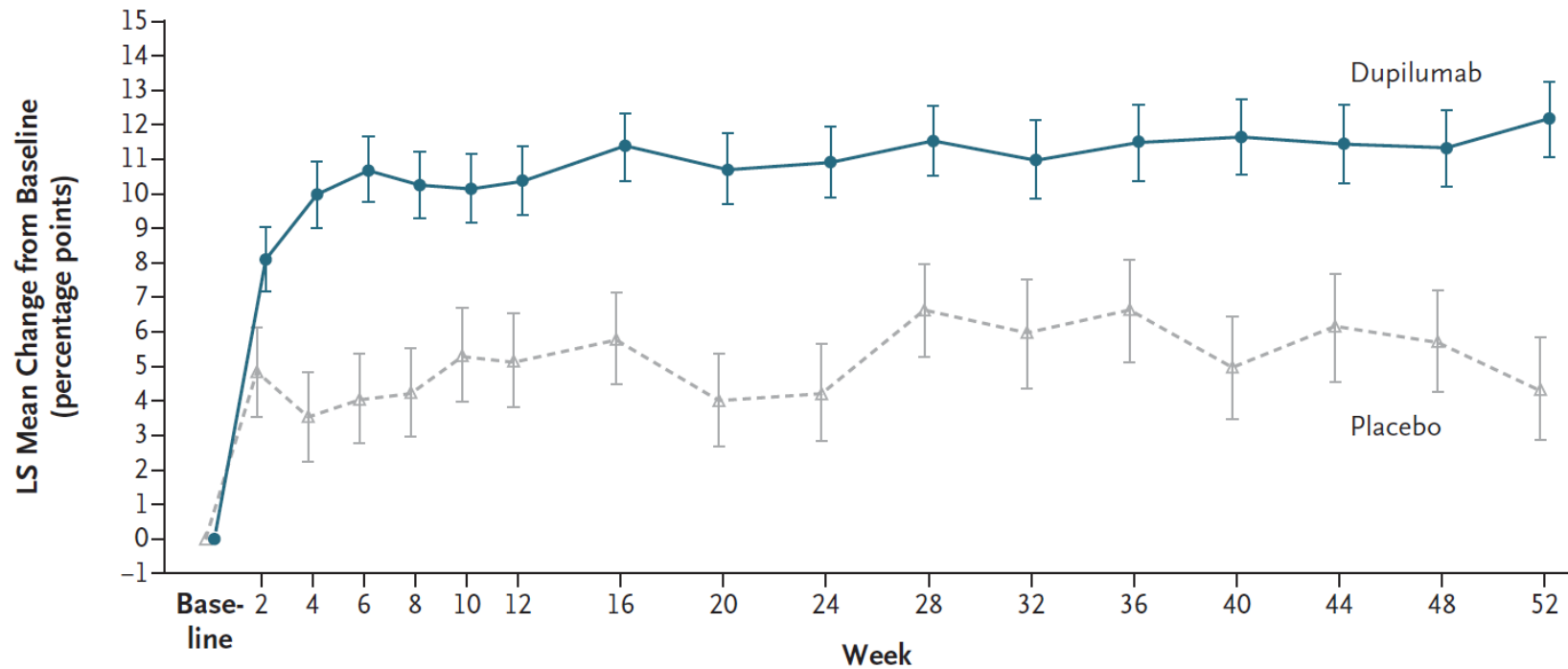


^aType 2 defined as EOS ≥150 cells/microliter or FeNO ≥20 ppb.

EOS, eosinophils; FeNO, fractional exhaled nitric oxide; ITT, intent to treat; PBO, placebo; ppb, parts per billion.

VOYAGE: Impact of Dupilumab on Lung Function

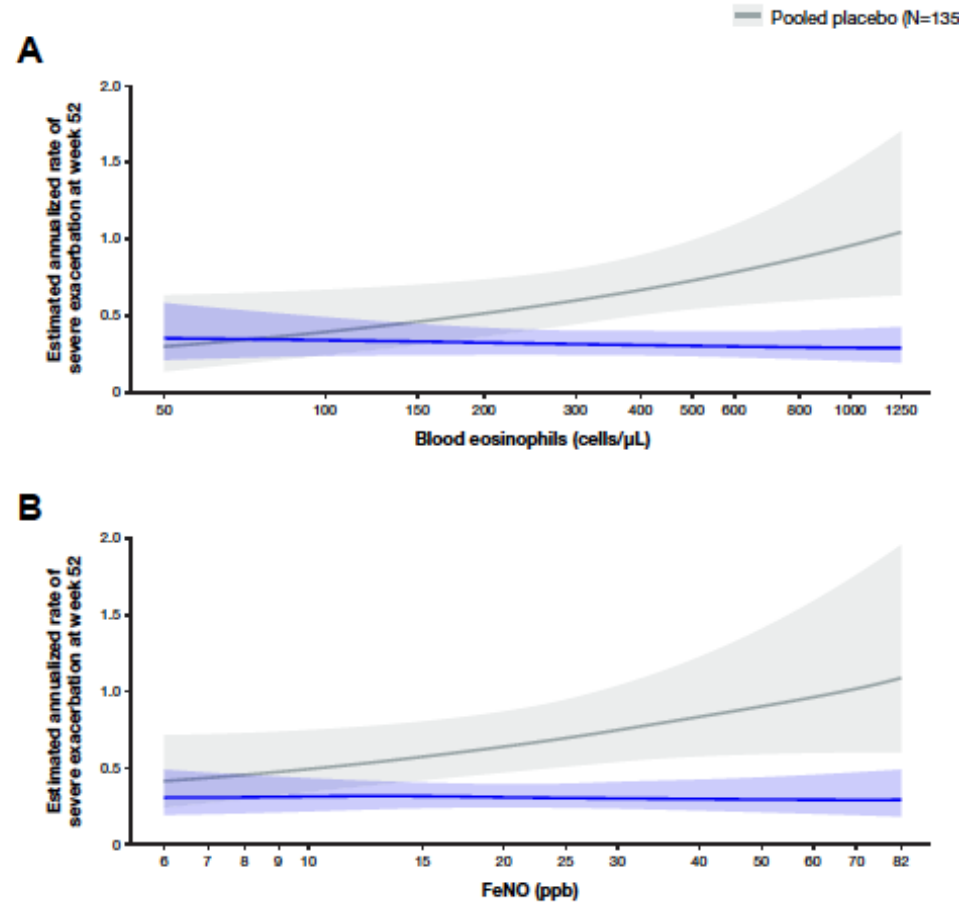
A Type 2 Inflammatory Phenotype



No. at Risk

Dupilumab	236	232	225	226	226	226	228	227	224	228	224	222	217	217	214	212	215
Placebo	114	108	109	112	112	112	111	110	112	113	112	110	111	107	107	109	106

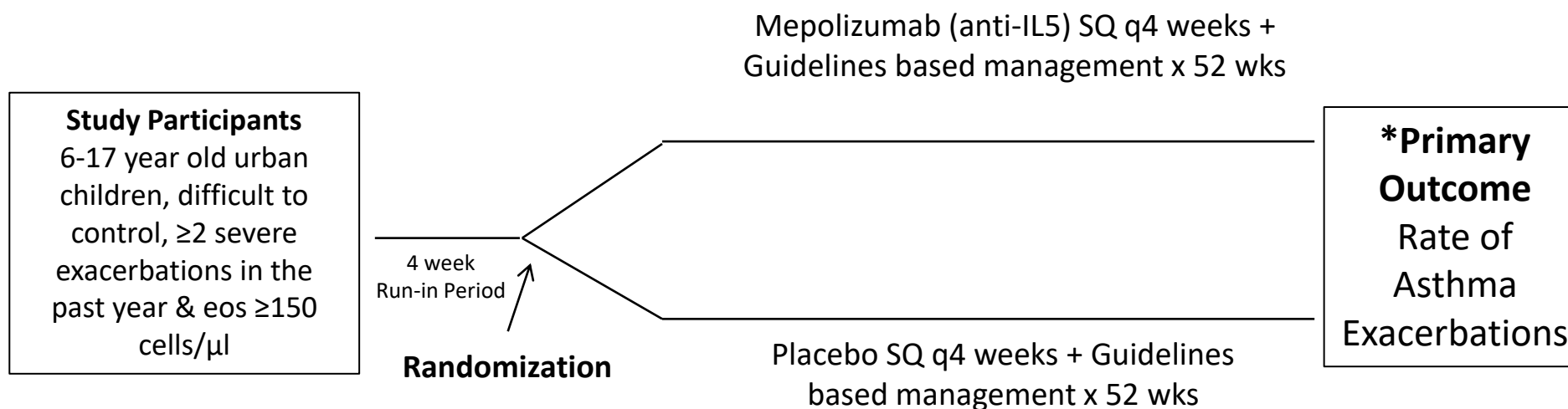
Blood Eosinophils & FeNO Predict Response to Dupilumab in Children



Targeting Eosinophils



MUPPITS-2: Mechanisms Underlying Asthma Exacerbations Prevented and Persistent with Immune-Based Therapy: A Systems Approach Phase 2

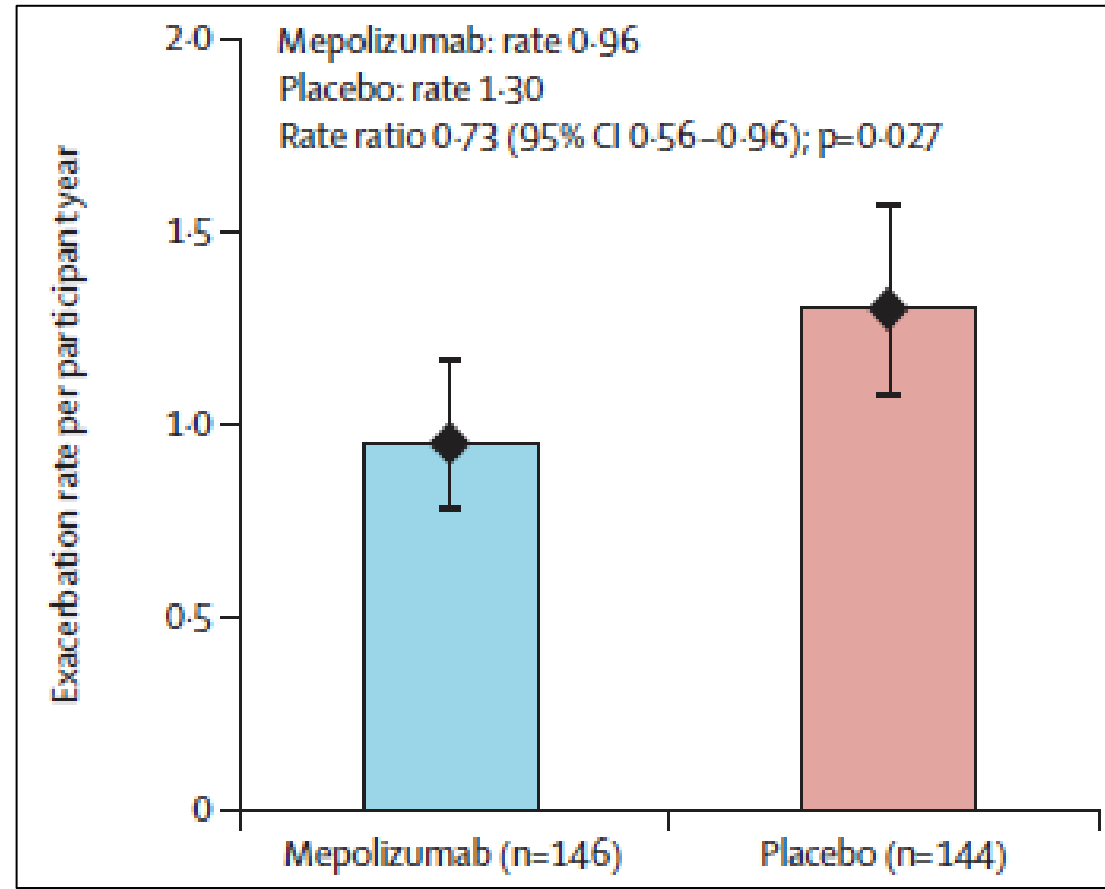


Integrated Ancillary/Mechanistic Studies

- 1) Airway & Blood Transcriptomics at baseline, 3 months & during colds/exacerbations (Matt Altman-Benaroya)
- 2) Baseline Eosinophil Characterization & Response to Therapy (Justin Schwartz/Patty Fulkerson)
- 3) Sputum Cytof (Geoff Chupp & Ruth Montgomery-Yale)



Primary Outcome: Rate of Asthma Exacerbations



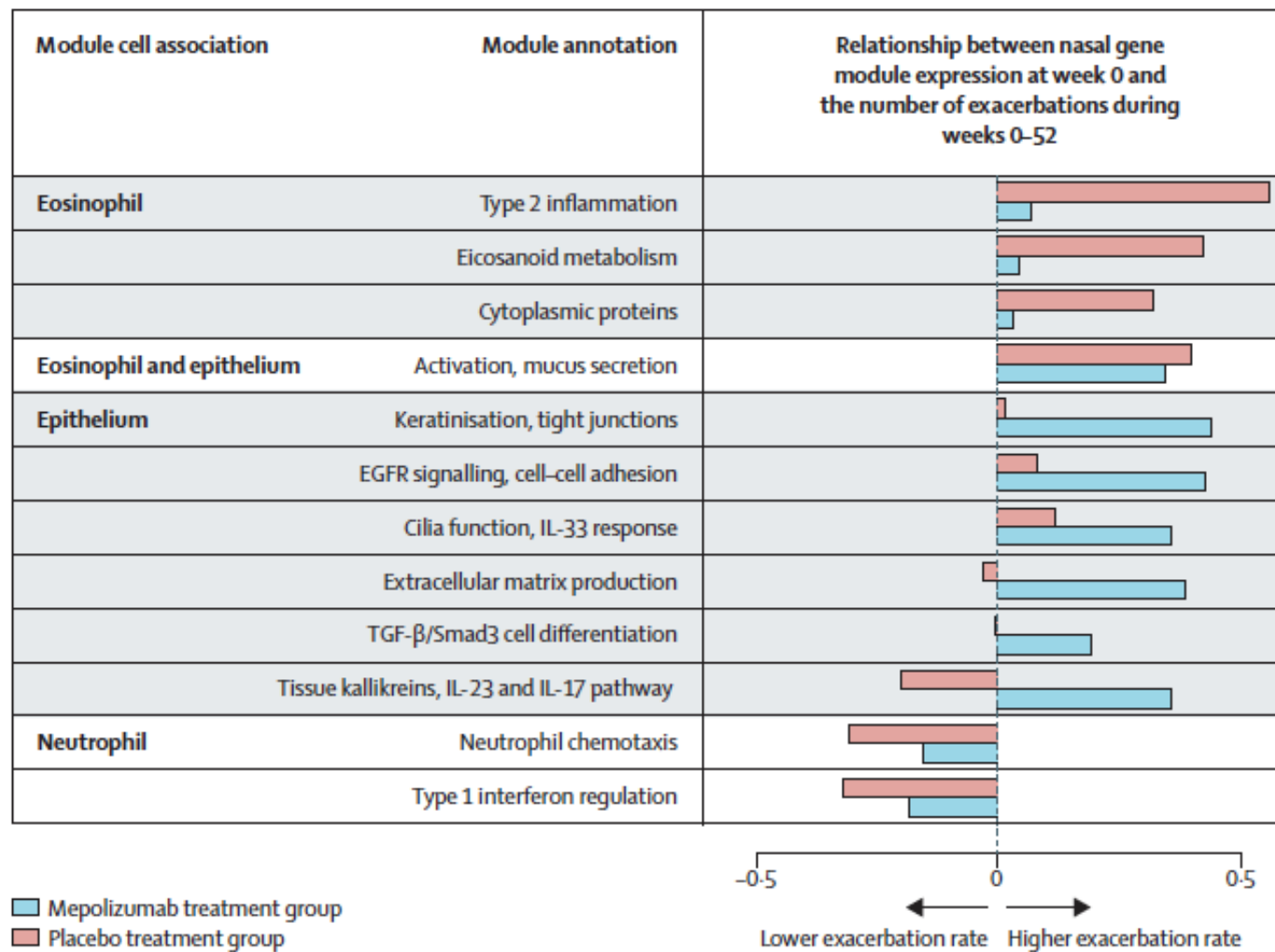


Mechanistic Research Question

What mechanisms underlie exacerbations
prevented with & persistent despite
mepolizumab?



Baseline Airway Gene Expression Differentially Associates with Exacerbation Risk



Jackson et al, *Lancet* 2022

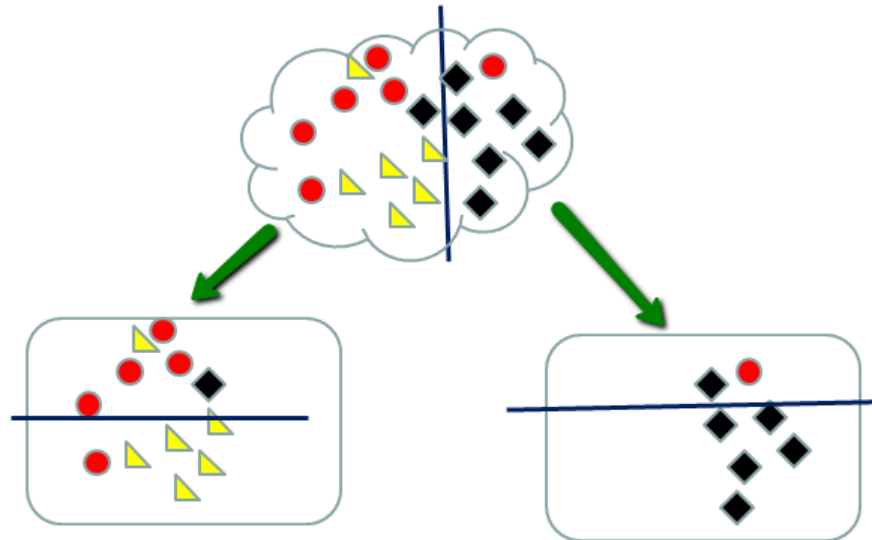


**Can a combination of modules
better predict response to
therapy?**



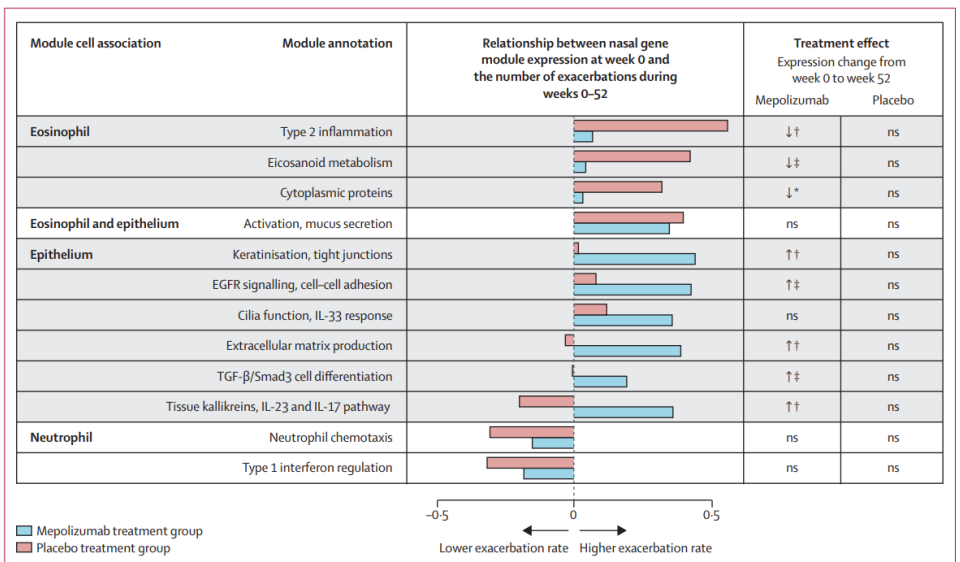
Model based recursive partitioning

- Flexible decision tree classifier / machine learning method
 - Allows for negative binomial distribution of Y variable (exacerbations)
 - Interaction of treatment and covariates

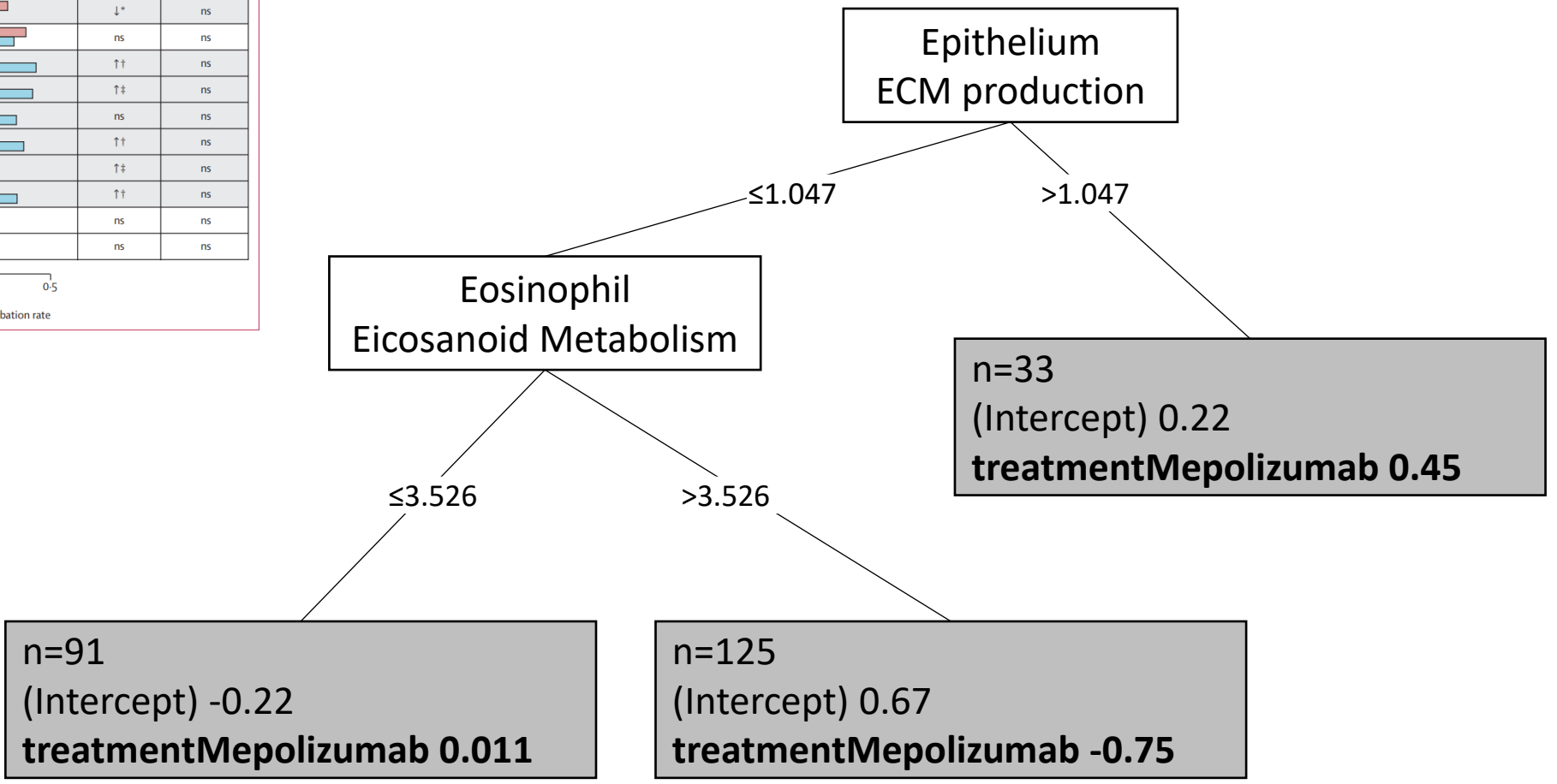




MBRP Selected an Eosinophil & Epithelial Module as Optimal Predictors of Response



→ MBRP testing: Exacerbation rate ~ treatment | module1...moduleN



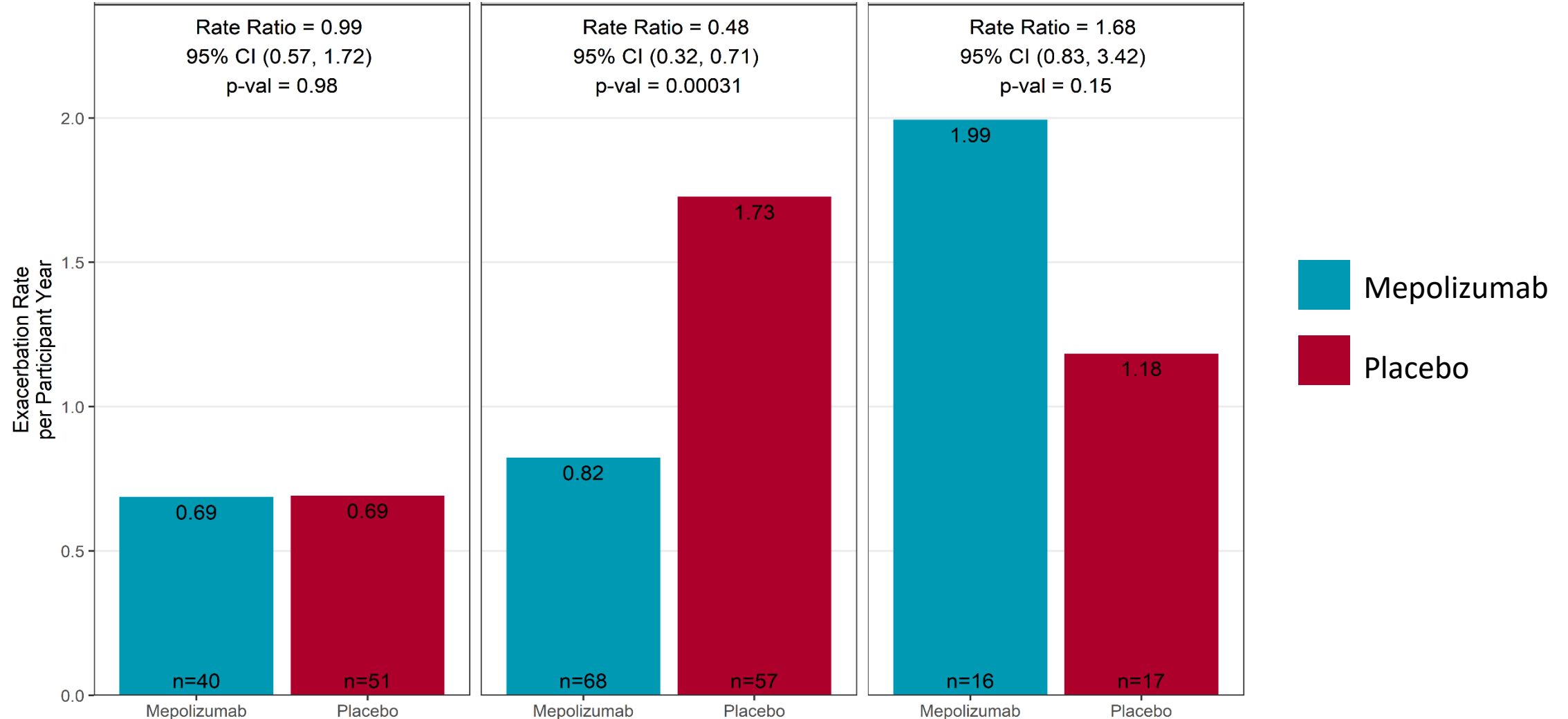


Prediction of Treatment Response

Low - Eosinophil eicosanoid metabolism
Low - Epithelial ECM production

High - Eosinophil eicosanoid metabolism
Low - Epithelial ECM production

High - Epithelial ECM production





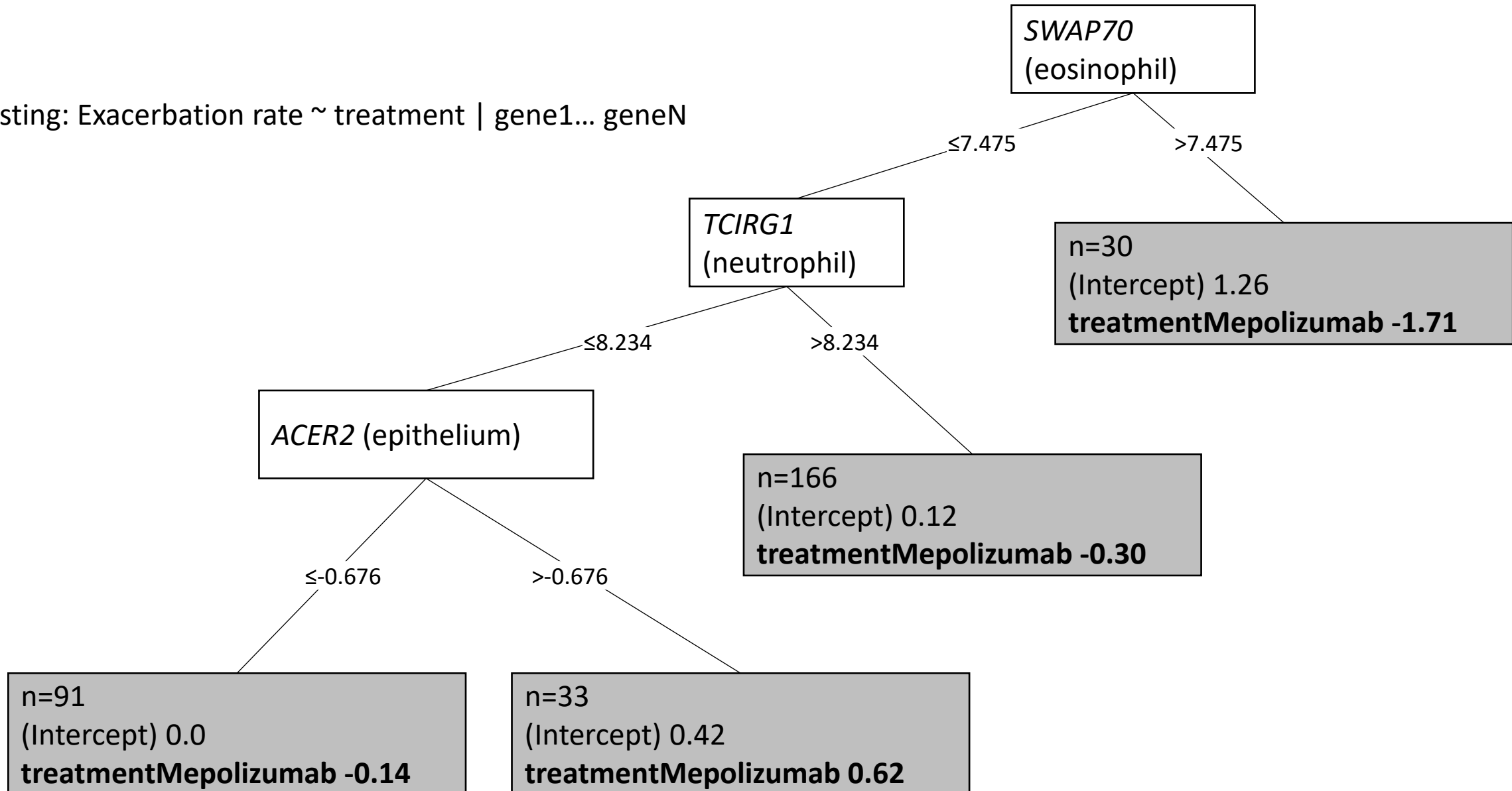
**Can a gene-based analysis better
predict response to therapy?**



Lasso selected genes

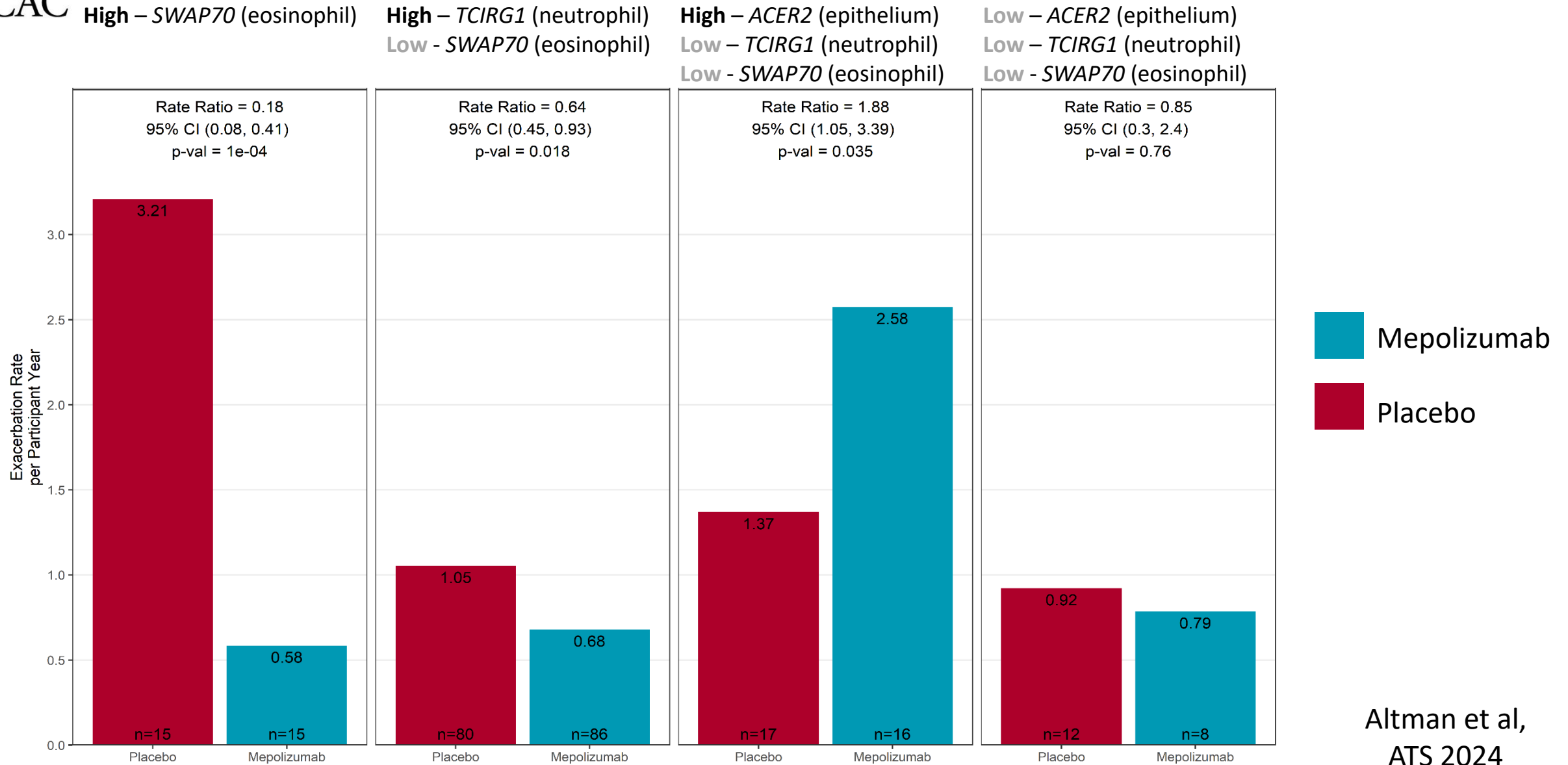
Lasso Selection of Genes Followed by MBRP

MBRP testing: Exacerbation rate \sim treatment | gene1... geneN





3-Gene Prediction of Treatment Response

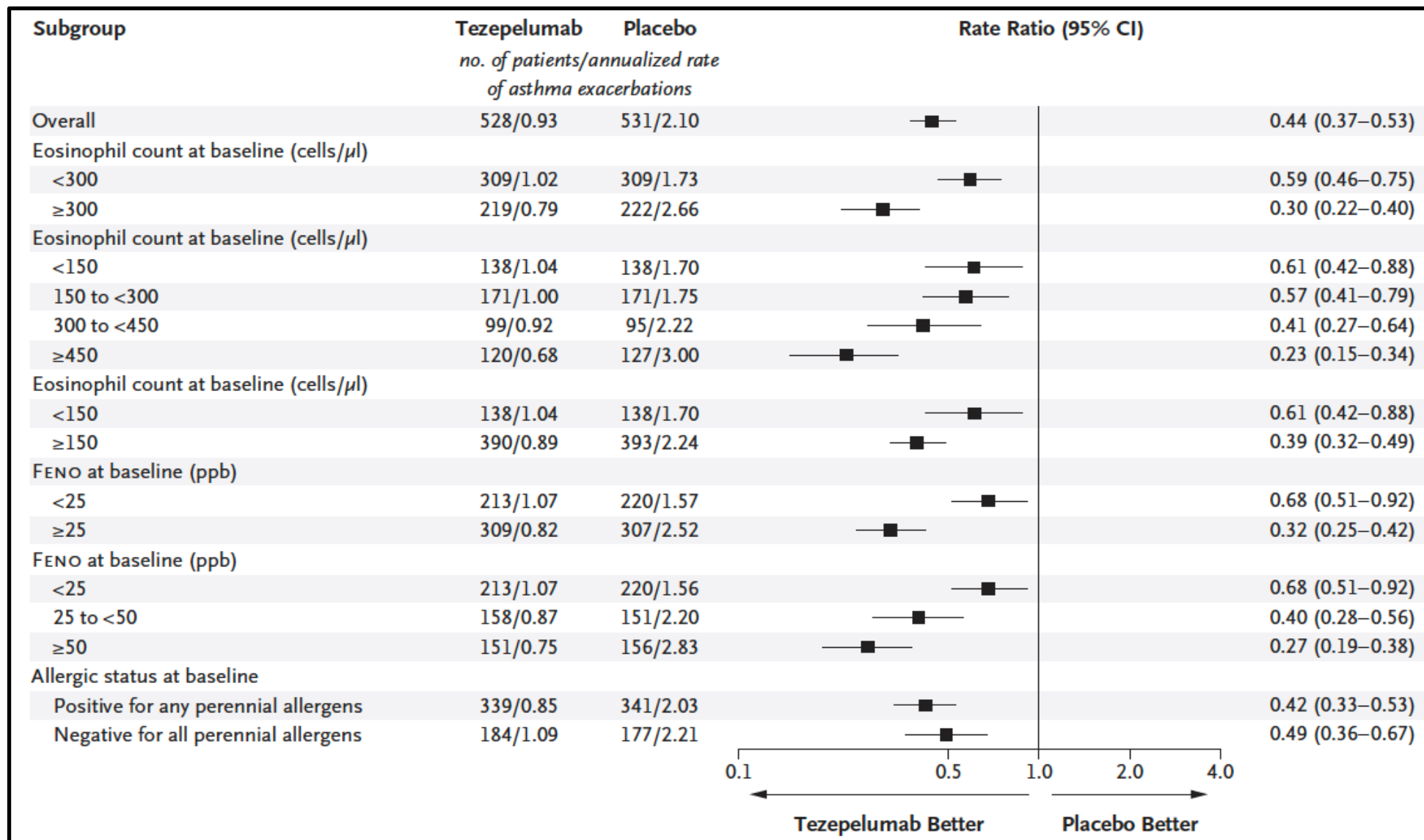


**Targeting TSLP
Beneficial in Both T2 High and
T2 Low Asthma?**

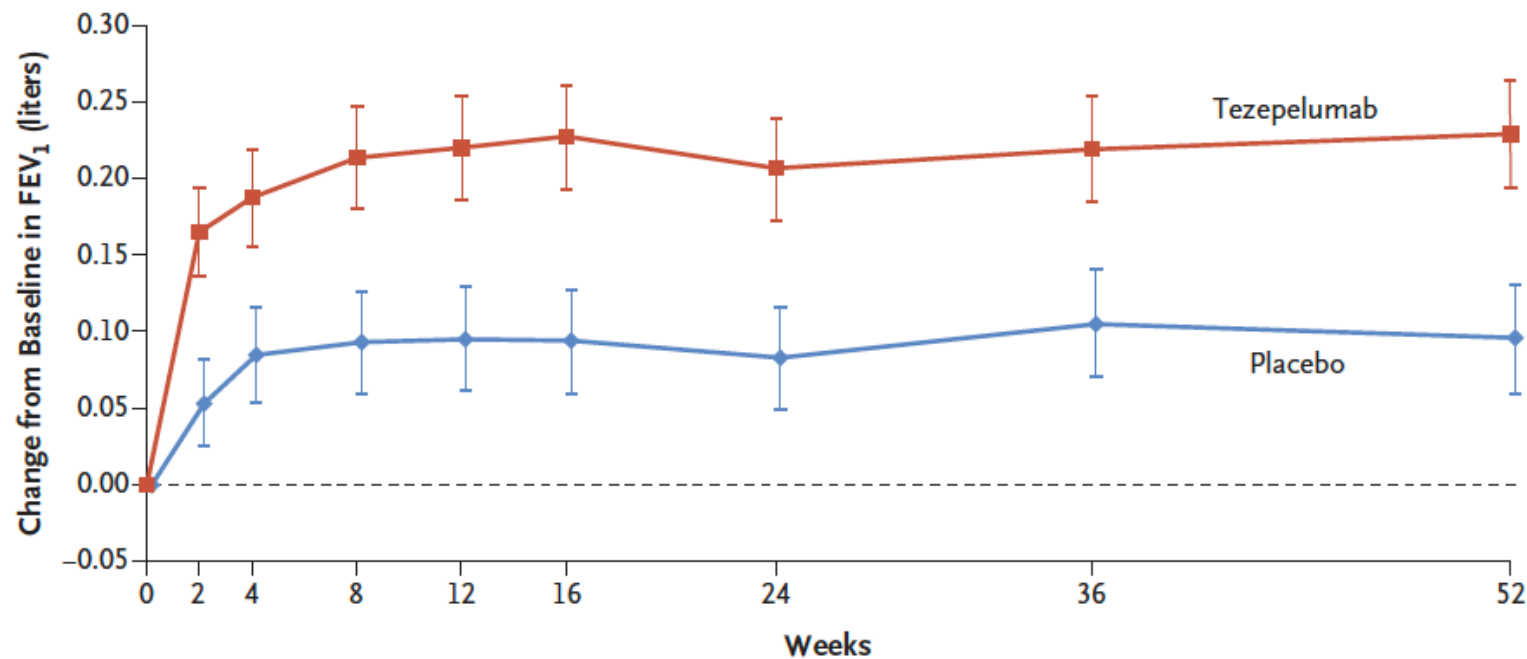
Tezepelumab in Adults & Adolescents with Severe, Uncontrolled Asthma

- 1061 participants 12+ y/o with severe asthma
 - Primary Outcome = rate of exacerbations
 - Secondary Outcomes – FEV1, ACQ-6, AQLQ, and ASD

Tezepelumab Reduced Exacerbations



Tezepelumab Improved all Secondary Outcomes



- Also significantly improved:
 - ACQ-6
 - AQLQ
 - ASD

Menzies-Gow et al. NEJM 2021

Conclusions

- Patient characteristics and biomarkers can identify those most likely to benefit from biologic therapy for severe asthma in children
 - Omalizumab, mepolizumab, and dupilumab have RCT data currently available in 6-11 y/o children
 - Comparative studies are not available
 - Opportunity for shared decision-making including dosing frequency, co-morbid conditions, location of injections, etc.
 - -Omic approaches hold tremendous promise to better select therapies for children with severe, exacerbation-prone asthma



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