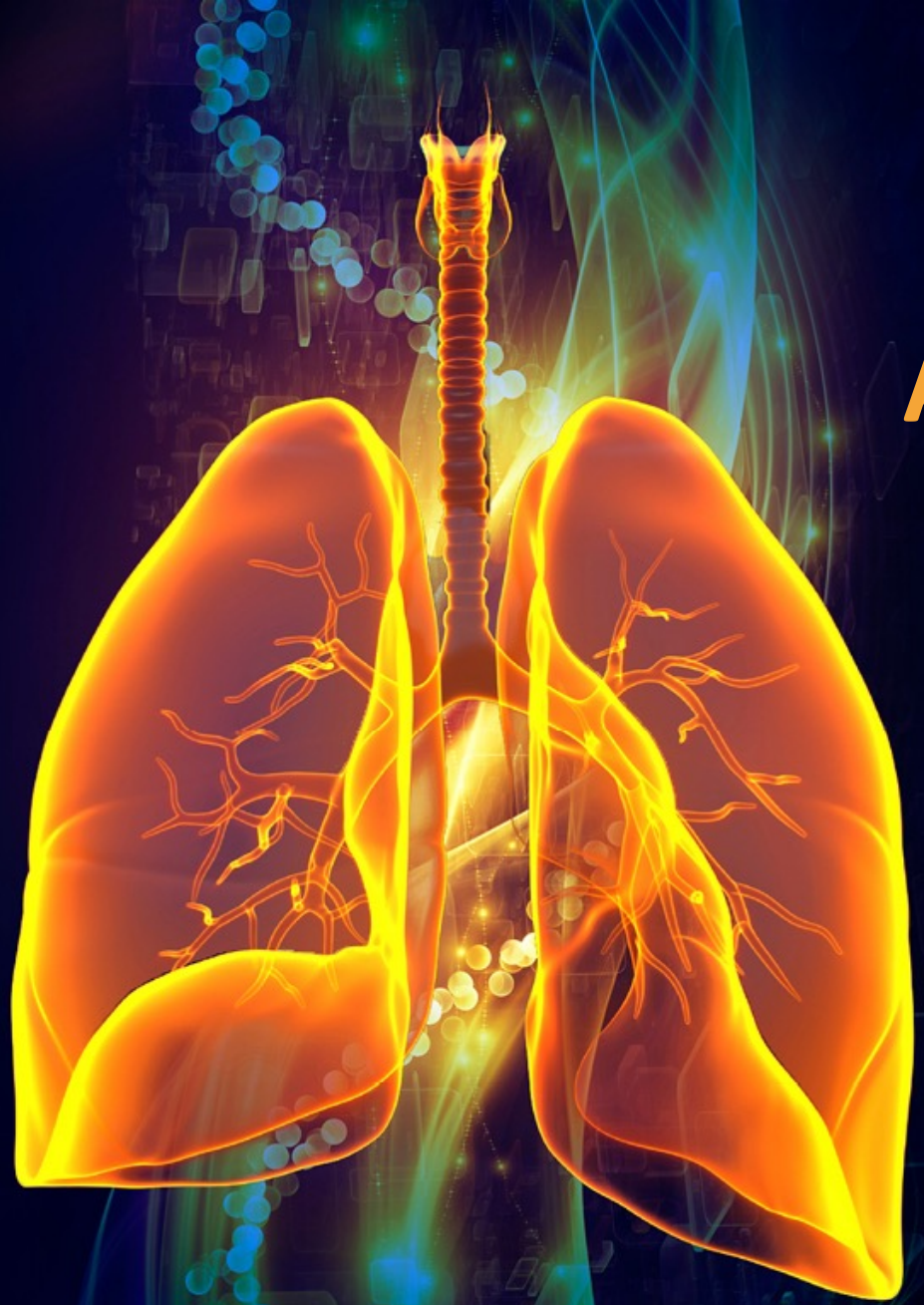

Asthma Biomarkers: What do They Really Tell Us?

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Breathing Science is Life.®

Disclosures

- Advisory & Speaking: AstraZeneca, Sanofi/Regeneron, Grifolis, Pharming
- Research: Amgen, GSK
- Professor of Medicine; National Jewish Health; University of Colorado, Denver
- Appeals Committee, Accreditation Council of Graduate Medical Education
- “Opinions and assertions herein are not representative of any of the named entities but are of my own opinion”

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Learning Objectives

1. Review the pathophysiology of asthma

2. Understand the predicative value and limitations of current biomarkers

3. Review the data for IgE, FeNO and eosinophil levels

4. Understand an evidenced based approach to choosing a biologic

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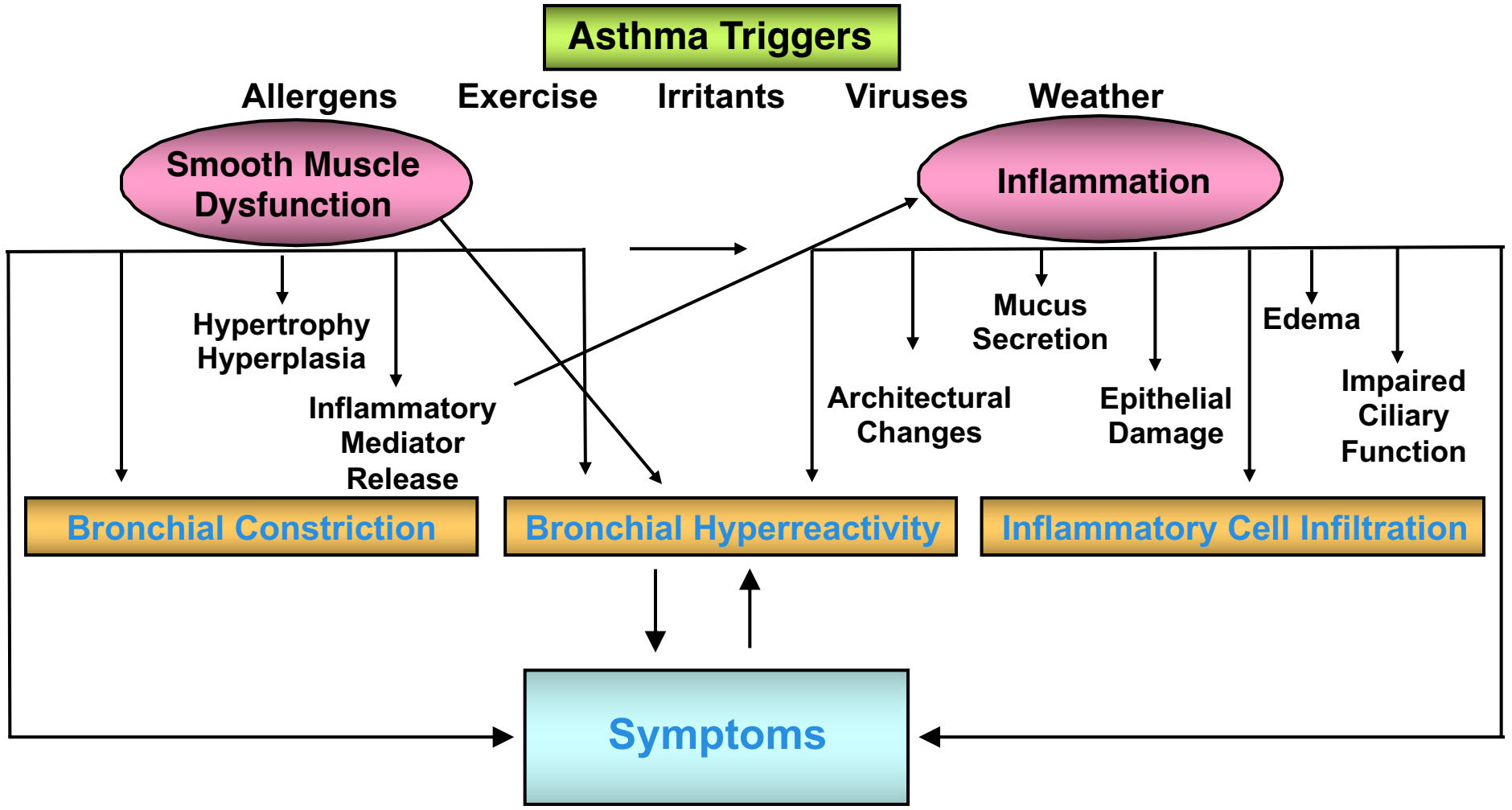
Mechanisms of Asthma Leading to Symptoms



Adapted from Creticos. *Adv Stud Med*. 2002;2:499-503.

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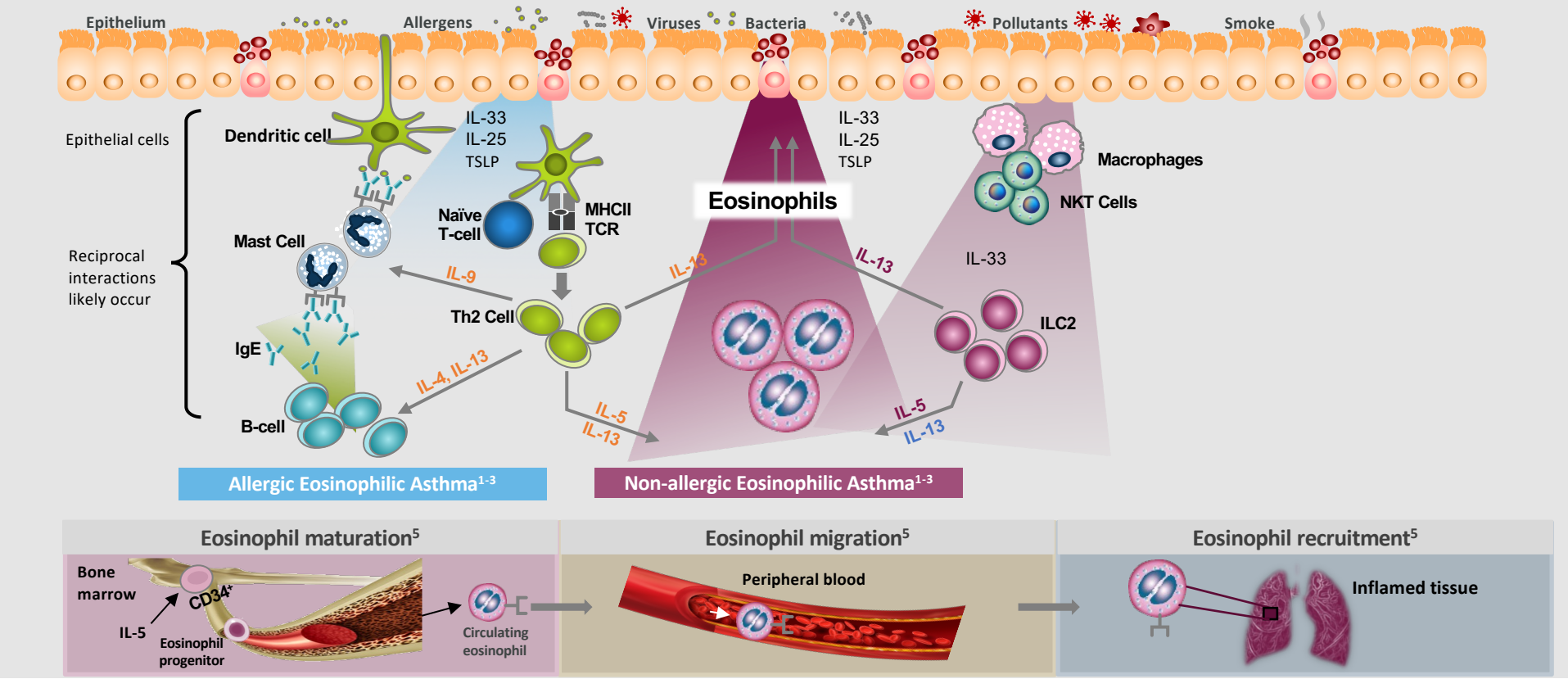
Systemic Inflammation



Jacobsen EA et al. *Annu. Rev. Immunol*. 2021. 39:719-757; 2. Brusselle GG et al. *Nat Med*. 2013;19:977-979; 3. Lambrecht BN et al. *Nat Immunol*. 2015;16:45-56; 4. Peters MC et al. *Lancet.* 2020;1;395:371-383; 5. Pelaia C et al. *Front. Physiol.* 2019.

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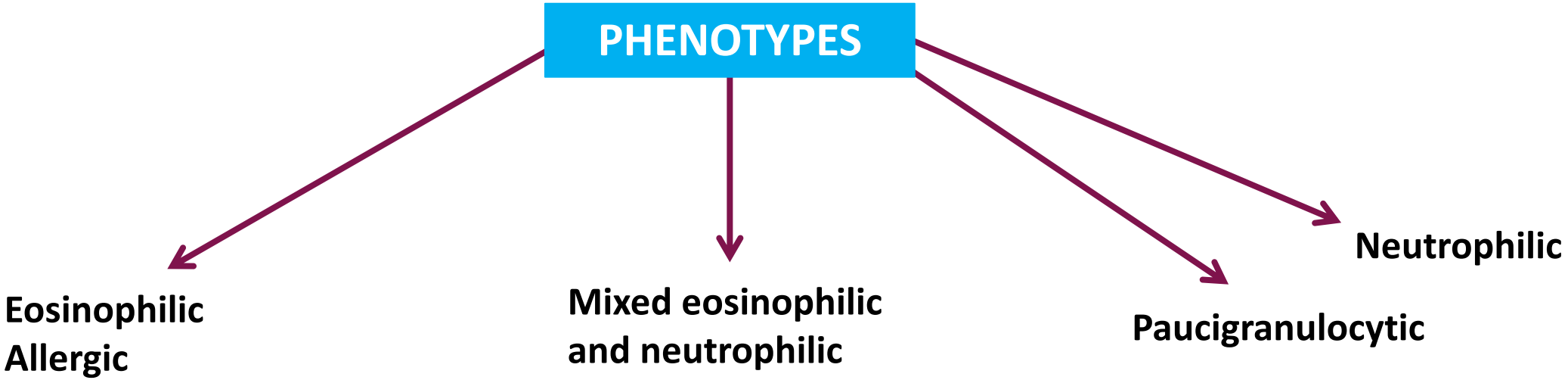
Inflammatory Subtypes of Asthma

Airway Inflammation

(Biomarkers: sputum, BAL, bronchial biopsies, FeNO, blood eosinophils, allergic sensitization)



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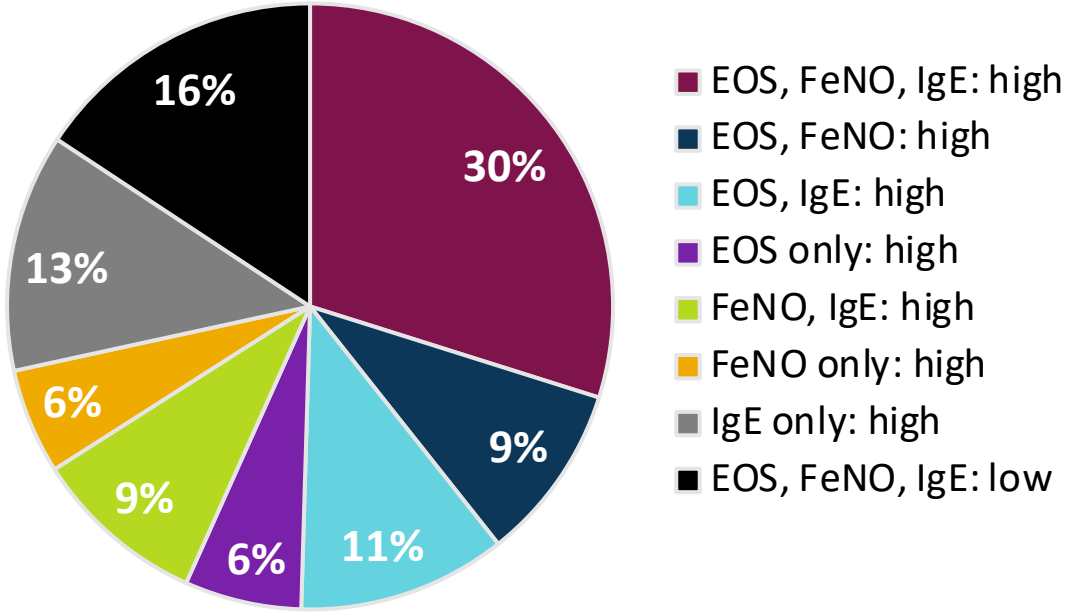
Biomarker	Treatment expected to produce a response	Associations	Comments (point of care, variability/fluctuation)
BLOOD			
Eosinophil	Anti-IL5 Anti -IgE Anti- IL-4/IL-13 Corticosteroids (CS) CRTH2 antagonists	Exacerbations LF decline Fixed airway obstruction	Easily available Significant fluctuation
Specific IgE	Anti-IgE AIT	Exacerbations AHR (AIT)	
Periostin Dipeptidyl peptidase-4 (DPP-4)	Anti-IL13	LF decline Exacerbations	Research type Assay dependent(ref)
INDUCED SPUTUM			
Eosinophils	Anti IL-5 ICS	Exacerbations	Research type Significant fluctuation(ref)
IL-13	Anti IL-13	?	Research type
EXHALED BREATH			
FeNO	Anti IL-5 Anti IgE Anti IL-13 ICS	Exacerbations, LF decline	Easily available Point of care Significant fluctuation(ref)
Metabolomics (VOC)	ICS	?	Research type

Most Patients with Severe Asthma Have Elevated T2 Biomarkers

Among 961 adults in the International Severe Asthma Registry:[1]

- **57%** had **EOS** ≥300 cells/µL
- **54%** had **FeNO** ≥25 ppb
- **63%** had **IgE** ≥75 kU/L
- **30%** were **EOS, FeNO, and IgE high**
- **29%** were **EOS and FeNO low**

Frequency of Each Biomarker Group (%)[1]



BRISAR = Biomarker Relatability in the International Severe Asthma Registry; EOS = eosinophils; FeNO = fractional exhaled nitric oxide; GINA = Global Initiative for Asthma; IgE = immunoglobulin E; ISAR = International Severe Asthma Registry; OCS = oral corticosteroid(s); T2 = Type 2.

1. Canonica GW. Presented at: WAC Congress; December 12–14, 2019; Lyon, France; 2. Busse WW. *Allergol Int*. 2019;68:158–166.

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Asthma Therapy – 1800s

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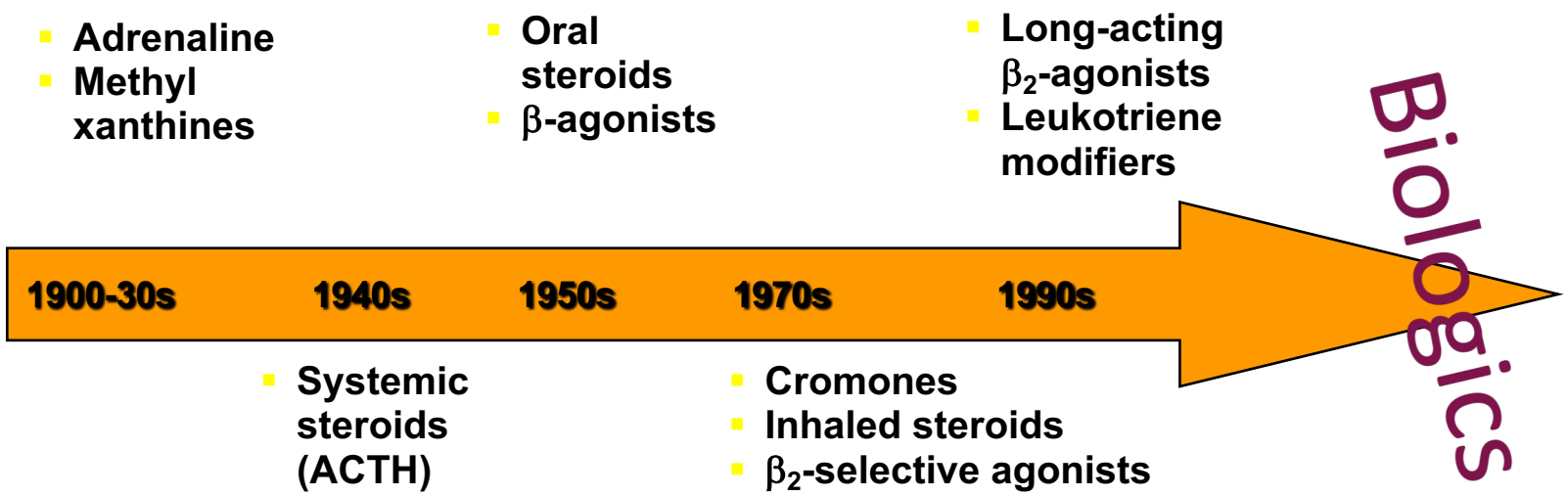
Asthma Therapy in the 1900s



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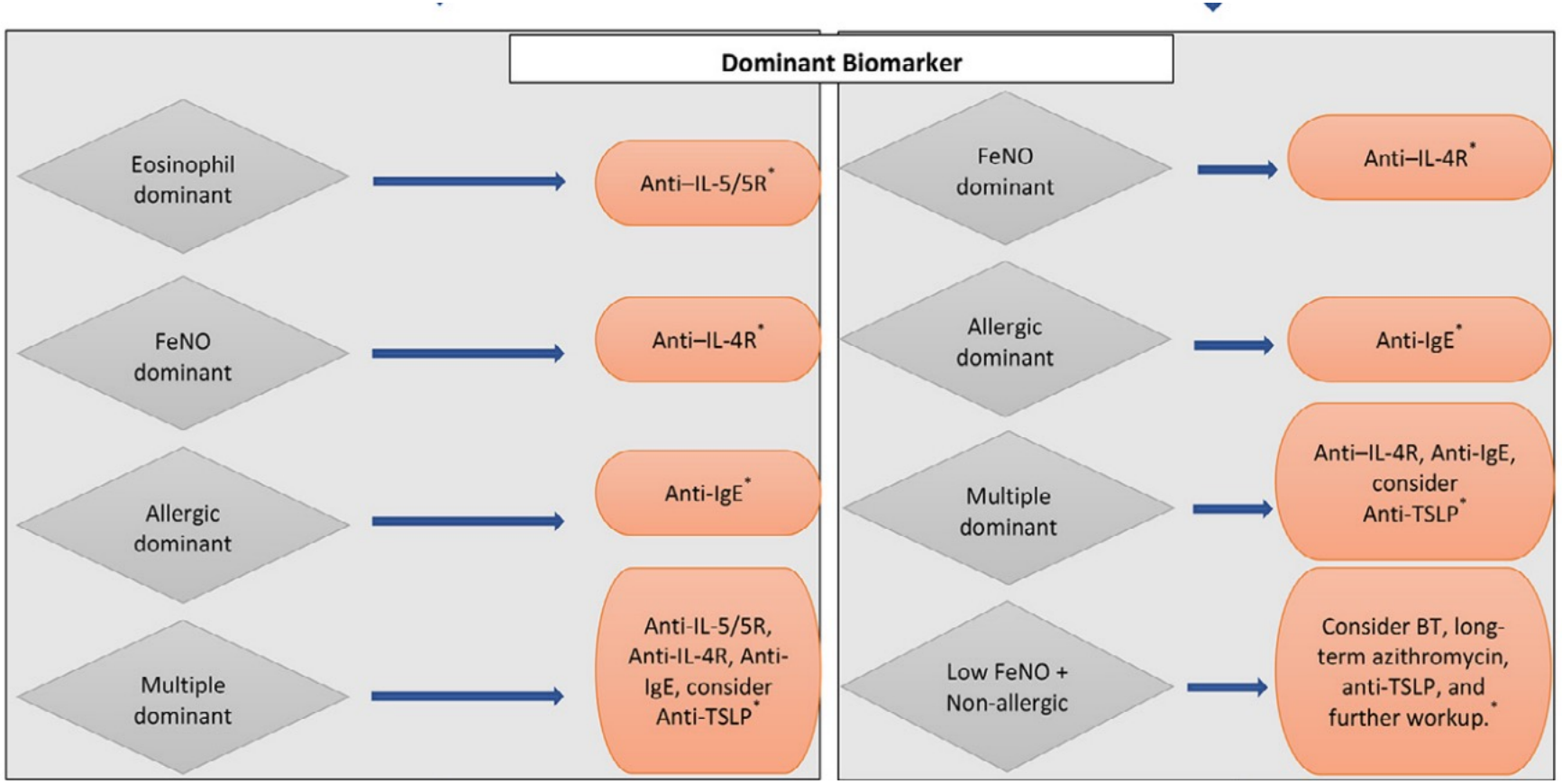
Biomarkers Determining Use of Biologic



Wang E, Weschler M, Ann Allergy, Asthma Immunol 2022: 128:379

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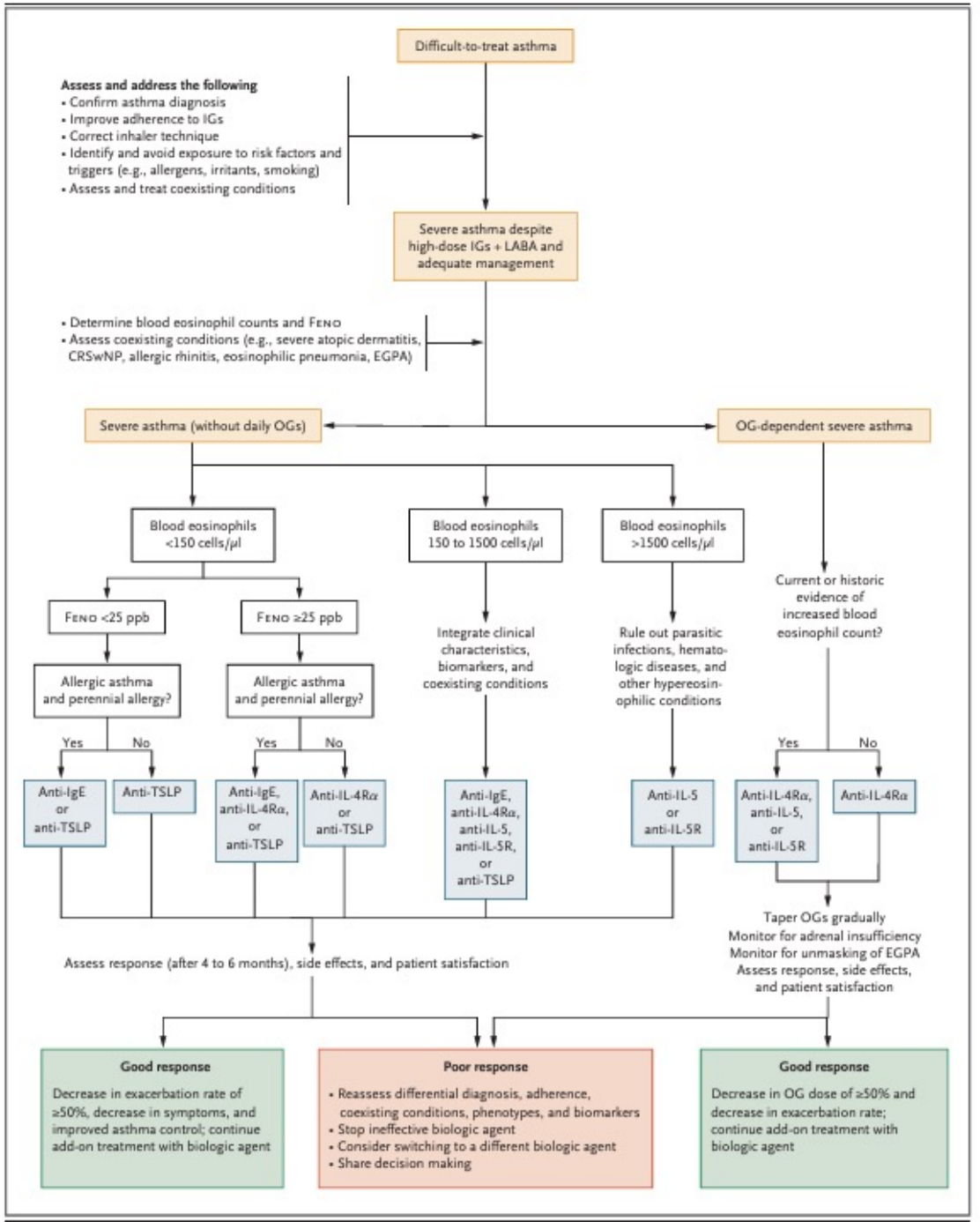
Biomarkers Determining Use of Biologics



Brusselle G, Koppelman. NEJM 2022; 386:157-71

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"If you don't reveal some insights soon, I'm going to be forced to slice, dice, and drill!"

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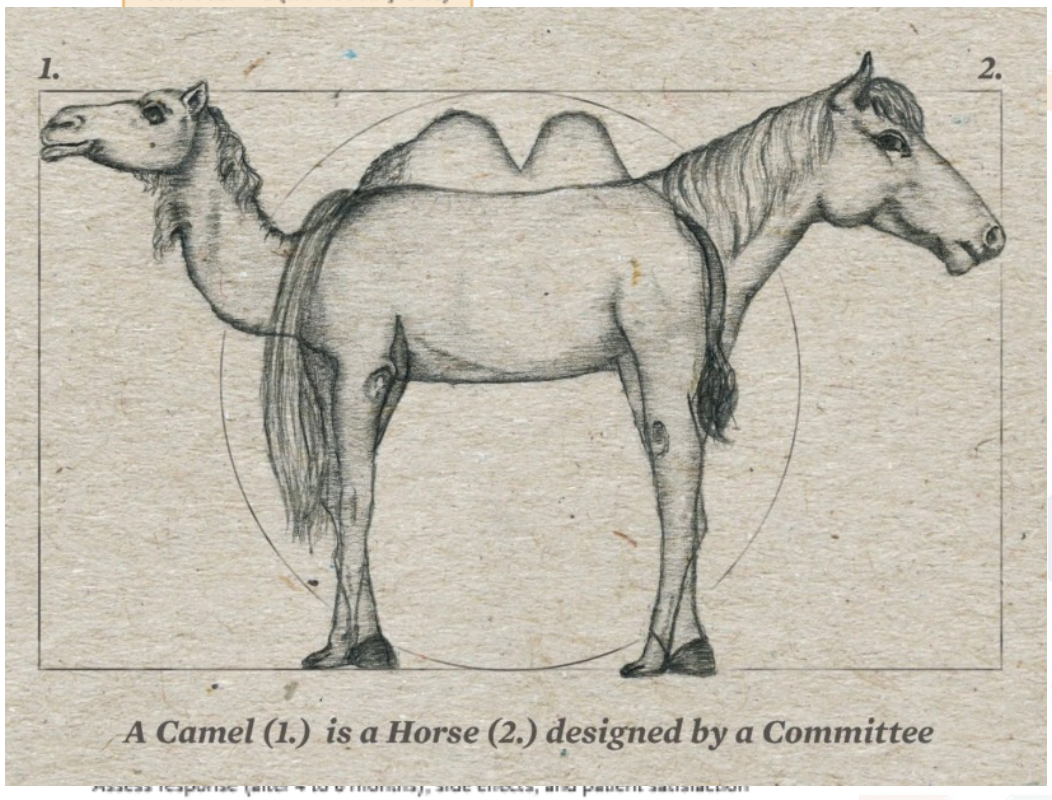
Biomarkers Determining Use of Biologics

Severe asthma (without daily OGs)



Brusselle G, Koppelman. NEJM 2022; 386:157-71

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Omalizumab Inclusion Criteria

Diagnosis of moderate to severe asthma

- Diagnosed ≥ 1 year; stable ≥ 1 month
- FEV_1 reversible ≥ 12% at screening
- Positive skin test to 1 or more perennial allergens

IgE levels

- 30 IU/mL to 700 IU/mL (body weight between 30 kg and 150 kg)

Level of disease control

- Residual symptoms (symptom score ≥ 3)
- FEV_1 ≥ 40% to ≤ 80% predicted

Nothing about FeNO or Eosinophils

Busse W, et al. *J Allergy Clin Immunol.* 2001;108:184-190; Soler M, et al. *Eur Respir J.* 2001;18:254-261.

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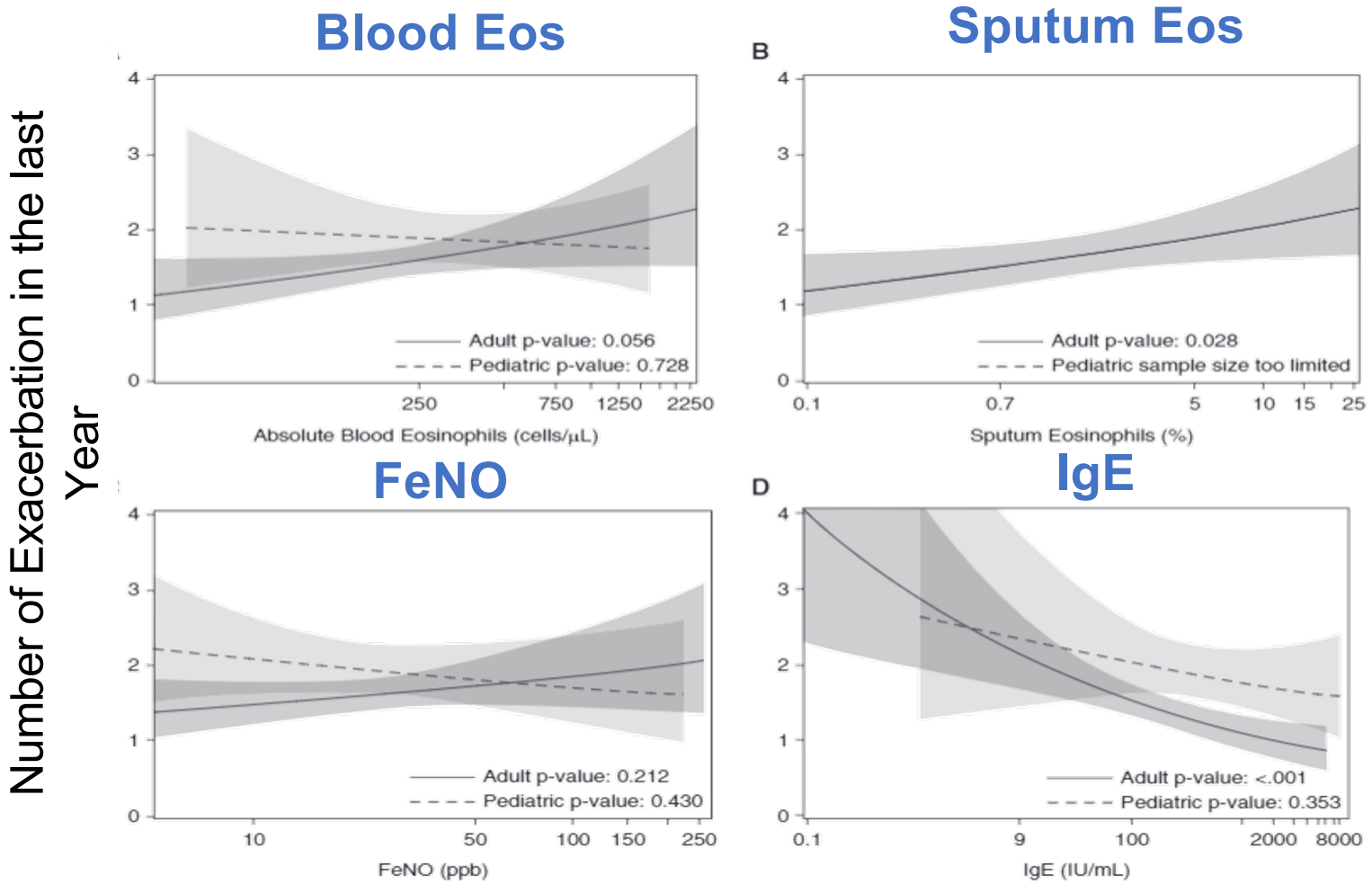
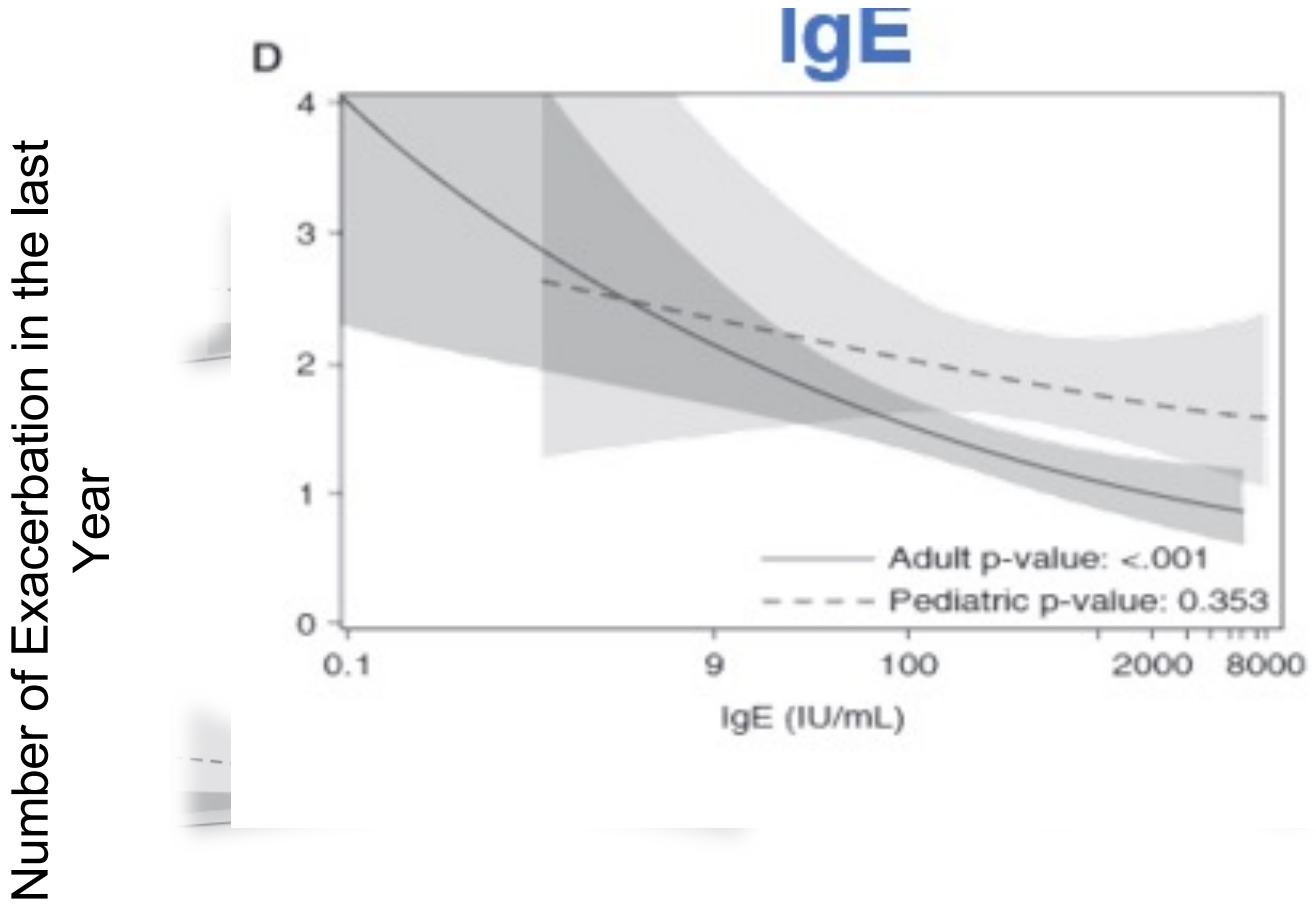
Baseline Eosinophil, Not IgE Predicts Exacerbation Risk



Note: Baseline data from the NHLBI Severe Asthma Research Program (SARP)-3.
FeNO: fraction of exhaled nitric oxide.

Denlinger LC et al. AJRCCM. 2017 Feb 1;195(3):302-313

Baseline Eosinophil, Not IgE Predicts Exacerbation Risk

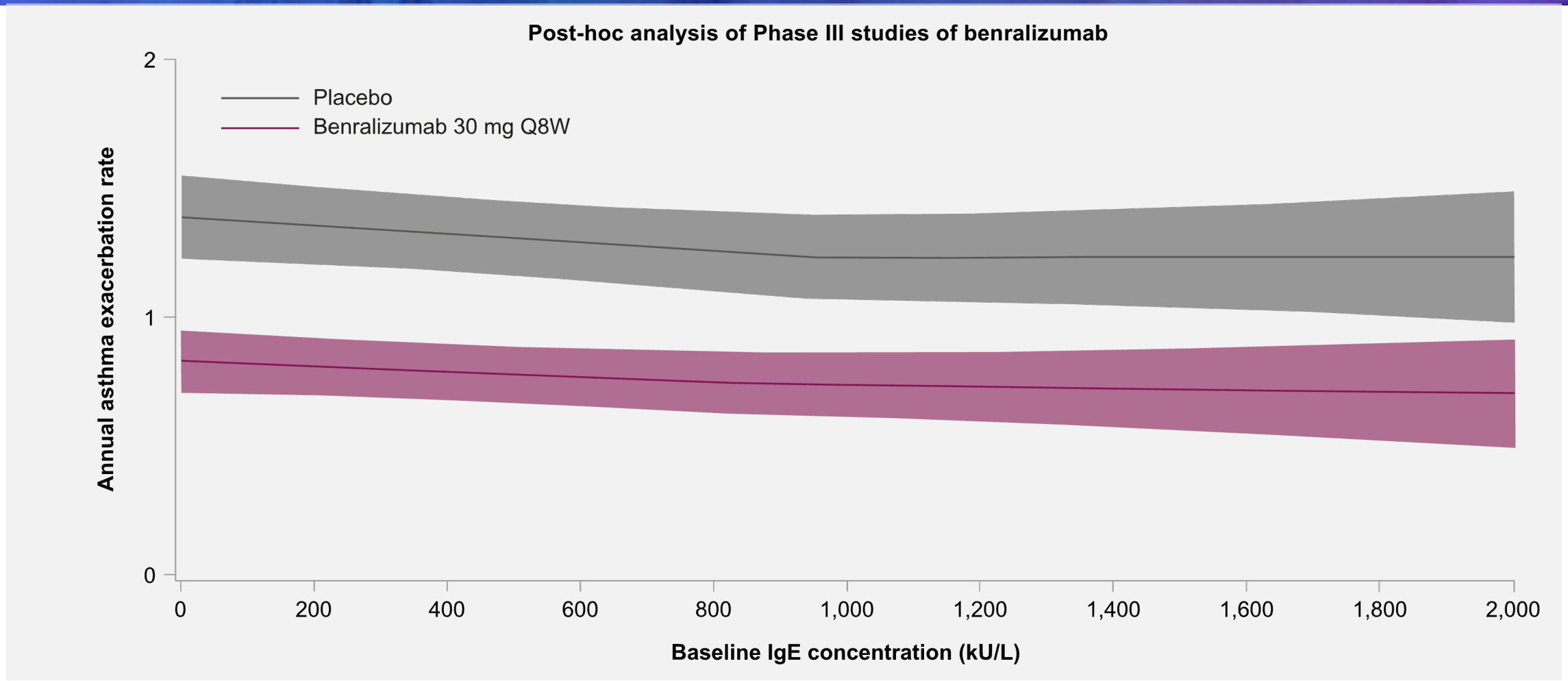


- "Exacerbation prone phenotype is not driven by allergic sensitization" nor by IgE

Note: Baseline data from the NHLBI Severe Asthma Research Program (SARP)-3.
FeNO: fraction of exhaled nitric oxide.

Denlinger LC et al. AJRCCM. 2017 Feb 1;195(3):302-313

Baseline IgE level does not relate to exacerbation rate or benralizumab efficacy in severe asthma[1]



IgE: immunoglobulin; Q8W: every eight weeks

1. Jackson DJ *et al*. Ability of serum IgE concentration to predict exacerbation risk and benralizumab efficacy for patients with severe eosinophilic asthma. *Advances in Therapy*. 2020; **37:** 718–29.

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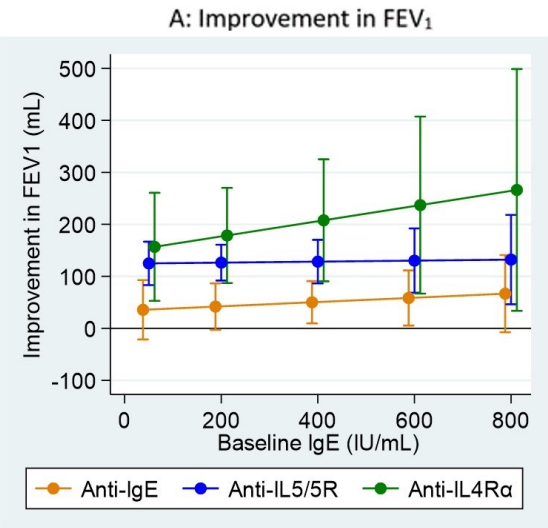
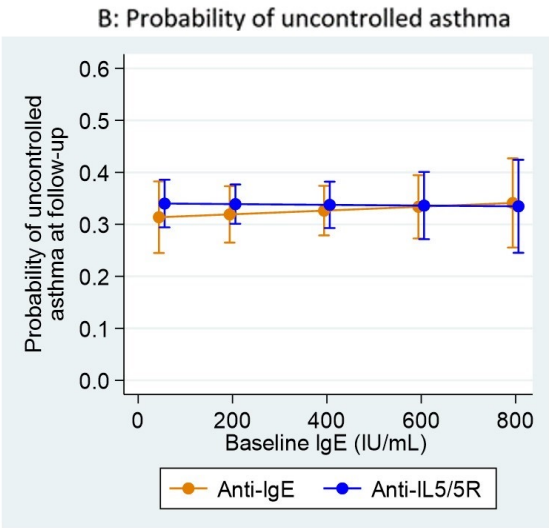
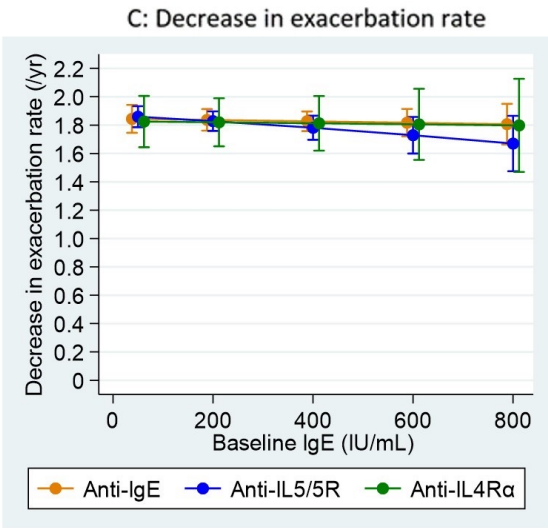
ISAR: IGNITE







Anti-IgE	Coeff (95% CI) = 41 (-97 - 179) N = 494 p = 0.557	
Anti-IL5/5R	Coeff (95% CI) = 10 (-127 - 147) N = 668 p = 0.890	
Anti-IL4Rα	Coeff (95% CI) = 146 (-205 - 497) N = 94 p = 0.415	
Interactions		
Anti-IgE vs anti-IL5/5R	p = 0.749	
Anti-IgE vs anti-IL4Rα	p = 0.587	
Anti-IL5/5R vs anti-IL4Rα	p = 0.479	

Anti-IgE	OR (95% CI) = 1.189 (0.553 - 2.557) N = 358 p = 0.658	
Anti-IL5/5R	OR (95% CI) = 0.967 (0.485 - 1.927) N = 573 p = 0.923	
Interaction		
Anti-IgE vs anti-IL5/5R	p = 0.694	

Anti-IgE	IRR (95% CI) = 1.143 (0.569 - 2.296) N = 389 p = 0.708	
Anti-IL5/5R	IRR (95% CI) = 1.803 (1.008 - 3.224) N = 654 p = 0.047	
Anti-IL4Rα	IRR (95% CI) = 1.098 (0.344 - 3.507) N = 126 p = 0.875	
Interactions		
Anti-IgE vs anti-IL5/5R	p = 0.326	
Anti-IgE vs anti-IL4Rα	p = 0.954	
Anti-IL5/5R vs anti-IL4Rα	p = 0.454	

Porsbjerg C, et al. Front. Immunol., Volume 15 - 2024 | https://doi.org/10.3389/fimmu.2024.1361891

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Total IgE as a Biomarker of Response

Allergen-specific IgE				
Omalizumab	Univariate analysis of INNOVATE[114]	Allergic[a]	Number of (severe) exacerbations[b]; responder analysis	Not predictive
Total IgE				
Omalizumab	Univariate analysis of 7 trials[115]	Allergic[c]	Number and rate of (severe) exacerbations[b]; AQLQ score; physician's overall assessment, FEV_1	Not predictive
Omalizumab	STELLAIR[50]	Severe allergic[c]	Physician's overall assessment; exacerbation[b] rate	≥75 IU/mL total IgE not predictive
Mepolizumab	Post hoc meta-analysis of MENSA and MUSCA[24]	Eosinophilic[d]	Exacerbation[e] rate; FEV_1; SGRQ; ACQ-5	Total IgE quartiles (≤ 30, >30-170, >170-450 and >450 UI/mL) not predictive
Benralizumab	Pooled data from SIROCCO and CALIMA[44]	Severe uncontrolled[f]	Exacerbation[e] rate	Total IgE quartiles (<62.0, ≥62.0-<176.2, ≥176.2-<453.4, ≥453.4 kU/L) not predictive
Dupilumab	Post hoc analysis of QUEST[15]	Severe uncontrolled[g]; allergic asthma[h] subgroup analysis	Exacerbation[d] rate; FEV_1; ACQ-5 score	Ø 700 IU/mL total IgE not predictive

J. Oppenheimer et al. / Ann Allergy Asthma Immunol 129 (2022) 169–180

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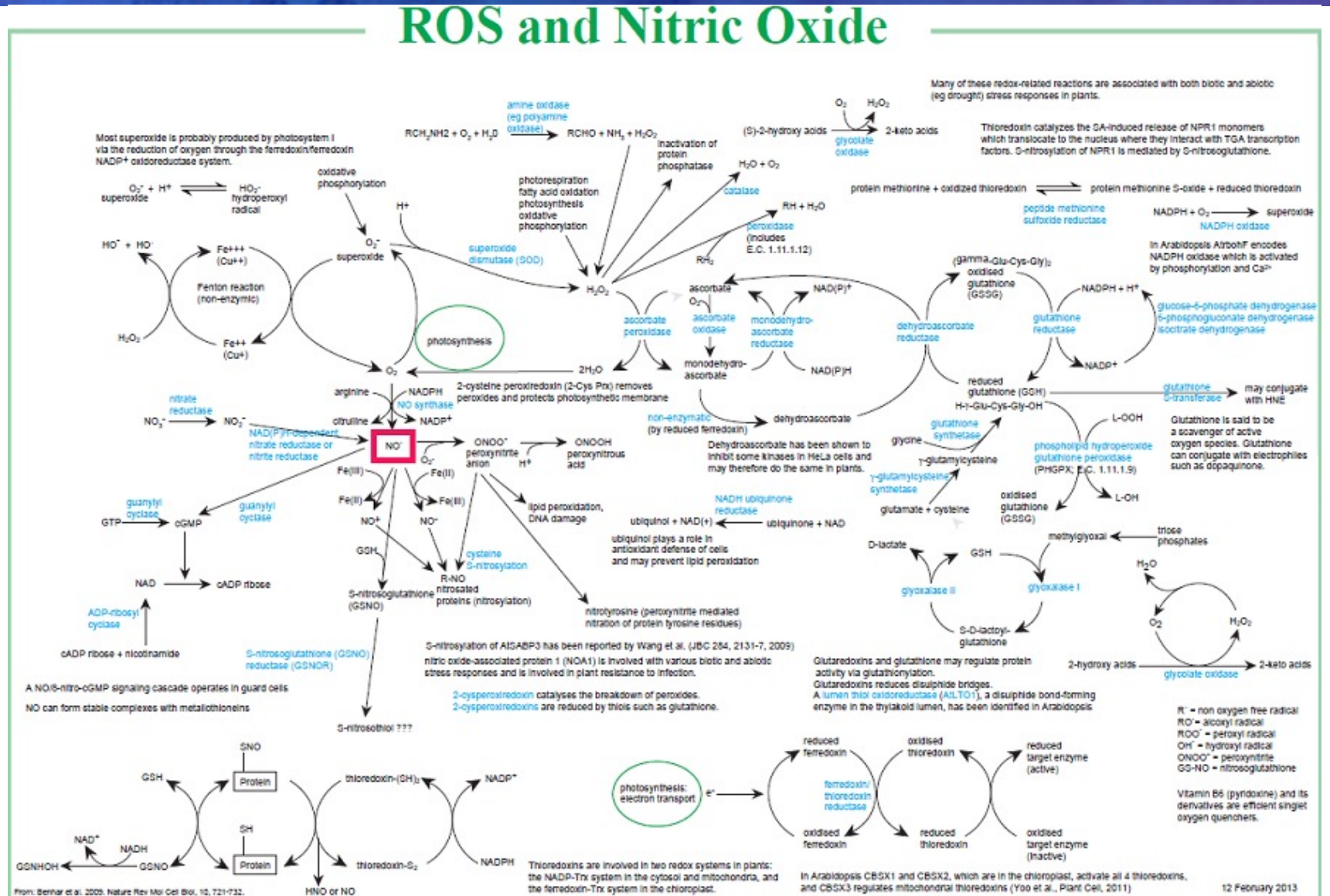
Biology NO



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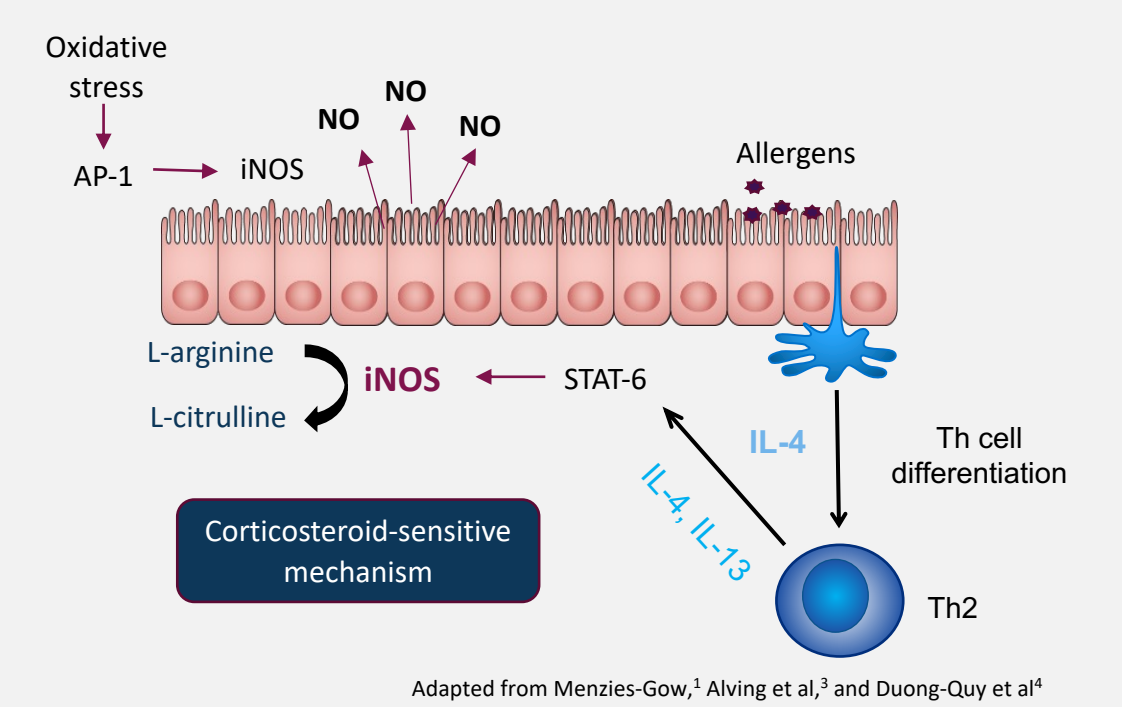
Nitric Oxide Production Regulated By NOS Enzymes, IL-4 & IL-13

- Derived endogenously from L-arginine[1]
- Synthesis catalyzed by 3 forms of the NO synthetase (NOS) enzyme: 2 constitutive forms and 1 inducible form[1]
- In asthma, iNOS expression is upregulated by IL-4 and IL-13, leading to increased levels of FeNO[1,2]
  - NO production by iNOS is corticosteroid sensitive[2]

NOS forms[1]	Expresed in:	Role
Constitutive NOS (eNOS, cNOS)	Platelets, neuronal, epithelial and endotelial cells	Physiological regulation of airway function
Inducible NOS (iNOS)	Macrophages, neutrophils, hepatocytes, epithelial, mesangial, endothelial and vascular smooth muscle cells	Produced in response to airway inflammation and in host defense against infection



Adapted from Menzies-Gow,[1] Alving et al,[3] and Duong-Quy et al[4]

NO=nitic oxide; AP=activator protein; IL-interleukin; STAT=signal transducer and activator of transcription; Th2= T-helper cell type 2

1. Menzies-Gow A et al. *Eur Respir J*. 2020; doi.org/10.1183/13993003.01633-2019. 2 Hoyte et al. *Immunol Allergy Clin N Am.* 2018; 38:573–585.
3. Alving K, Malinosvchi A. *Eur Respir Mon*. 2010;49: 1–31. 4. . Duong-Quy C. *J Asthma Allergy*. 2019:12 331–341.

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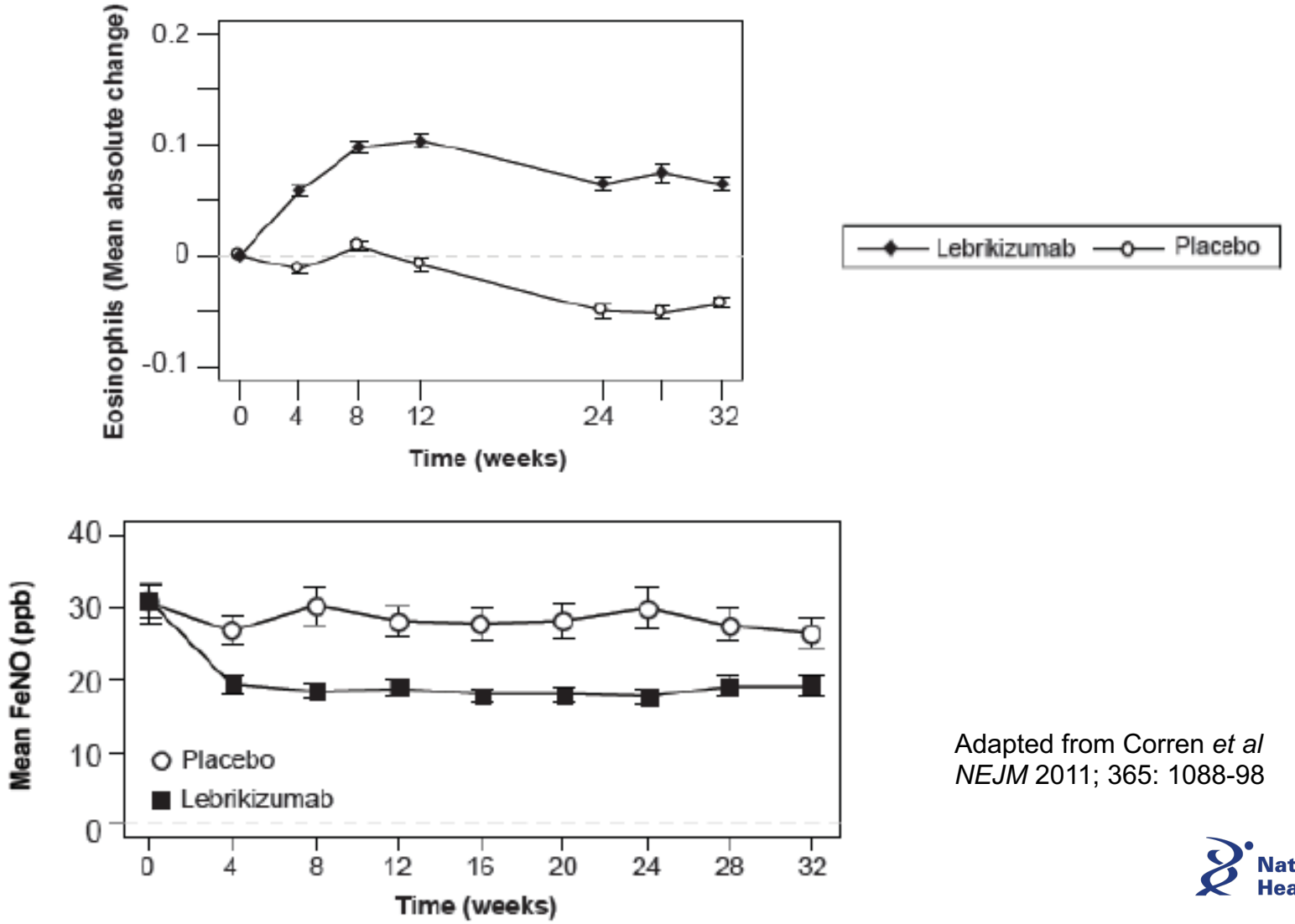
FeNO and Eosinophils After Anti-IL-13 Treatment



Adapted from Corren *et al* *NEJM* 2011; 365: 1088-98

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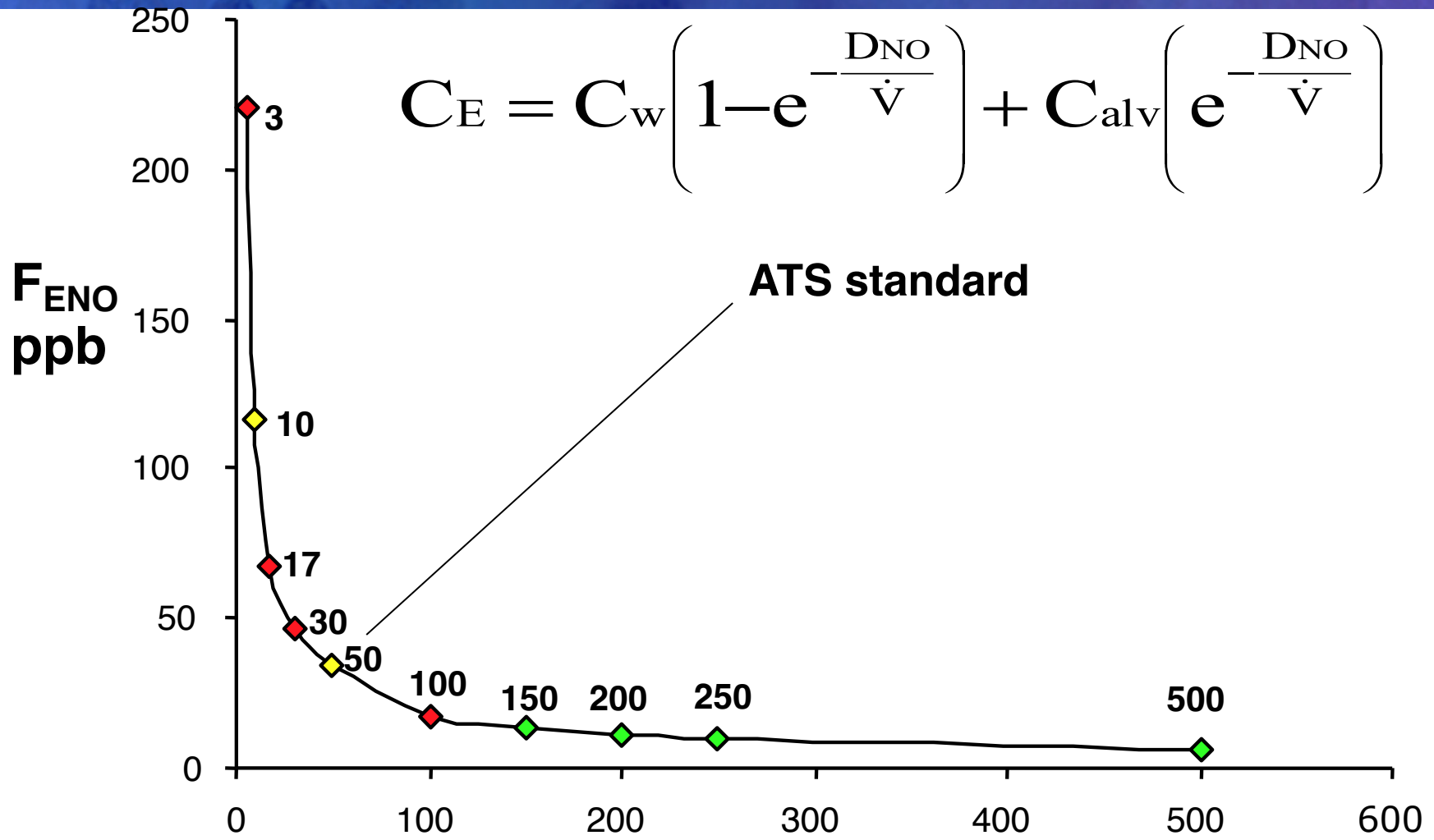
Multiple Flows

$$C_E = C_w\left(1 - e^{-\frac{D_{NO}}{\dot{V}}}\right) + C_{alv}\left(e^{-\frac{D_{NO}}{\dot{V}}}\right)$$



Silkoff, P. E., Pietrapaoli, P., & Tsoulias, G. (1997). Flow dependence of nitric oxide in the airway. *American Journal of Respiratory and Critical Care Medicine*, 156(3), 867–872.

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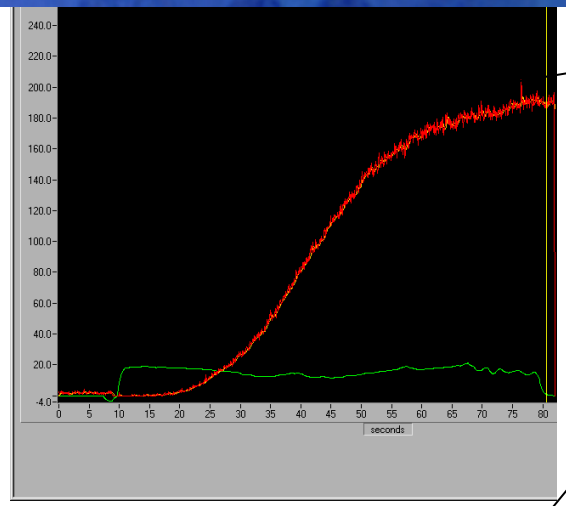
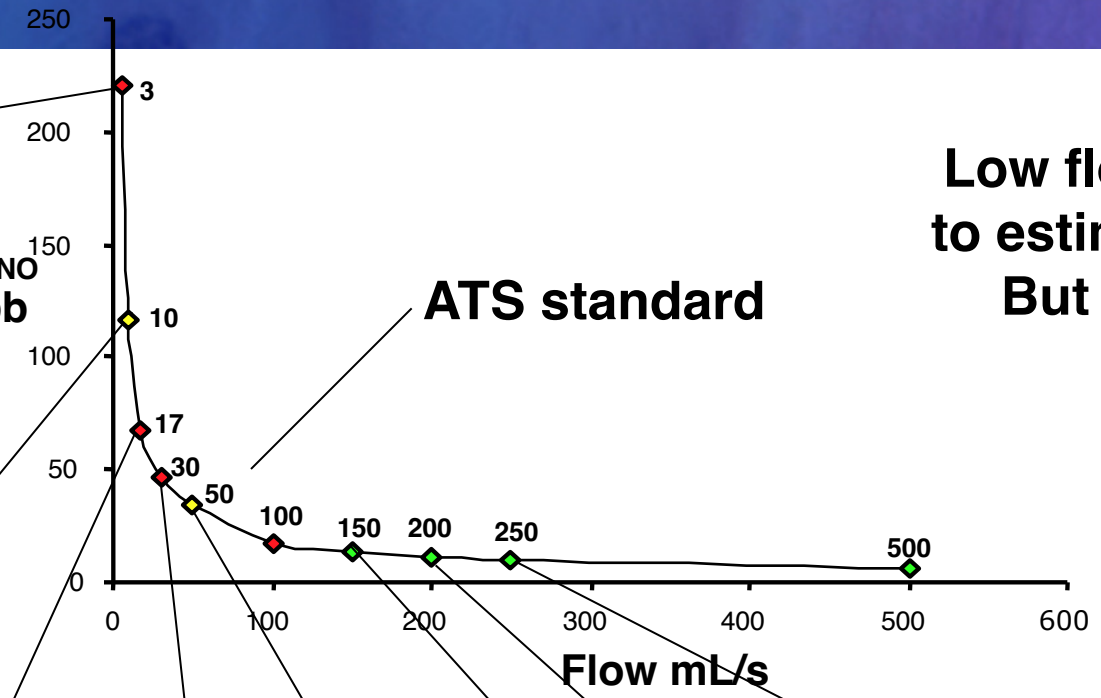
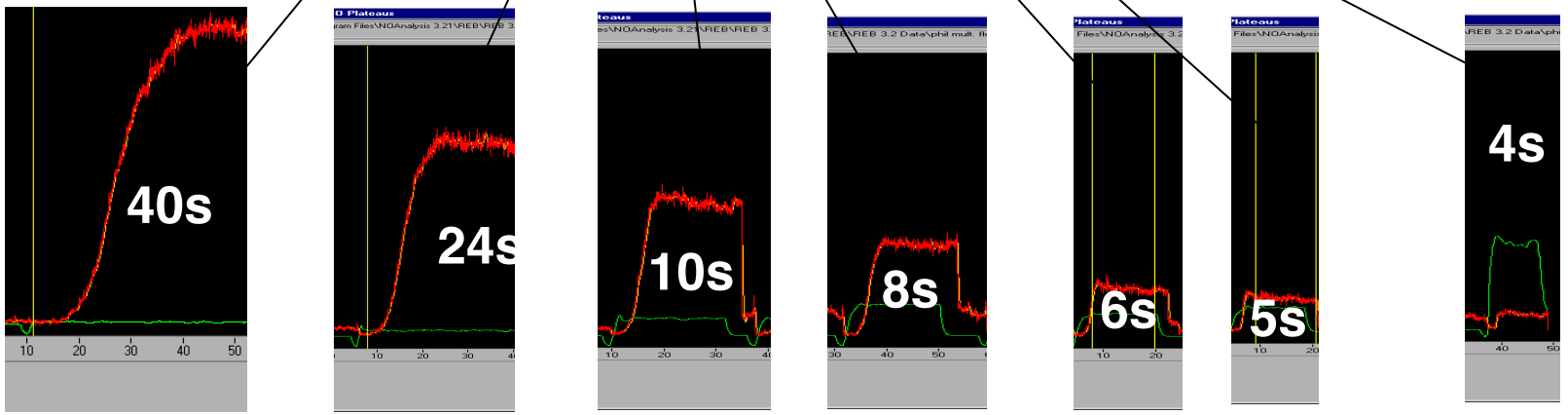
Seconds to FeNO Plateau





Low flows are essential to estimate DNO and Cw But are impractical



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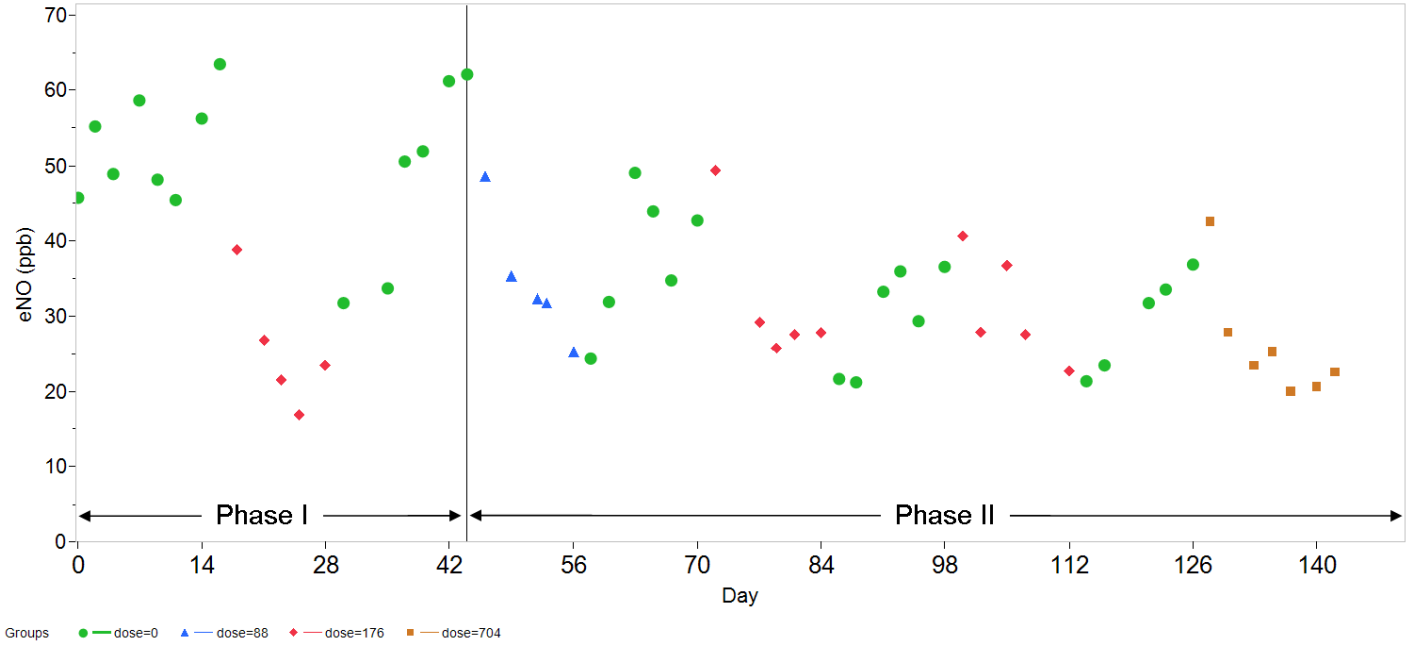
FeNO Steroid Dose Response

Phase I

Run-in (16 days) — **Treatment** 176 mcg/day (14 days) — **Washout** (14 days)

Phase II

Treatment Period 1 (14 days) — **Washout** (14 days) — **Treatment** Period 2 (14 days) — **Washout** (14 days) — **Treatment** Period 3 (14 days) — **Washout** (14 days) — **Treatment** Period 4 (14 days)



Circles: placebo (run-in and washout), Triangles: 88 mcg/day dose, Diamonds: 176 mcg/day dose, Squares: 704 mcg/day dose

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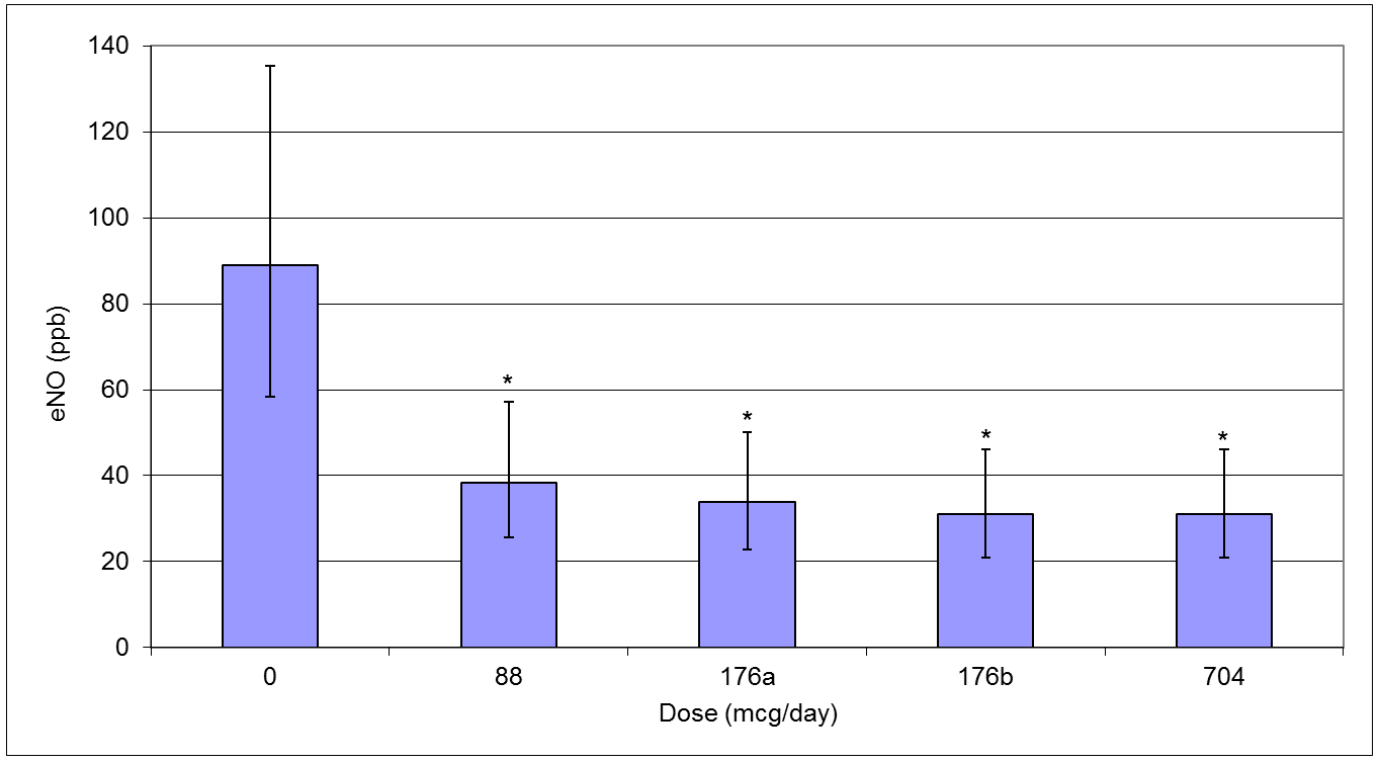
FeNO Steroid Dose Response

Phase I

Run-in (16 days)	Treatment 176 mcg/day (14 days)	Washout (14 days)

Phase II

Treatment Period 1 (14 days)	Washout (14 days)	Treatment Period 2 (14 days)	Washout (14 days)	Treatment Period 3 (14 days)	Washout (14 days)	Treatment Period 4 (14 days)



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FDA Labeling of NIOX

1. Approved in children > 4yrs old and adults 18-65 yrs old

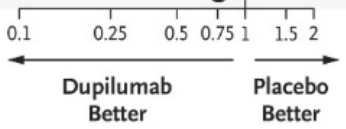
2. Approved for monitoring the effect of anti-inflammatory medications, titration of dose of medications

3. Caution advised as not all patients exhibit a raised exhaled NO and some do not show a fall after steroids- (compliance?, resistance?)

Dupilumab Phase 3 Biomarker Data

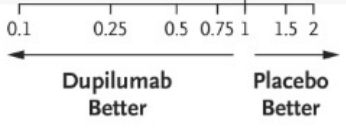
A Dupilumab, 200 mg Every 2 Wk, vs. Matched Placebo

Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	317	631	0.52 (0.41–0.66)
Eosinophil count			
≥300 cells/mm³	148	264	0.34 (0.24–0.48)
≥150 to <300 cells/mm³	84	173	0.64 (0.41–1.02)
<150 cells/mm³	85	193	0.93 (0.58–1.47)
FE_{NO}			
≥50 ppb	71	119	0.31 (0.18–0.52)
≥25 to <50 ppb	91	180	0.39 (0.24–0.62)
<25 ppb	149	325	0.75 (0.54–1.05)



B Dupilumab, 300 mg Every 2 Wk, vs. Matched Placebo

Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	321	633	0.54 (0.43–0.68)
Eosinophil count			
≥300 cells/mm³	142	277	0.33 (0.23–0.45)
≥150 to <300 cells/mm³	95	175	0.56 (0.35–0.89)
<150 cells/mm³	83	181	1.15 (0.75–1.77)
FE_{NO}			
≥50 ppb	75	124	0.31 (0.19–0.49)
≥25 to <50 ppb	97	186	0.44 (0.28–0.69)
<25 ppb	144	317	0.79 (0.57–1.10)



Castro M, et al. NEJM 2018; 378:2486-2496.

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Tezepelumab Reduced Hospitalizations Across Phenotypes and Irrespective of Biomarker Levels

Pooled Analysis from PATHWAY and NAVIGATOR: Annualized rate of exacerbations that required hospitalization or ED visit

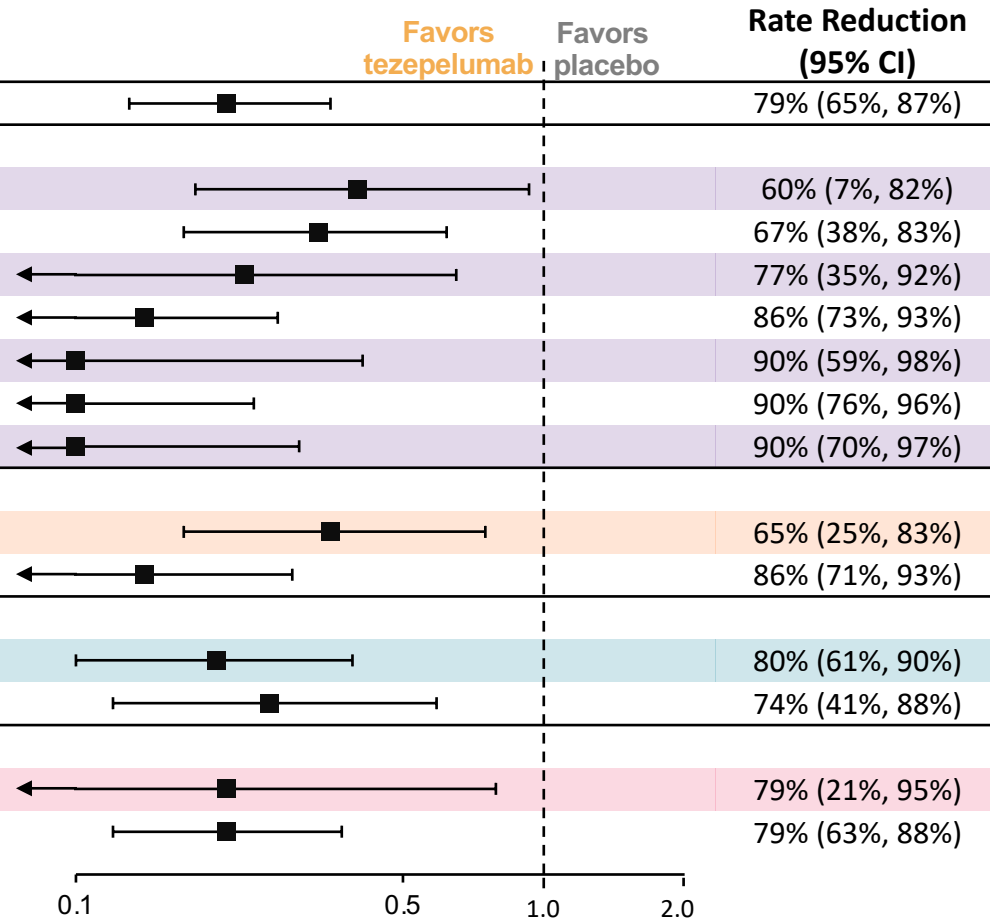
With or without elevated blood eos count

With or without elevated FeNO

Regardless of allergic status

Regardless of OCS use

	Tezepelumab 210 mg Q4W (n/rate)	Placebo (n/rate)	Rate Reduction (95% CI)
Overall	665/0.06	669/0.26	79% (65%, 87%)
Baseline blood eos count, cells/µL			
<150	166/0.12	171/0.30	60% (7%, 82%)
<300	379/0.07	382/0.22	67% (38%, 83%)
≥150 to <300	213/0.04	211/0.15	77% (35%, 92%)
≥150	499/0.03	498/0.24	86% (73%, 93%)
≥300 to <450	127/0.02	116/0.23	90% (59%, 98%)
≥300	286/0.03	287/0.32	90% (76%, 96%)
≥450	159/0.04	171/0.39	90% (70%, 97%)
Baseline FeNO level, ppb			
<25	291/0.07	294/0.19	65% (25%, 83%)
≥25	366/0.05	370/0.33	86% (71%, 93%)
Baseline perennial allergic status			
Allergic[a]	410/0.05	405/0.25	80% (61%, 90%)
Nonallergic[b]	241/0.07	243/0.26	74% (41%, 88%)
Maintenance OCS use at study entry			
Yes	58/0.12	65/0.59	79% (21%, 95%)
No	607/0.05	604/0.23	79% (63%, 88%)



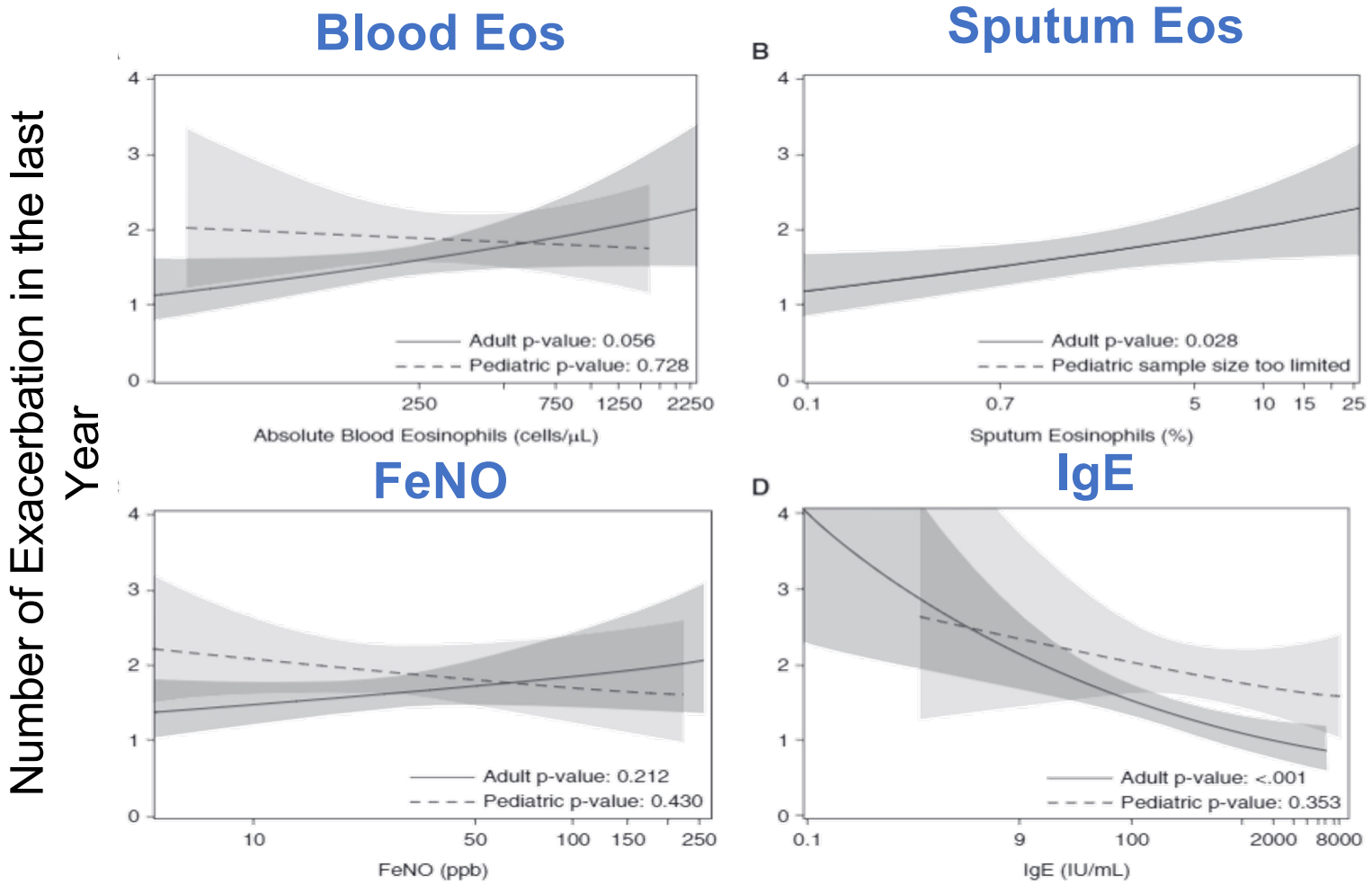
Data are from a negative binomial regression analysis with treatment, study (PATHWAY and NAVIGATOR), history of exacerbations (< 2 or ≥ 2 in the past 12 months), subgroup, and treatment-by-subgroup interaction as covariates.

[a]Any perennial aeroallergen FEIA+; [b]All perennial aeroallergens FEIA-.

CI = confidence interval; Eos = eosinophils; FEIA = fluoroenzyme immunoassay; FeNO = fractional exhaled nitric oxide; OCS = oral corticosteroids; ppb = parts per billion; Q4W = every 4 weeks.

Corren J et al. *Am J Respir Crit Care Med.* 2023;208(1):13-24.

Baseline Eosinophil, Not IgE Predicts Exacerbation Risk



- "Exacerbation prone phenotype is not driven by allergic sensitization" nor by IgE

Note: Baseline data from the NHLBI Severe Asthma Research Program (SARP)-3.
FeNO: fraction of exhaled nitric oxide.

Denlinger LC et al. AJRCCM. 2017 Feb 1;195(3):302-313

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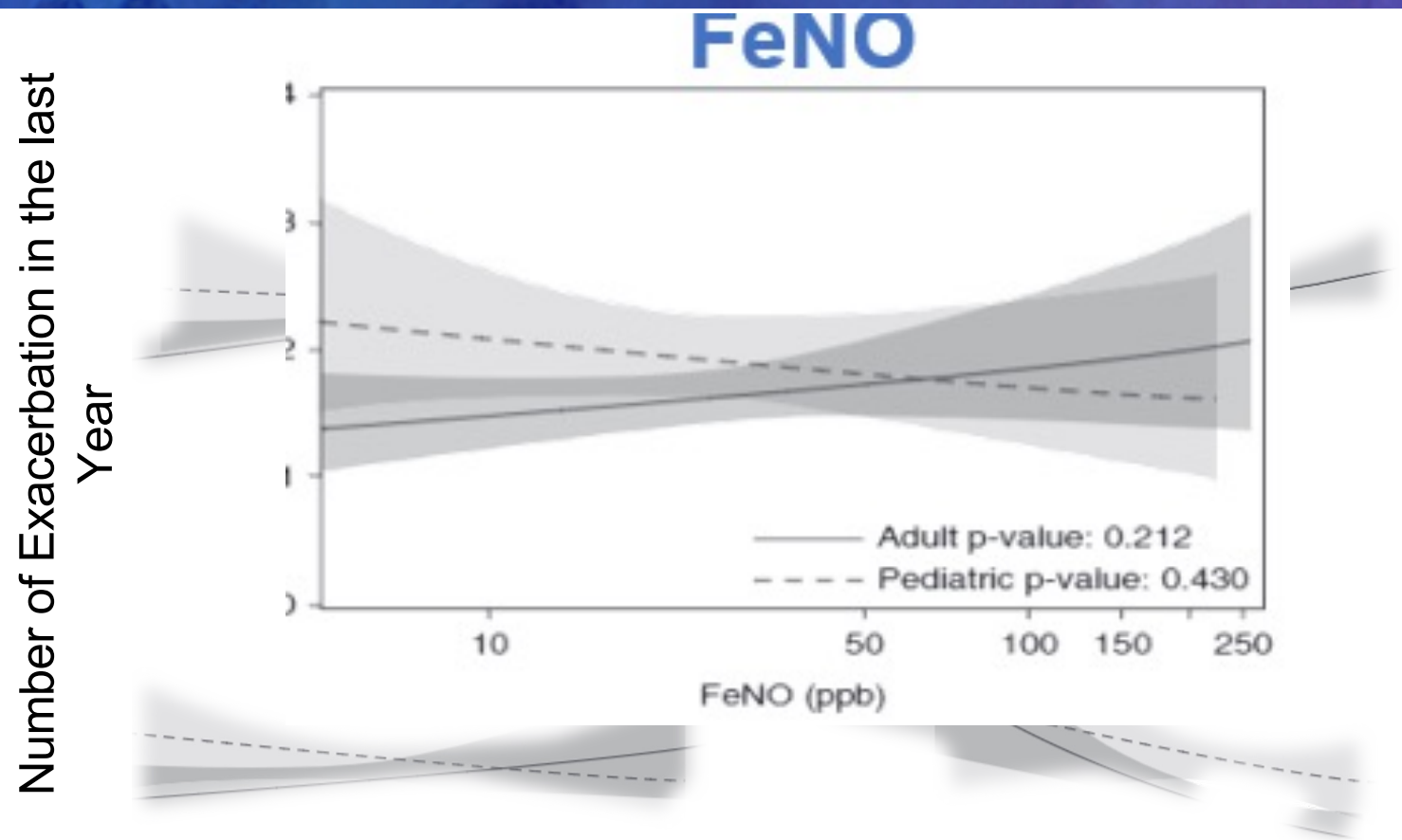
Baseline Eosinophil, Not IgE Predicts Exacerbation Risk



Note: Baseline data from the NHLBI Severe Asthma Research Program (SARP)-3.
FeNO: fraction of exhaled nitric oxide.

Denlinger LC et al. AJRCCM. 2017 Feb 1;195(3):302-313

High Feno And High B-eos In Combination Associated With Significantly Increased Exacerbation Rates In Patients With Moderate to Severe Asthma

Estimated annualized severe exacerbation rates over 52 weeks by baseline FeNO and b-EOS level in placebo-treated patients from Dupilumab Phase III LIBERTY ASTHMA QUEST study

		FeNO (ppb)		
		<25	≥25 to <50	≥50
Blood Eosinophils (cells/µL)	≥300	0.84 (n=89)	1.24 (n=97)	1.78 (n=98)
	≥150 to <300	0.82 (n=96)	1.14 (n=53)	0.48 (n=25)
	<150	0.56 (n=106)	0.62 (n=35)	0.53 (n=21)

In patients with b-EOS ≥300, the risk of exacerbations increases with increases in FeNO, while for those with b-EOS <300 the rates are similar regardless of FeNO

FeNO=fraction exhaled nitric oxide; b-EOS-blood eosinophils; ppb=parts per billion

Busse WW et al. Poster presented at American Academy of Asthma, Allergy, and Immunology; 2020 Virtual Annual Meeting; Virtual Poster Hall. Poster 063.

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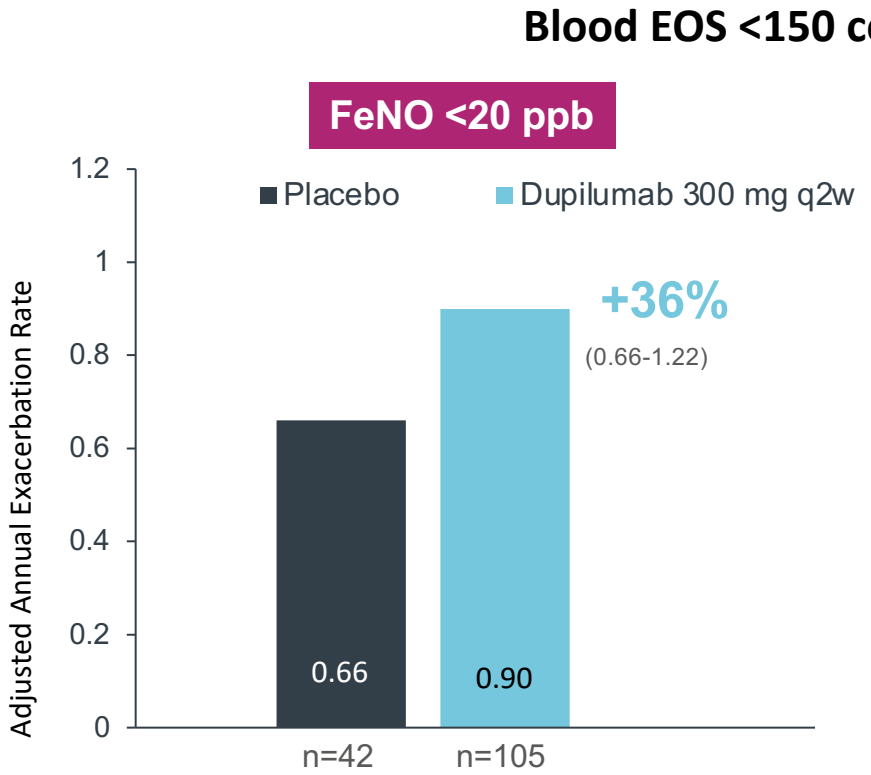
Dupilumab Inclusion Criteria

- Mod/High Dose ICS/LABA
- ACQ >1.5
- Reversibility
- All comers of eos with prespecified analysis > 150 or 300
- 429/611 eos > 150

- **Large percentage eosinophilic and NO randomization based on FeNO**

Castro M, et al. NEJM 2018; 378:2486-2496.

Combination of high b-EOS / high FeNO Predicts higher exacerbation risk



In high b-EOS/high FeNO group, baseline b-EOS increased along with FeNO

b-EOS=blood eosinophils; FeNO=fraction of exhaled nitric oxide; BL=baseline; ppb=parts per billion
*Baseline values are the combined values across both dupilumab dosing groups studied: dupilumab 200 mg q2w and dupilumab 300 mg q2w.
1. Pavord ID et al. Eur Resp J. 2019;54:suppl 63, OA3807. 2. Pavord ID et al. Presentation at: European Respiratory Society International Congress 2019; Madrid, Spain; Sept 28-Oct 2, 2019.

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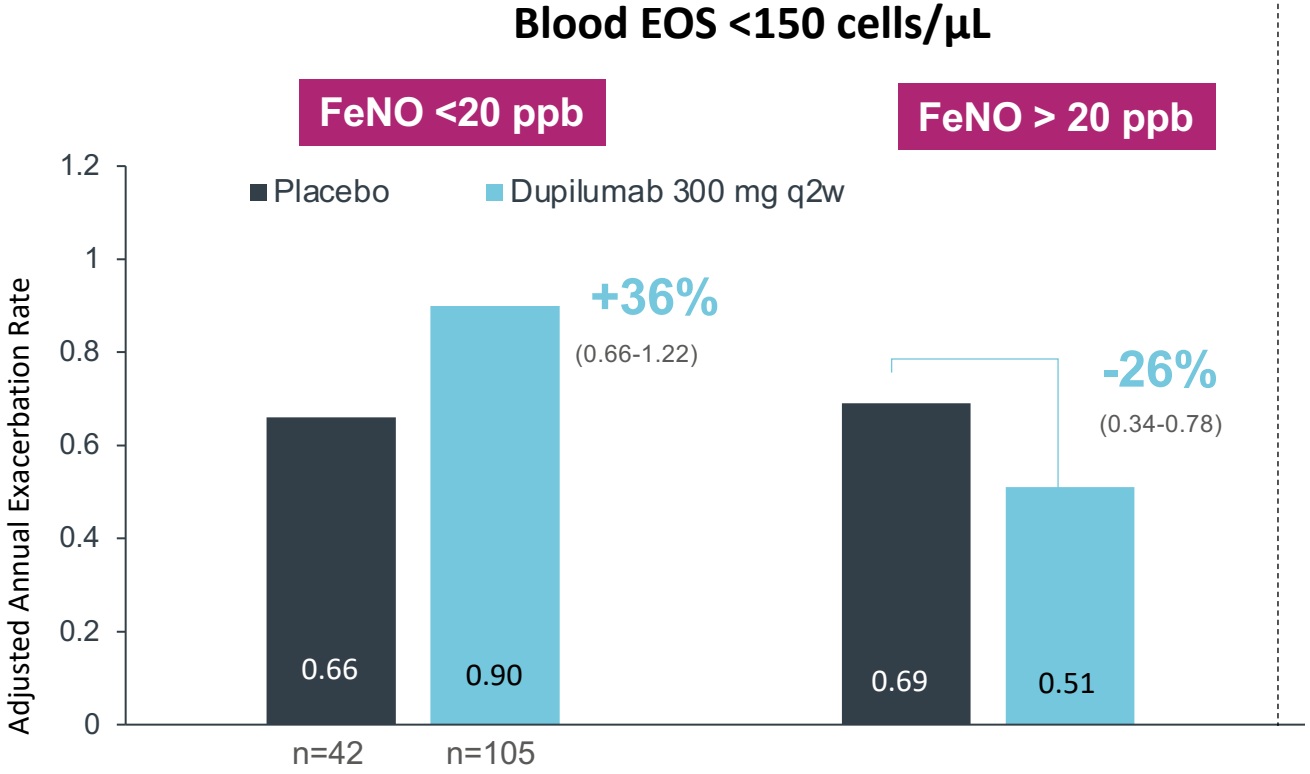
Combination of high b-EOS / high FeNO Predicts higher exacerbation risk



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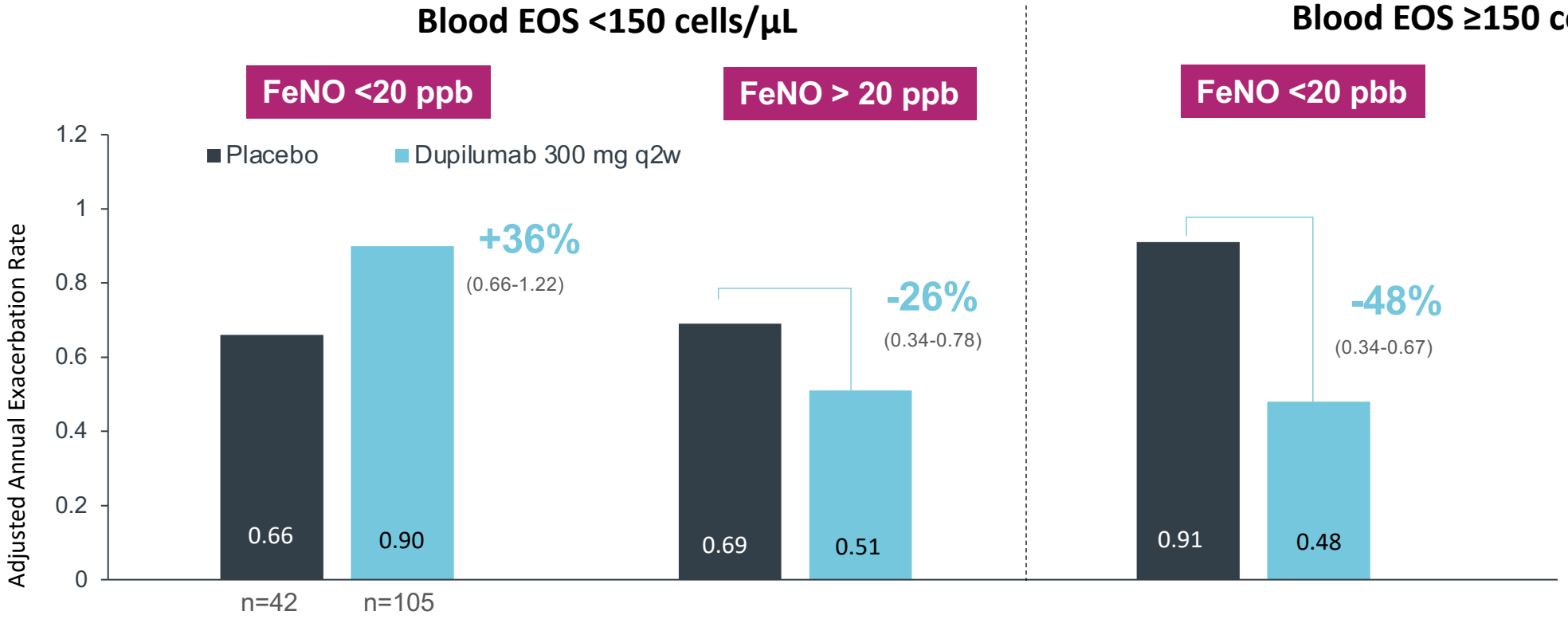
Combination of high b-EOS / high FeNOPredicts higher exacerbation risk



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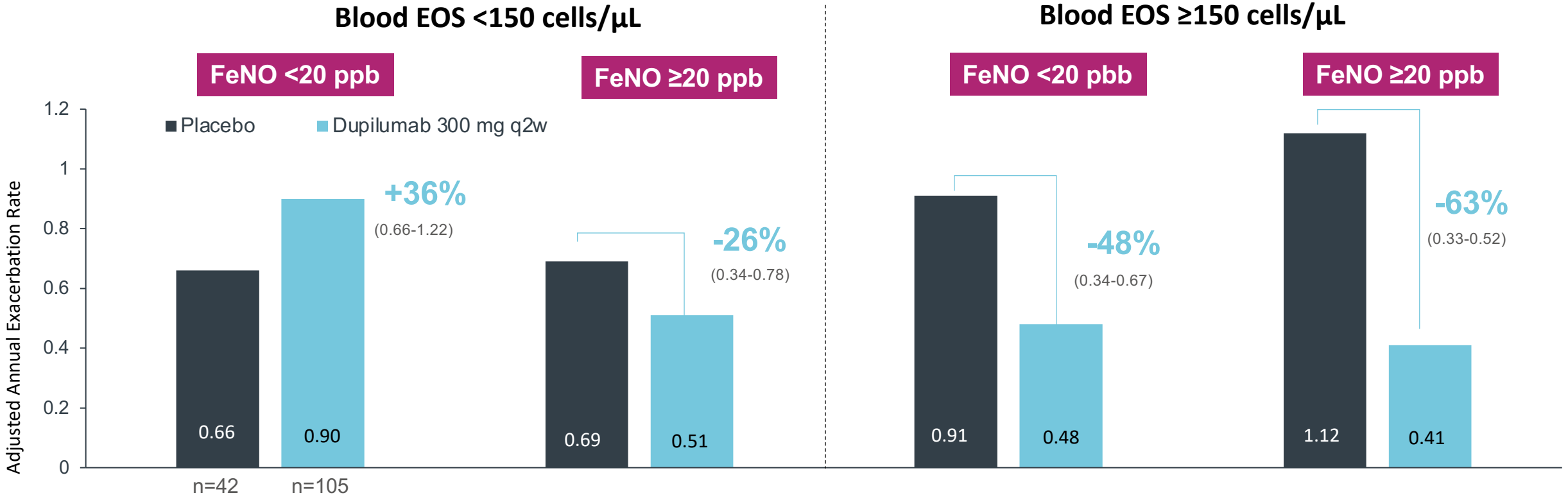

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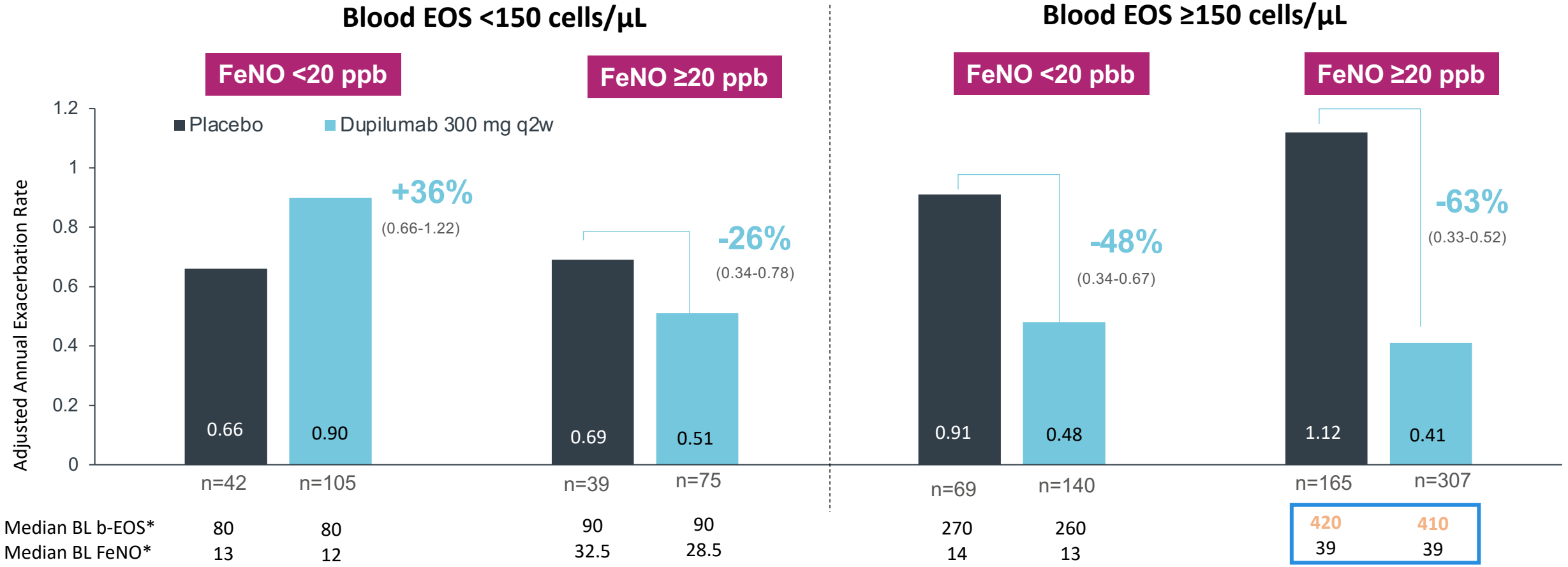

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1. Pavord ID et al. Eur Resp J. 2019;54:suppl 63, OA3807. 2. Pavord ID et al. Presentation at: European Respiratory Society International Congress 2019; Madrid, Spain; Sept 28-Oct 2, 2019.

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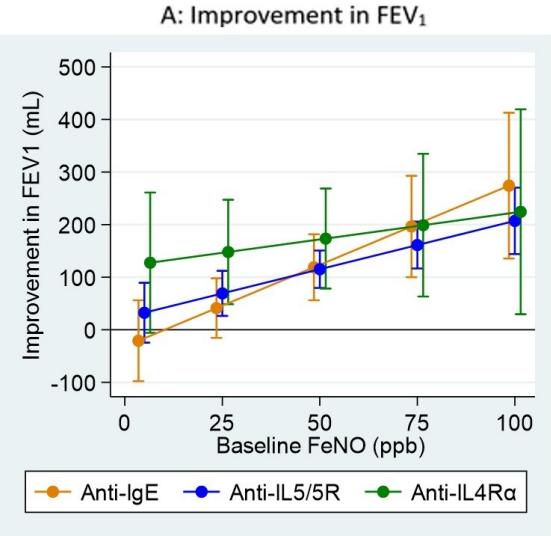
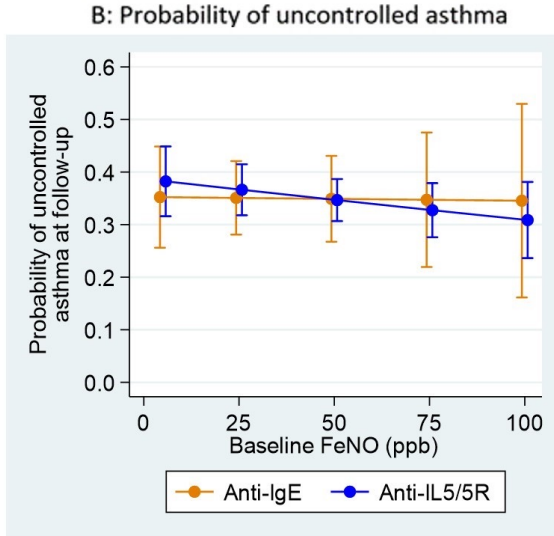
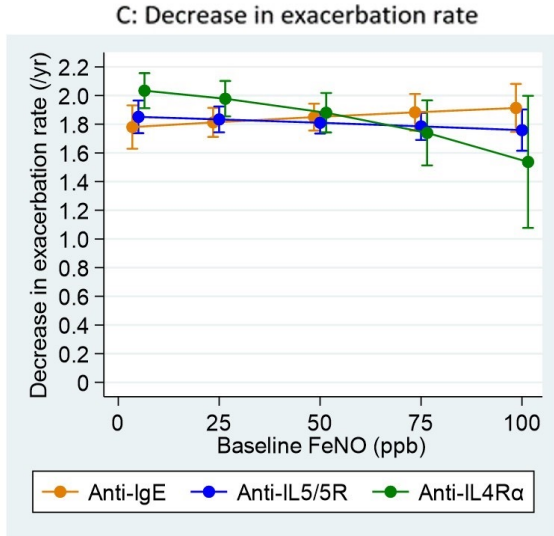
ISAR: IGNITE







Anti-IgE	Coeff (95% CI) = 310 (119 - 502) N = 254 p = 0.002	Anti-IgE	OR (95% CI) = 0.968 (0.310 - 3.022) N = 186 p = 0.956	Anti-IgE	IRR (95% CI) = 0.669 (0.288 - 1.551) N = 211 p = 0.348
Anti-IL5/5R	Coeff (95% CI) = 184 (82 - 286) N = 588 p < 0.001	Anti-IL5/5R	OR (95% CI) = 0.692 (0.389 - 1.229) N = 517 p = 0.209	Anti-IL5/5R	IRR (95% CI) = 1.282 (0.736 - 2.234) N = 559 p = 0.381
Anti-IL4Rα	Coeff (95% CI) = 102 (-183 - 387) N = 92 p = 0.483			Anti-IL4Rα	IRR (95% CI) = 4.295 (1.282 - 14.394) N = 116 p = 0.018
Interactions		**Interactions**		**Interactions**	
Anti-IgE vs anti-IL5/5R	p = 0.253	Anti-IgE vs anti-IL5/5R	p = 0.605	Anti-IgE vs anti-IL5/5R	p = 0.205
Anti-IgE vs anti-IL4Rα	p = 0.234			Anti-IgE vs anti-IL4Rα	p = 0.013
Anti-IL5/5R vs anti-IL4Rα	p = 0.596			Anti-IL5/5R vs anti-IL4Rα	p = 0.075

Porsbjerg C, et al. Front. Immunol., Volume 15 - 2024 | https://doi.org/10.3389/fimmu.2024.1361891

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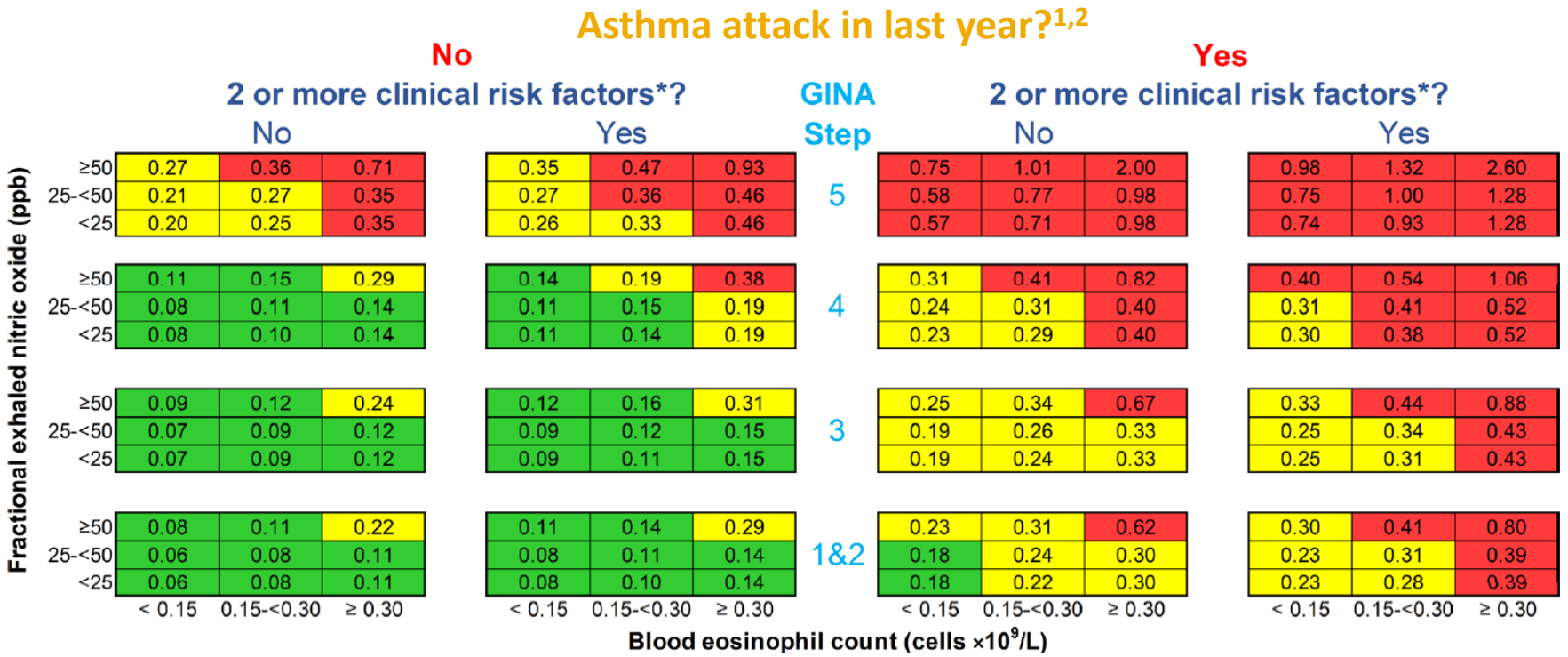
Predicting Risk of Asthma Attack, Which May Be Modified by Anti-Inflammatory Treatment: ORACLE[1]



*Risk factors are defined by the Global Initiative for Asthma (GINA) guidelines: poor symptom control (Asthma Control Questionnaire score ≥1.5), low lung function (forced expiratory volume in 1 second <80% predicted), adherence issues, reliever overuse (>200 dose of salbutamol canister/month), intubation or intensive care unit admission for asthma previously, comorbidities (one of chronic rhinosinusitis, obesity, and psychiatric disease), and environmental exposures (one of smoking, allergens, and pollution).

FeNO, fractional exhaled nitric oxide; GINA, Global Initiative for Asthma; ORACLE, Oxford Asthma Attack Risk Scale; ppb, parts per billion.

1. Couillard S, et al. *ERJ Open Res.* 2022;8(1):00570-2021. 2. Couillard S, et al. *Thorax.* 2022;77(2):199-202.

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QUEST Phase 3 Program

Original Article

Dupilumab Reduces Exacerbations Independent of Changes in Biomarkers in Moderate-to-Severe Asthma

Ian D. Pavord, FMedSci[a], Thomas B. Casale, MD[b], Jonathan Corren, MD[c], Mark J. FitzGerald, MD[d], Yamo Deniz, MD[e], Arman Altincatal, MS[f], Rebecca Gall, MD[e], Nami Pandit-Abid, PharmD[g], Amr Radwan, MD[e], Juby A. Jacob-Nara, MD[g], Paul J. Rowe, MD[g], and William W. Busse, MD[h] *Oxford, United Kingdom; Tampa, Fla; Los Angeles, Calif; Tarrytown, NY; Cambridge, Mass; Bridgewater, NJ; and Madison, Wis*

(J Allergy Clin Immunol Pract 2024;12:1763-72

- "However, dupilumab treatment reduced exacerbation rates independently of fold change in FeNO and Eos"

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The Role of Feno In Clinical Decision Making is Still Evolving: Lack Of Clear Consensus

FeNO should not be used alone to assess asthma control or manage asthma treatment

– **It may be used in addition to clinical assessment including physical exam, spirometry, and symptoms[2]**

ERS/ATS[1]

- FeNO used as a biomarker has a role in mild to moderate asthma
- Not recommended to guide therapy in adults or children with severe asthma

GINA[2]

- FeNO modestly associated with blood and sputum eosinophils
- Not recommended for asthma diagnosis
- Should not be used alone to assess asthma control or manage asthma

ATS[3]

- FeNO supports an asthma diagnosis (moderate quality of evidence)
- Low evidence to support use to monitor airway inflammation

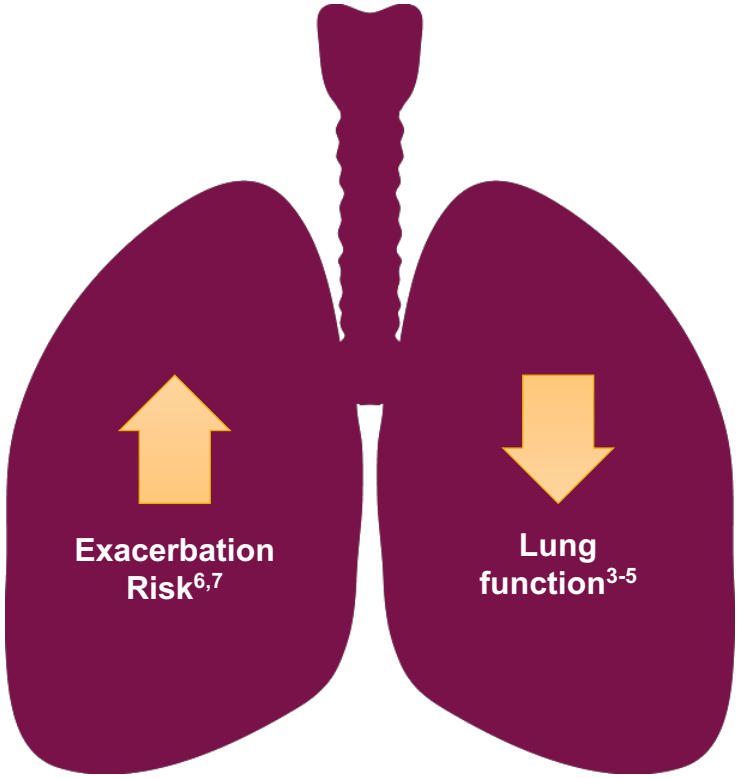
NICE[4]

- Offer a FeNO test to adults (aged ≥17 years) if a diagnosis of asthma is being considered
- Do not routinely use to monitor asthma control

FeNO = fractional exhaled nitric oxide; NICE = National Institute for Health and Care Excellence; ERS=European Respiratory Society; ATS=American Thoracic Society; GINA=Global Initiative for Asthma; NICE=National Institute for Health and Care Excellence

1. Chung KF et al. *Eur Respir J.* 2014;43:343-373. 2. Global Initiative for Asthma (GINA) 2020. http://www.ginasthma.org. 3. Dweik. RA. *Am J Respir Crit Care Med.* 2011;184:602-615. 4. National Institute for Health and Care Excellence (NICE) 2017. https://www.nice.org.uk/guidance/ng80/resources/asthma-diagnosis-monitoring-and-chronic-asthma-management-pdf-1837687975621.

Summary: Increased Eosinophils in Asthma



Elevated eosinophils were correlated with:

- Increased asthma severity[1,2]
- Worsening lung function[3-5]
- Increased risk of exacerbations[6,7]
- Increased rates of hospitalizations and ED visits[6]

1. Bousquet J et al. *N Engl J Med*. 1990;323;1033-1039; 2. Louis R et al. *Am J Respir Crit Care Med.* 2000;161;9-16; 3. Broekema M et al. *Respir Med.* 2010;104:1254-1262; 4. Woodruff PG et al. *J Allergy Clin Immunol*. 2001;108:753-758; 5. McGrath KW et al. *Am J Respir Crit Care Med*. 2012;185:612-619; 6. Zeiger RS et al. *J Allergy Clin Immunol Pract*. 2014;2:741-750; 7. Price D et al. *J Asthma Allergy.* 2016;9:1-12.

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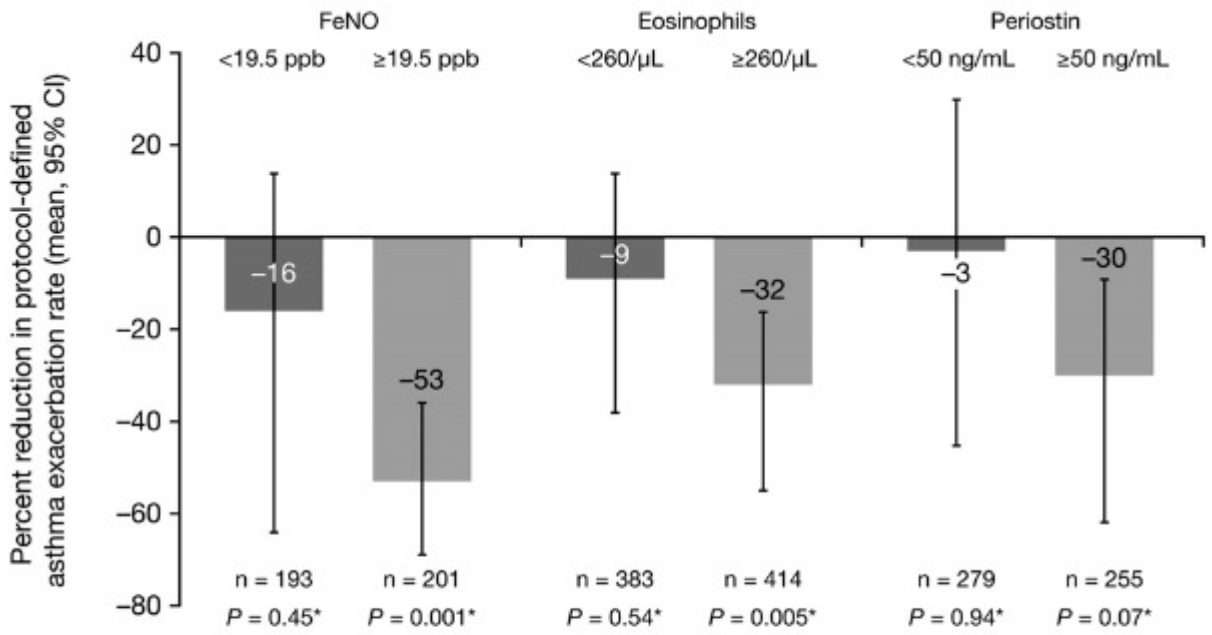
Exacerbation Reduction in Patient Subsets

EXTRA Trial



Exacerbation rates						
	Low FeNO at baseline	High FeNO at baseline	Low eosinophils at baseline	High eosinophils at baseline	Low periostin at baseline	High periostin at baseline
Omalizumab	0.60	0.50	0.65	0.70	0.73	0.66
Placebo	0.71	1.07	0.72	1.03	0.72	0.93

Hanania NA et al. AJRCC 2013;187: 804-11.

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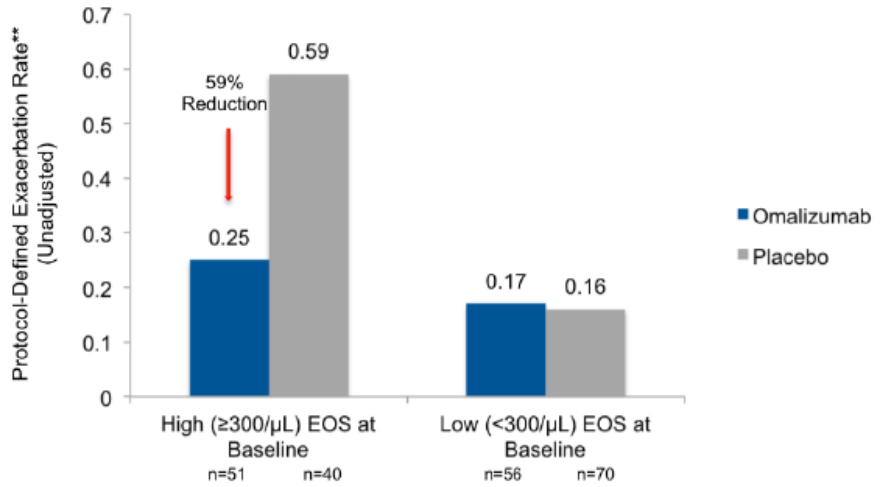
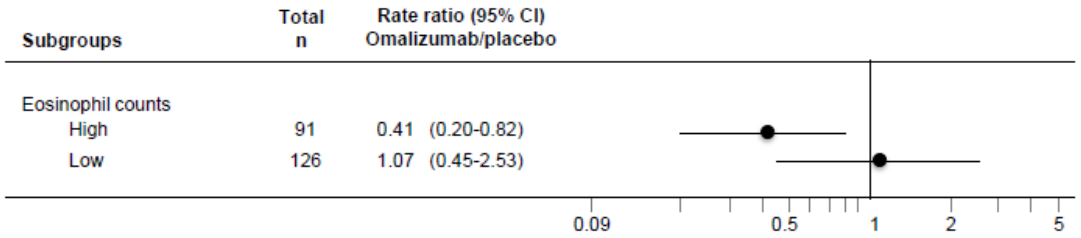
EXACT *Asthma Exacerbation Rates*



Rate ratio (95% CI) of protocol-defined asthma exacerbation by subgroup



Patients with high eosinophils at baseline had a greater reduction in asthma exacerbations compared to placebo

**Number of protocol-defined asthma exacerbations/total patient-treatment period.

Busse et al. *JACI.* 2013;132(2):485-486e11.

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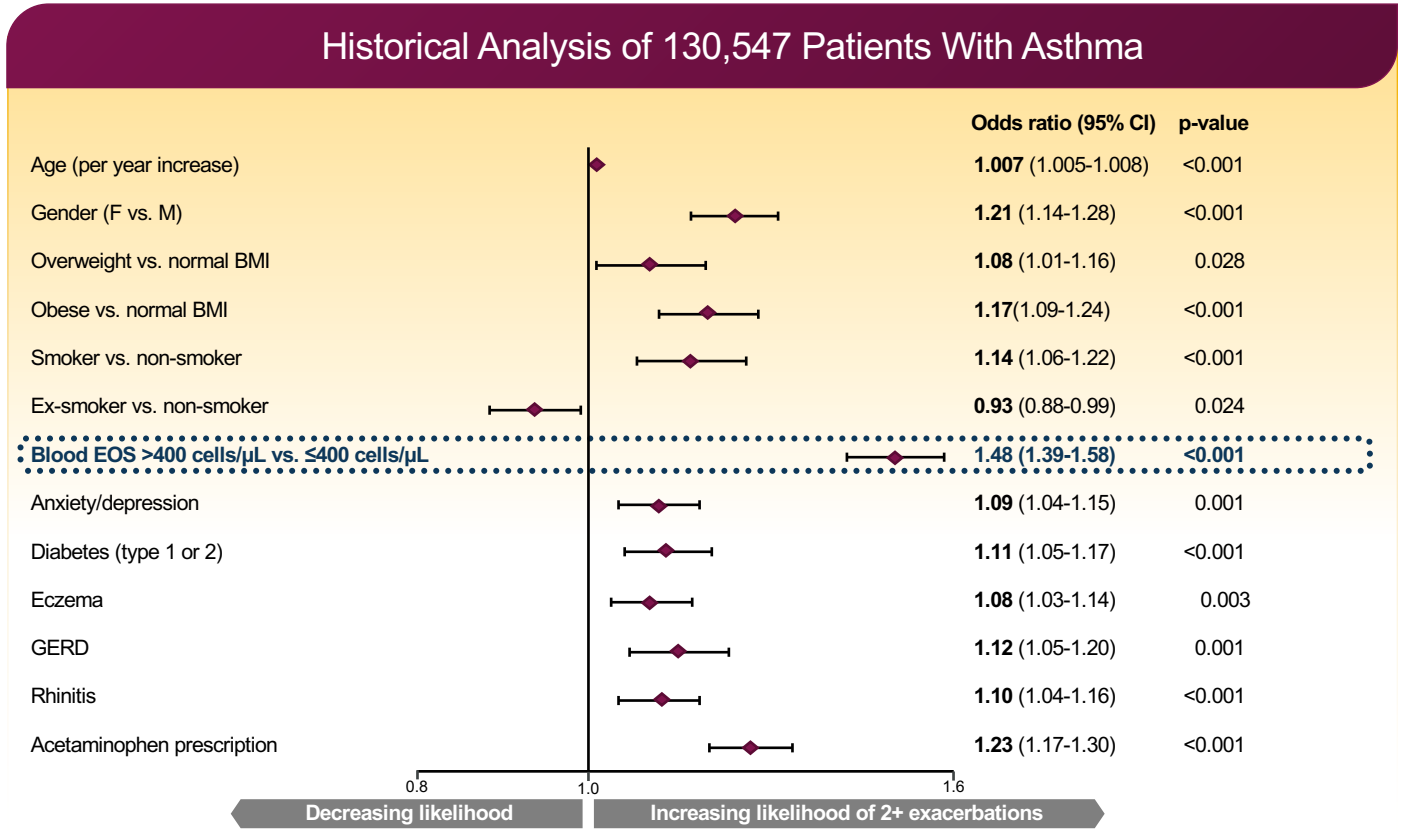
Increased Eosinophils in Asthma: Major Risk Factor for Exacerbations



Blood eosinophil >400 cells/µL:

- **Single best predictor of multiple exacerbations**
- **↑ likelihood of ≥2 exacerbations by 1.5-fold**

BMI = body mass index; CI = confidence interval; EOS = eosinophils; F = female; GERD = gastroesophageal reflux disease; M = male.

Price D et al. J *Asthma Allergy*. 2016;9:1-12.

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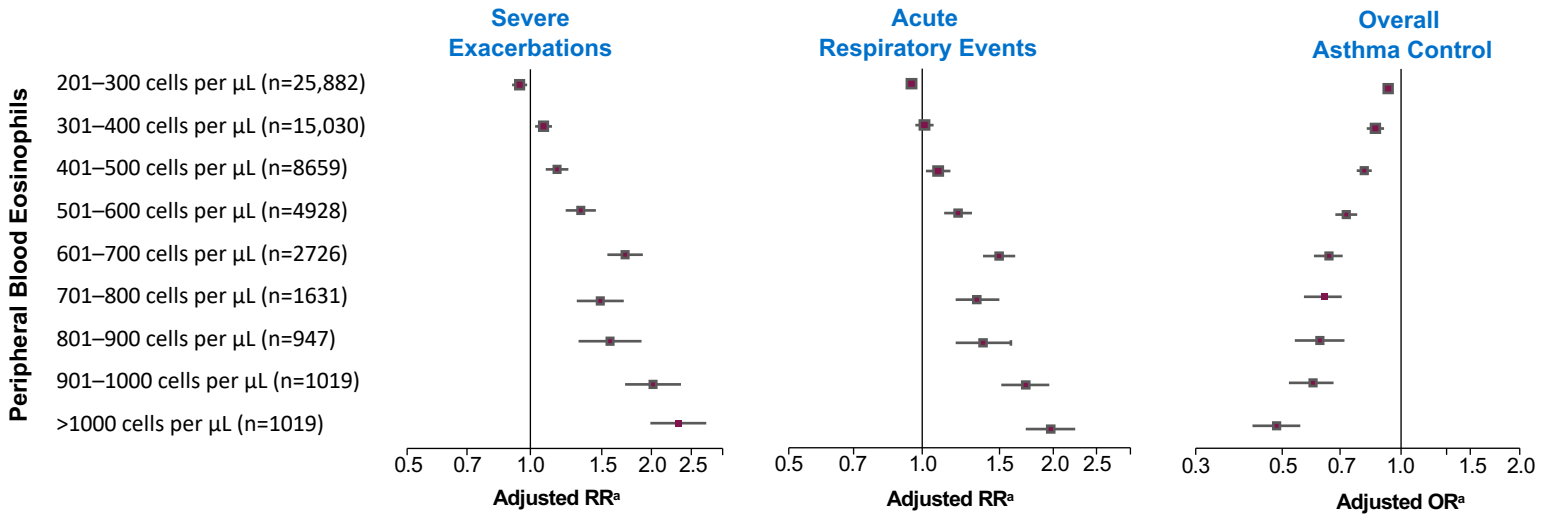
Peripheral Blood Eosinophil Levels Have Been Correlated With Both Asthma Severity and Control



Severe Exacerbation - an asthma-related hospitalization, attendance at an accident and an emergency department, or a prescription for acute oral OCS

Acute Respiratory Event - defined more broadly as an asthma-related hospital attendance or admission, or accident and an emergency department attendance, a prescription for acute OCS, or prescription for antibiotics in conjunction with an asthma-related primary care consultation

Overall Asthma Control - the absence of any acute respiratory event (as defined above) or asthma-related outpatient department visit with an average daily dose of 200 µg or less of salbutamol or 500 µg or less of terbutaline

[a]Data from medical records of patients with asthma who were aged 12-80 years and had 2 years of continuous records, including 1 year before (baseline) and 1 year after (outcome) their most recent eosinophil count. Patients were assigned to 9 eosinophil count categories and were compared with a reference category of ≤200 cells/µL (n=68,407). Data adjusted for age, gender, body mass index, smoking status, and Charlson comorbidity index score.

OCS = oral corticosteroids; OR = odds ratio; RR = rate ratio.

Price DB et al. *Lancet Respir Med.* 2015;3:849-858.

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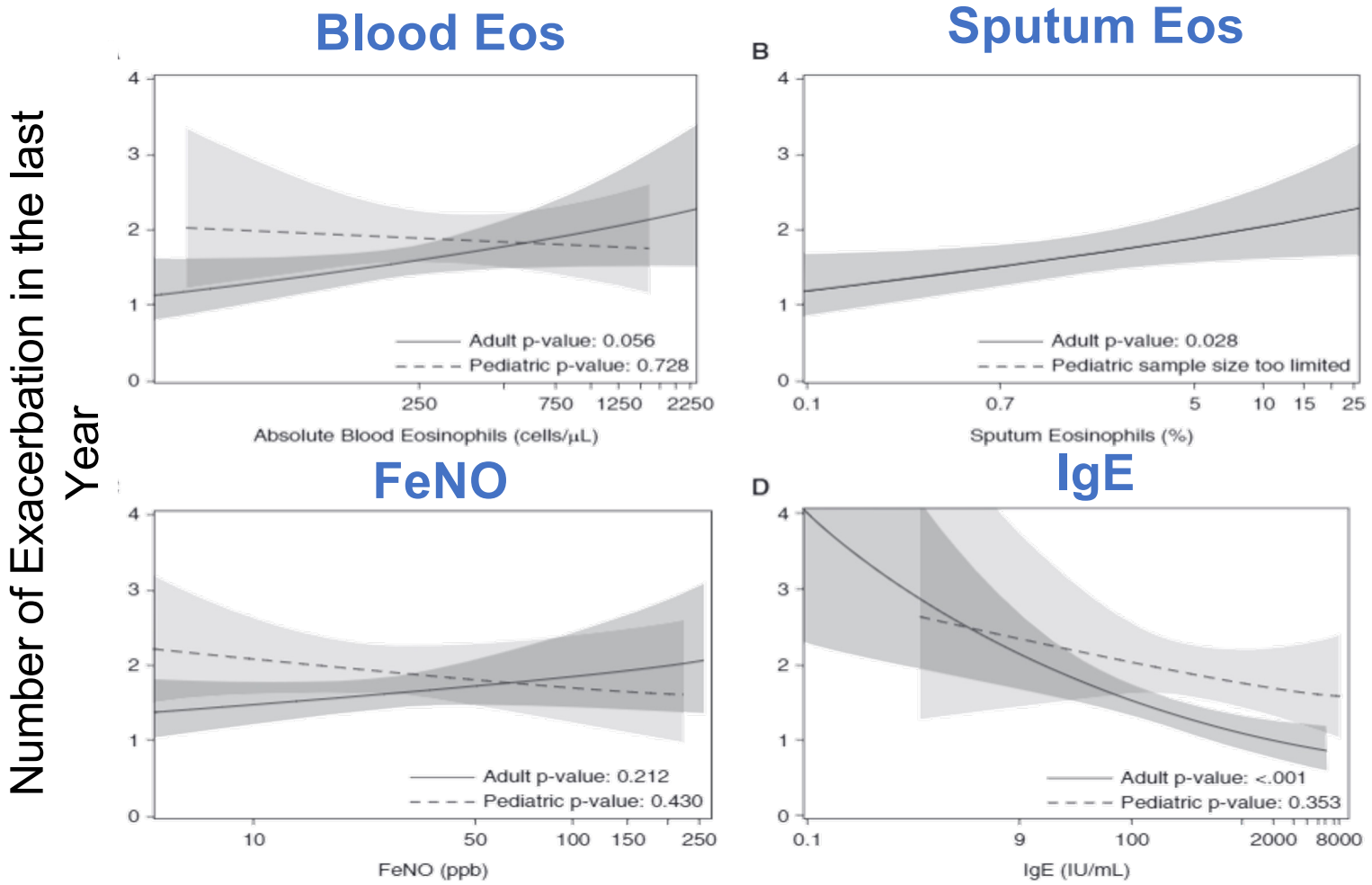
Baseline Eosinophil, Not IgE Predicts Exacerbation Risk



Note: Baseline data from the NHLBI Severe Asthma Research Program (SARP)-3.
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- Denlinger LC et al. AJRCCM. 2017 Feb 1;195(3):302-313

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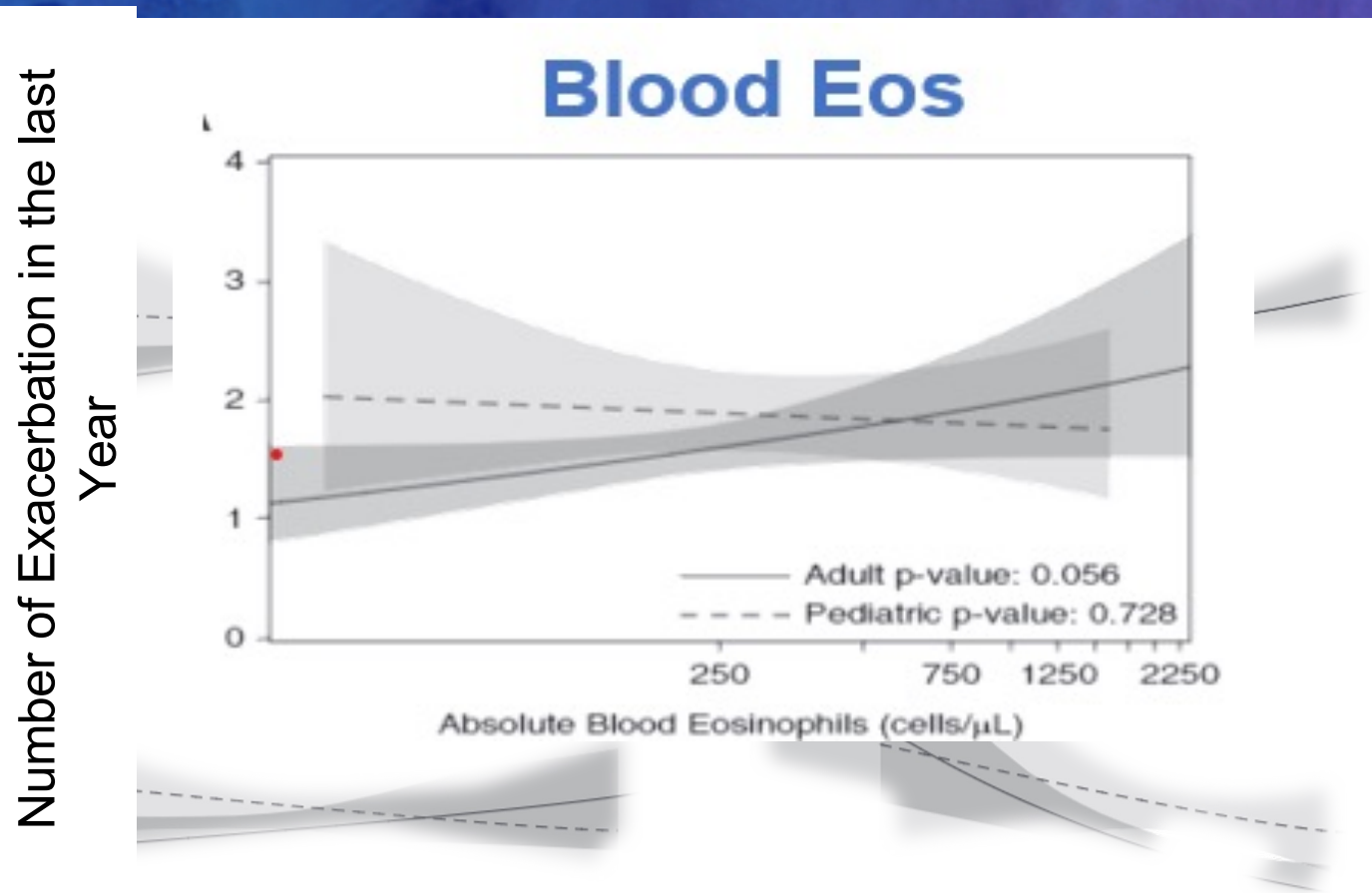

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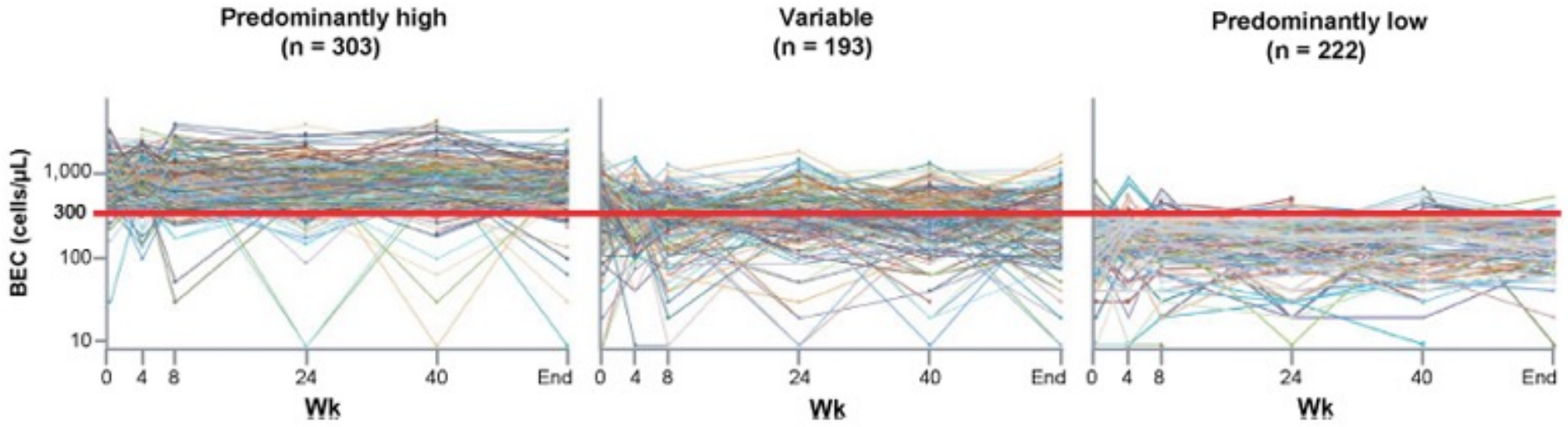
FeNO: fraction of exhaled nitric oxide.

Denlinger LC et al. AJRCCM. 2017 Feb 1;195(3):302-313

Variability in Eos and Exacerbations

- The predominantly high and variable BEC groups had comparable prospective AAERs
- The prospective risks of asthma exacerbations were 39% and 36% greater among patients in the predominantly high and variable BEC groups, respectively, than among patients in the predominantly low BEC group



- Bleecker E, et al. JACIIP 2023;11: 1805-13

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Success of Therapy Based on Biomarkers: Anti-IL-5 Therapy in Patients with Elevated Eosinophils

Table 1—*Response to Anti-IL-5 and Eosinophil Phenotype*

Study/Year	Intervention	Sputum Eosinophil at Entry	Success
Flood-Page et al[18]/2007	Mepolizumab	5% of patients had >3% eos	X
Kips et al[19]/2003	Reslizumab	~30% of patients had >3% eos	X
Haldar et al[14]/2009	Mepolizumab	All patients had >3% eos on one occasion in 2 y	√
Castro et al[15]/2011	Reslizumab	All patients had >3% eos at randomization	√√
Nair et al[13]/2009	Mepolizumab	All patients had >3% eos on ≥3 occasions	√√√

√ = grade of success of intervention; eos = eosinophils; X = intervention unsuccessful.

- Success in response to Anti-IL-5 Therapy is based on eosinophil phenotype
- In 2 of the 5 studies that measured sputum eosinophils and in the three RCTs, the greater the certainty that an increase in eosinophils was persistent, the greater the success of treatment

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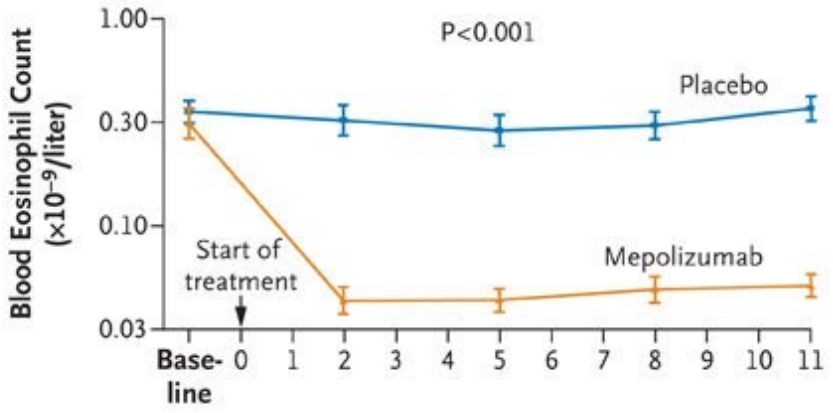
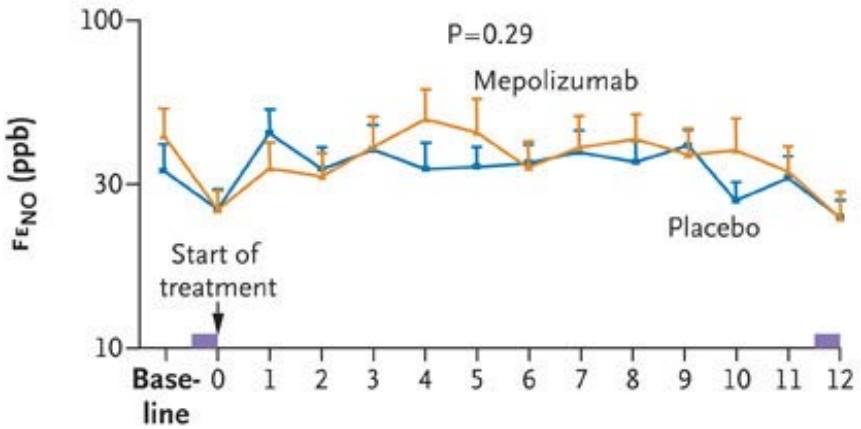
FeNO and Eosinophils After Anti-IL-5 Treatment





Adapted from Haldar et al; NEJM 2009; 360: 973-84

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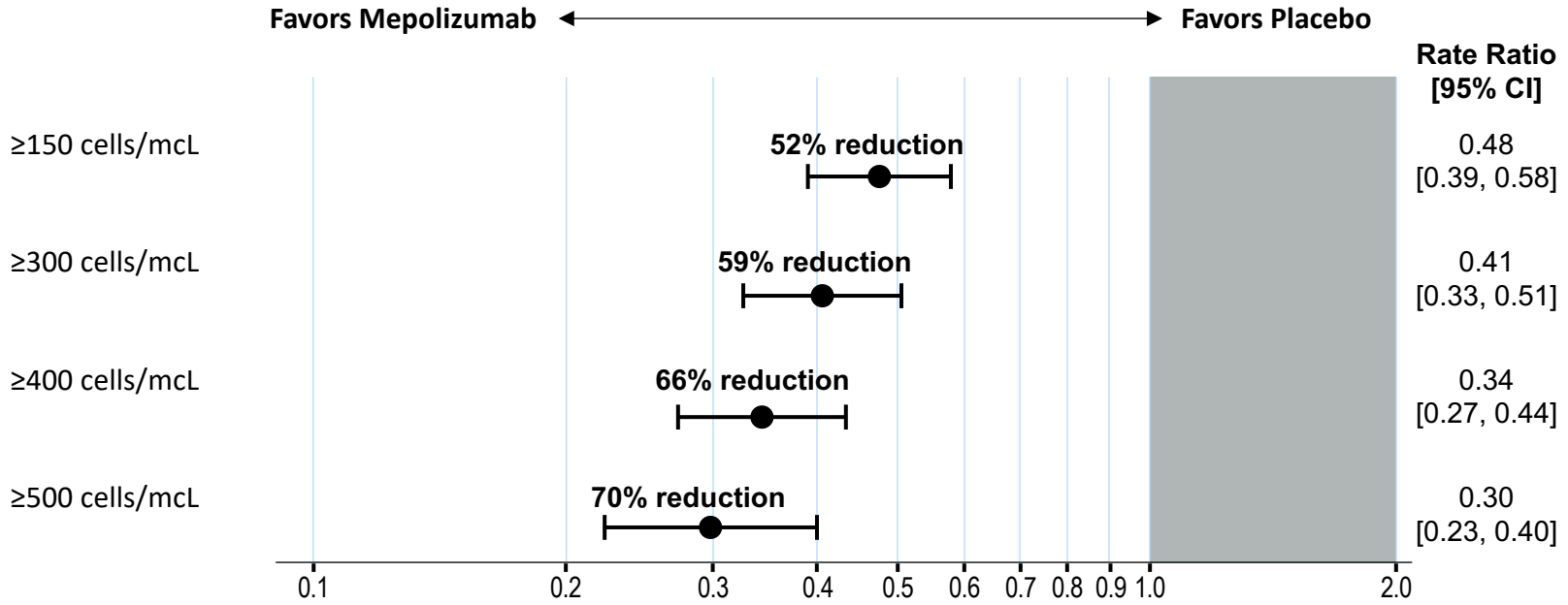
DREAM and MENSA: *Post-hoc* Analysis

Reduction in Exacerbation Rate Stratified by Baseline Blood Eosinophil Thresholds

- *Post-hoc* analysis using the ITT populations of DREAM and MENSA trials
  - All mepolizumab doses (75 mg, 250 mg, 750 mg IV: and *Nucala*) combined for analysis
  - Primary Measure: Annualized rate of exacerbations in patients stratified by baseline blood eosinophil counts: ≥150, ≥300, ≥400, and ≥500 cells/mcL
  - **Results of Analysis (ITT population, n = 344 placebo, n = 841 mepolizumab)***



*Seven patients had missing baseline eosinophil values in MENSA and were excluded from this analysis. Covariate modeling was applied to each study separately and to the combined dataset; ITT = intention-to-treat;

Ortega et al. *Lancet Respir Med* 2016.

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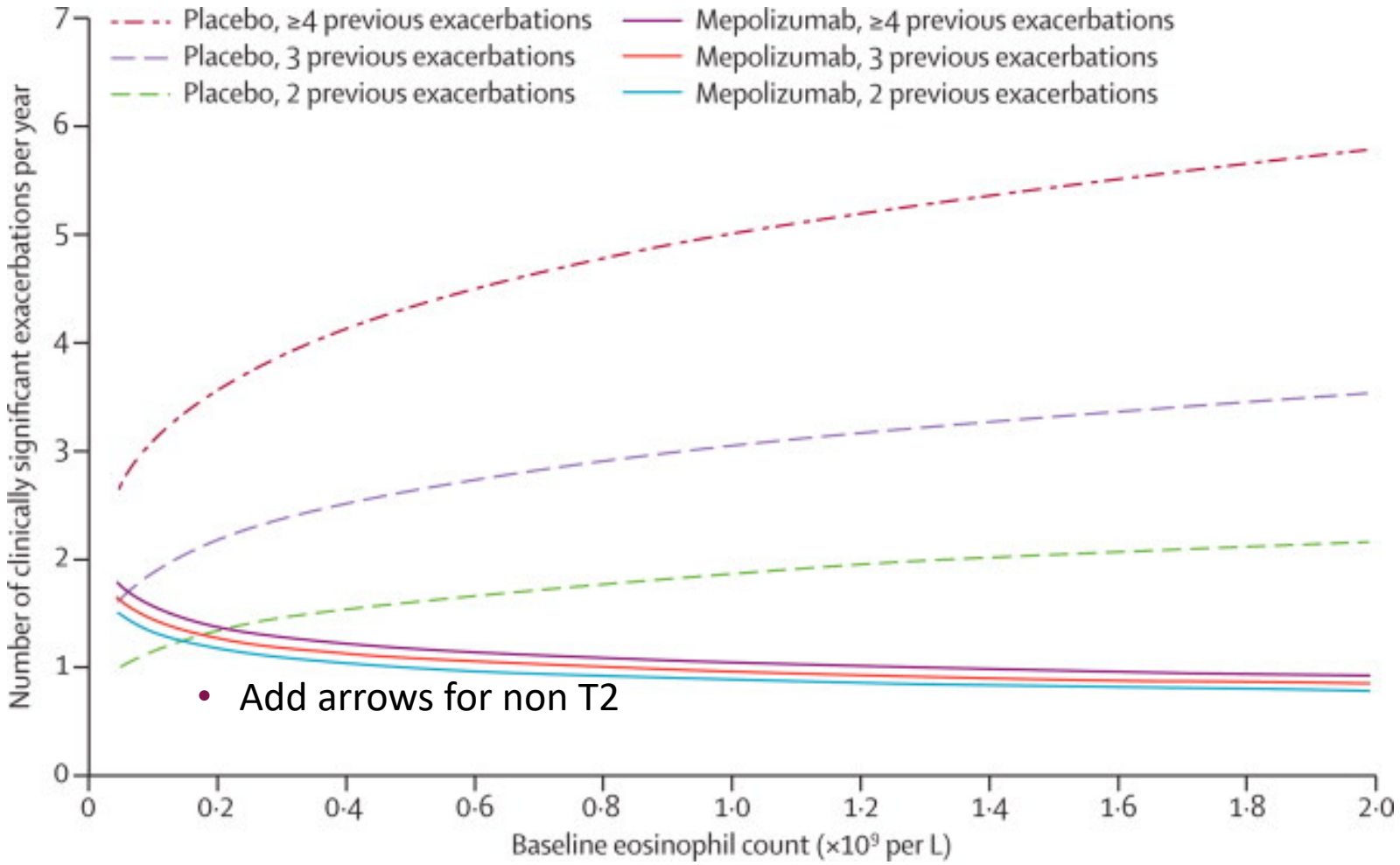
Blood eosinophil and number of exacerbations in the prior year



- Add arrows for non T2

Lancet 2012; 380: 651–59

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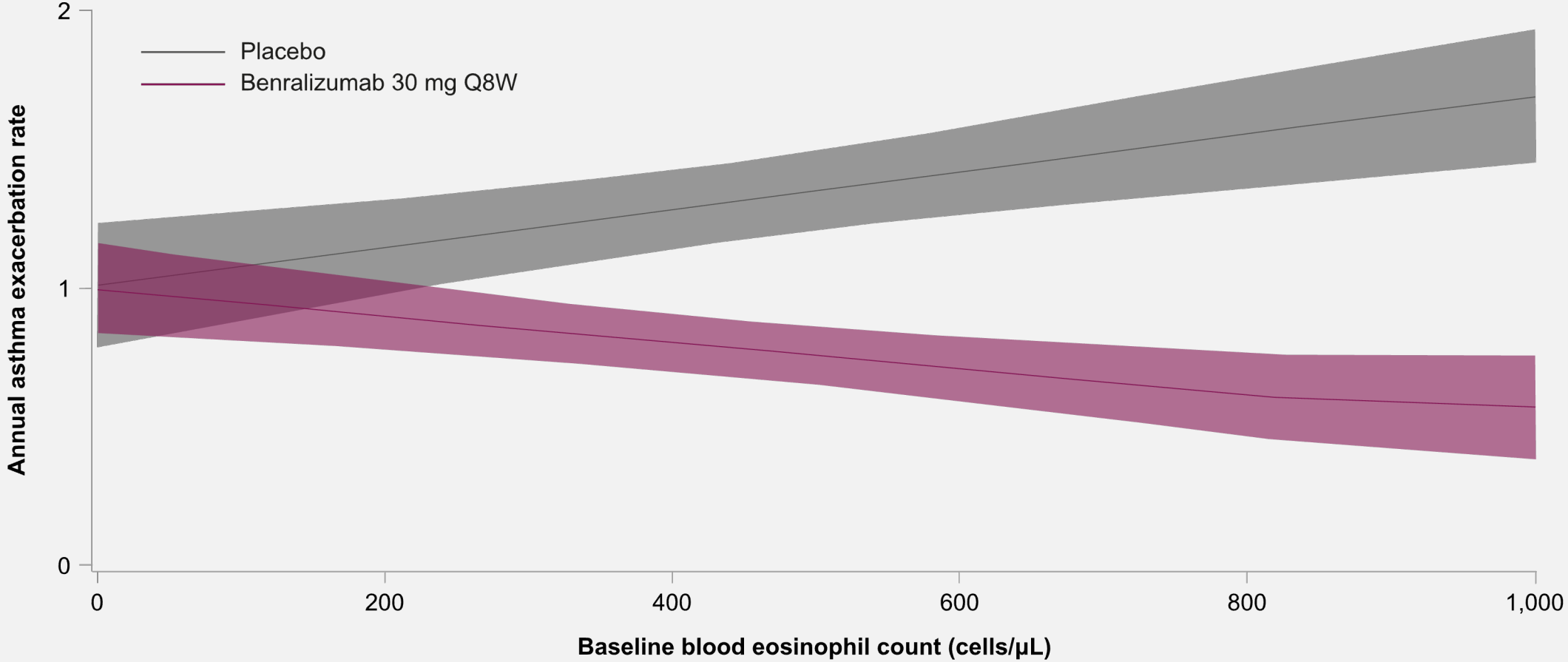
Increasing baseline blood eosinophil counts is associated with exacerbation frequency in severe asthma[1]



- Q8W: every eight weeks

1. Jackson DJ *et al*. Ability of serum IgE concentration to predict exacerbation risk and benralizumab efficacy for patients with severe eosinophilic asthma. *Advances in Therapy*. 2020; **37:** 718–29.

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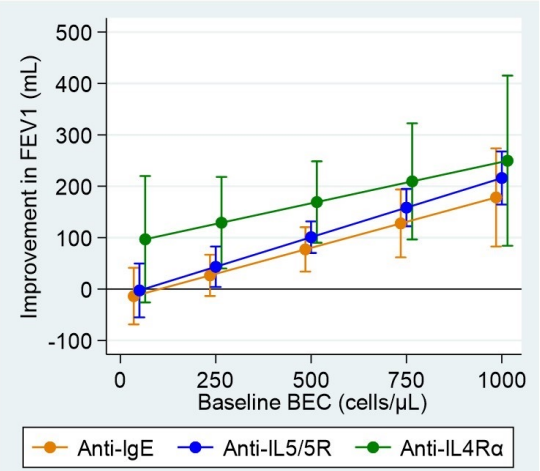
ISAR: IGNITE

A: Improvement in FEV_1



Anti-IgE Coeff (95% CI) = 202 (68 - 336)
N = 512
p = 0.003

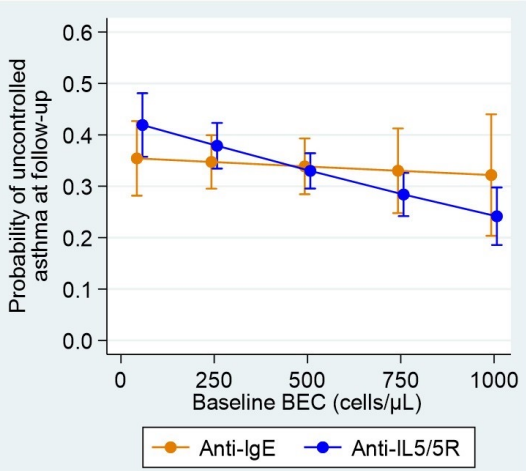
Anti-IL5/5R Coeff (95% CI) = 230 (141 - 319)
N = 789
p < 0.001

Anti-IL4Rα Coeff (95% CI) = 161 (-95 - 416)
N = 125
p = 0.217

Interactions

Anti-IgE vs anti-IL5/5R p = 0.733
Anti-IgE vs anti-IL4Rα p = 0.779
Anti-IL5/5R vs anti-IL4Rα p = 0.616

B: Probability of uncontrolled asthma



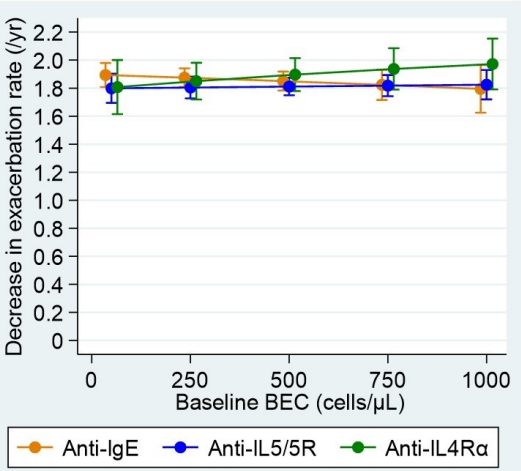
Anti-IgE OR (95% CI) = 0.852 (0.380 - 1.909)
N = 347
p = 0.697

Anti-IL5/5R OR (95% CI) = 0.392 (0.230 - 0.668)
N = 681
p = 0.001

Interaction

Anti-IgE vs anti-IL5/5R p = 0.115

C: Decrease in exacerbation rate



Anti-IgE IRR (95% CI) = 1.343 (0.720 - 2.506)
N = 412
p = 0.354

Anti-IL5/5R IRR (95% CI) = 0.933 (0.592 - 1.470)
N = 772
p = 0.765

Anti-IL4Rα IRR (95% CI) = 0.565 (0.186 - 1.711)
N = 172
p = 0.312

Interactions

Anti-IgE vs anti-IL5/5R p = 0.355
Anti-IgE vs anti-IL4Rα p = 0.182
Anti-IL5/5R vs anti-IL4Rα p = 0.411

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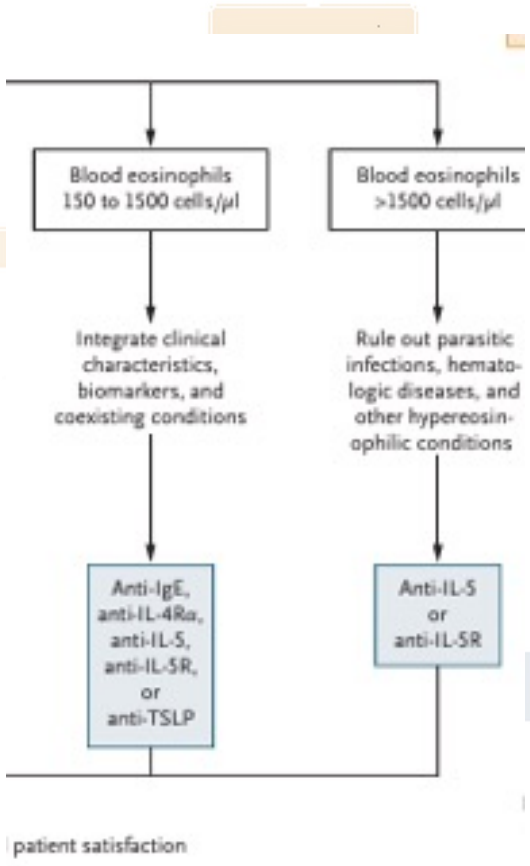
Biomarkers Determining Use of Biologics



Brusselle G, Koppelman. NEJM 2022; 386:157-71

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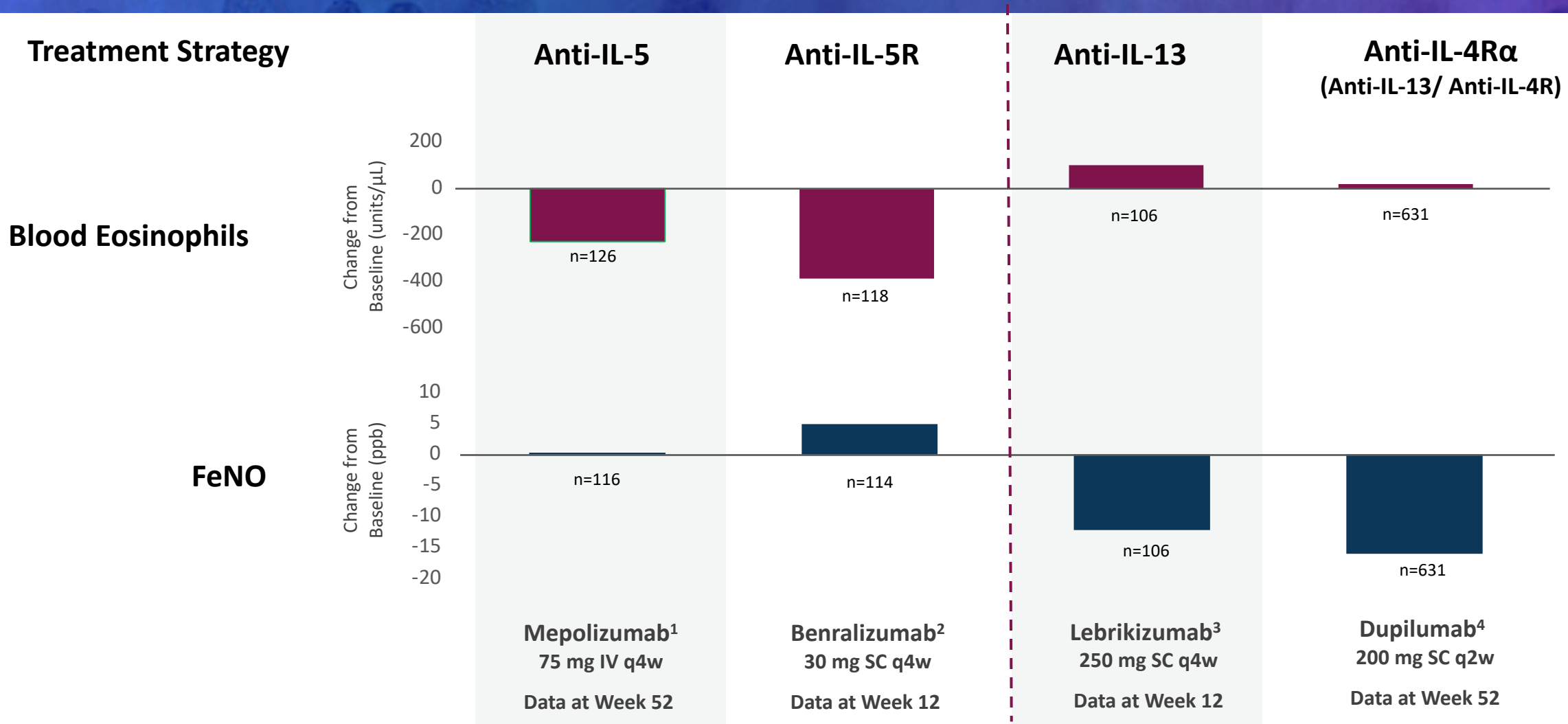
Clinical data support the different mechanisms driving airway inflammation



IL-interleukin; FeNO=fraction of exhaled nitric oxide; SC=subcutaneous

1. DREAM Clinical Study Report. https://www.gsk-studyregister.com/en/trial-details/?id=112997. 2. Panettieri RA et al. Article and supplemental material. *J Asthma Allergy*. 2020;13:115-126. 3. Corren J et al. Supplementary Appendix. *N Engl J Med*. 2011;365:1088-1098. 4. Castro M et al. Supplementary Appendix. *N Engl J Med*. 2018;378:2486-2496.

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Key Points Summary

- Current therapies
  - Anti IgE: omalizumab: No response markers, probably works in same T2 population as others but not studied as such
  - Anti IL-5: mepolizumab, reslizumab: Works in T2 high asthma as defined by a eosinophilic population
  - Anti-IL5R: benralizumab: Works in T2 high asthma as defined by a eosinophilic population
  - Anti IL4αR alpha/Anti IL-13: dupilumab: also works in T2 high as defined by Eos > 150 but capped at 1500
  - Anti- TSLP: Tezepelumab: Works in both T2 low and high, although majority of population was eosinophilic with no upper cap

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Key Points Summary

- FeNO has not been prospectively validated just cross sectional cuts
- Increased bEos at basleime predicts risk of future exacerabtions
- All T2 biologics work in this population of Eos high pts with appropriate upper limit caveat
- Do not confuse pharmacodynamic effect of engaging a target with disease pathophysiology

Conclusion: Choosing a Biologic

- First I look at book ends: T2 high or Low
  - Low: tezepleumab
  - High: Eos > 1500: mepolizumab, reslizumab (IV only), benralizumab, tezepelumab

- Second: T2 high but Eos 150-1500: All work for asthma
  - Look at other characteristics, co-morbidities (varying indications across the drugs), dosing frequence, coverage

- Our biomarkers do not differentiate these drugs currently

Questions

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