Severe asthma treatment evolution

Professor Peter Howarth

Professor of Allergy and Respiratory Medicine

Southampton, UK

&

Global Clinical Scientific Lead

GSK

TSPCCM
Kaohsiung, Taiwan
December 8th 2019

Disclosures: Professor Peter Howarth

Research support/ involvement	Clinical study involvement with GSK and Boehringer Ingelheim
Employee	Employee of GSK
Consultant	Part-time Professor of Allergy and Respiratory Medicine at Southampton University, UK
Major stockholder	Has share options in GSK
Speakers' bureau	No relevant conflicts of interest to declare
Honoraria	No relevant conflicts of interest to declare
Scientific Advisory Board	GSK

Asthma treatment evolution

2020

2000s

1970s-80s

1950s

Biologics

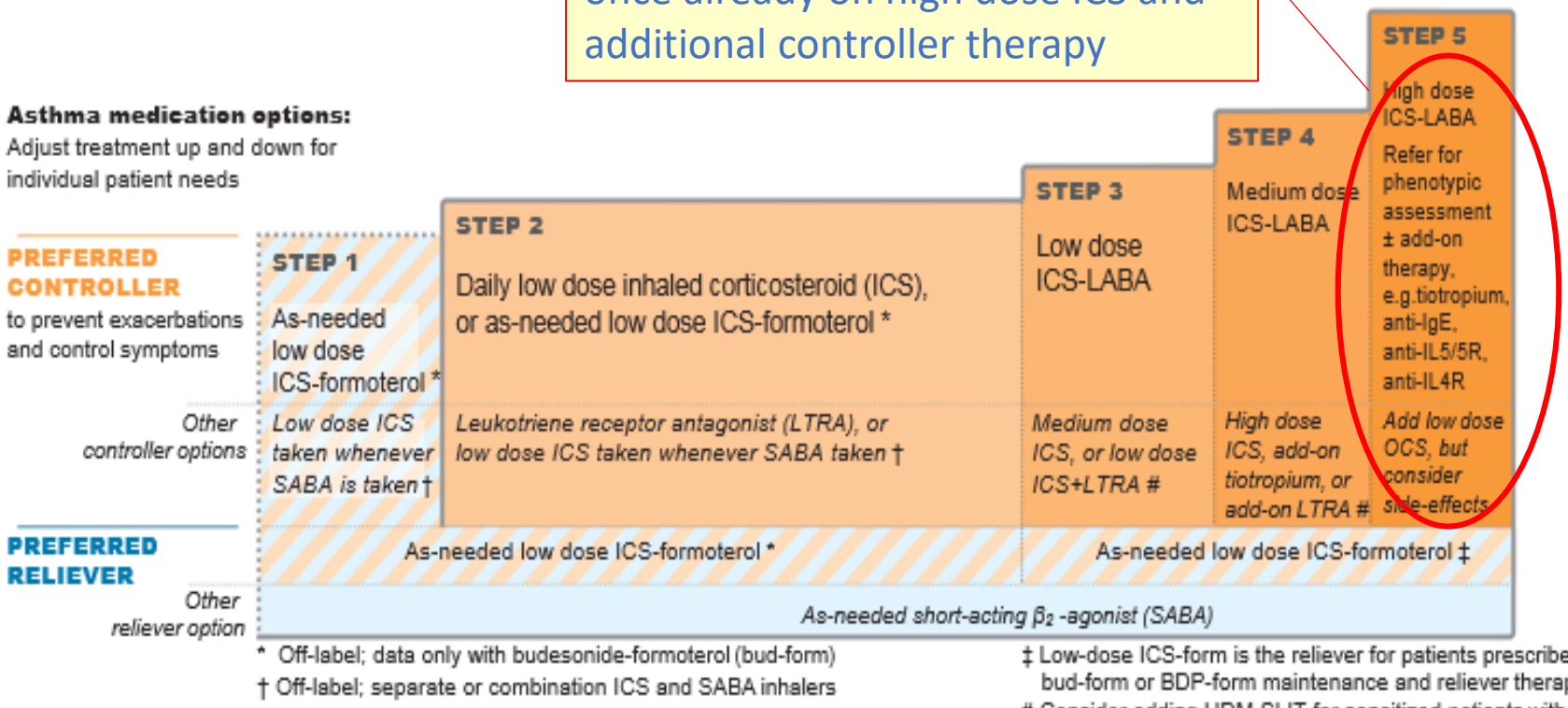
Anti-inflammatory

Bronchodilators

Global initiative for asthma 2019 (GINA 2019)

Adult asthma

Biologic therapy an option at Step 5 of asthma management guidelines once already on high dose ICS and additional controller therapy



* Off-label; data only with budesonide-formoterol (bud-form)

† Off-label; separate or combination ICS and SABA inhalers

‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy

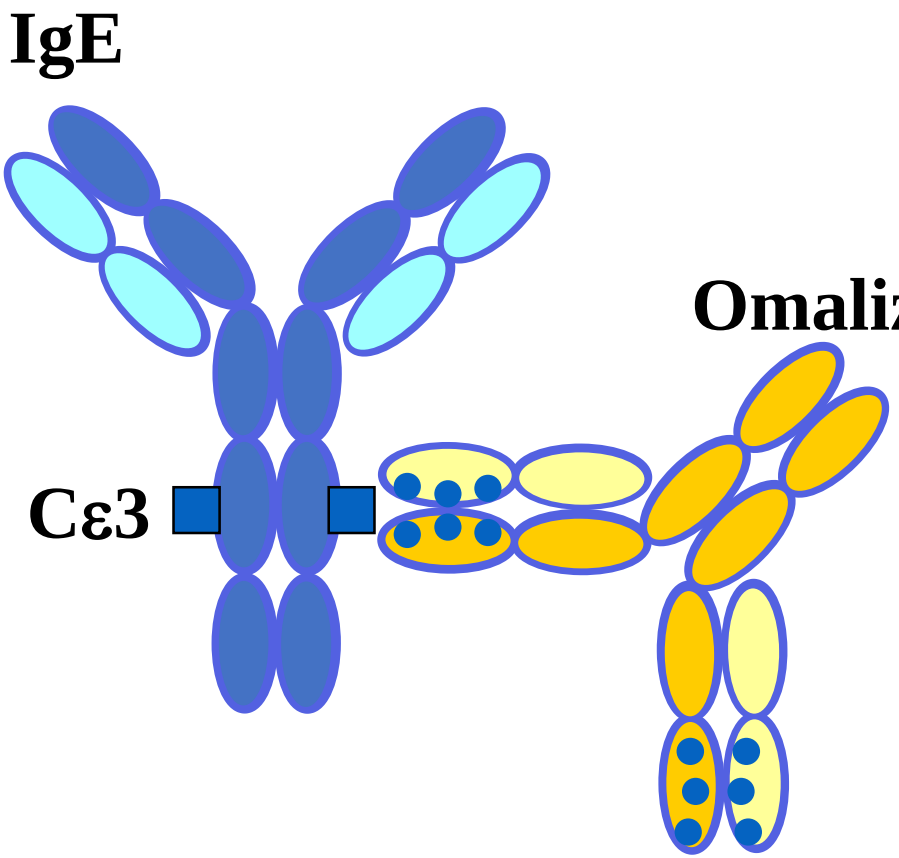
Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV >70% predicted

ICS, inhaled corticosteroid; LABA, long-acting β-agonist; LTRA, leukotriene receptor antagonists; OCS, oral corticosteroid; SABA, short-acting β2-agonist

Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2019. Available from: www.ginasthma.org (Accessed April 2019).

Omalizumab: Humanized monoclonal anti-IgE antibody

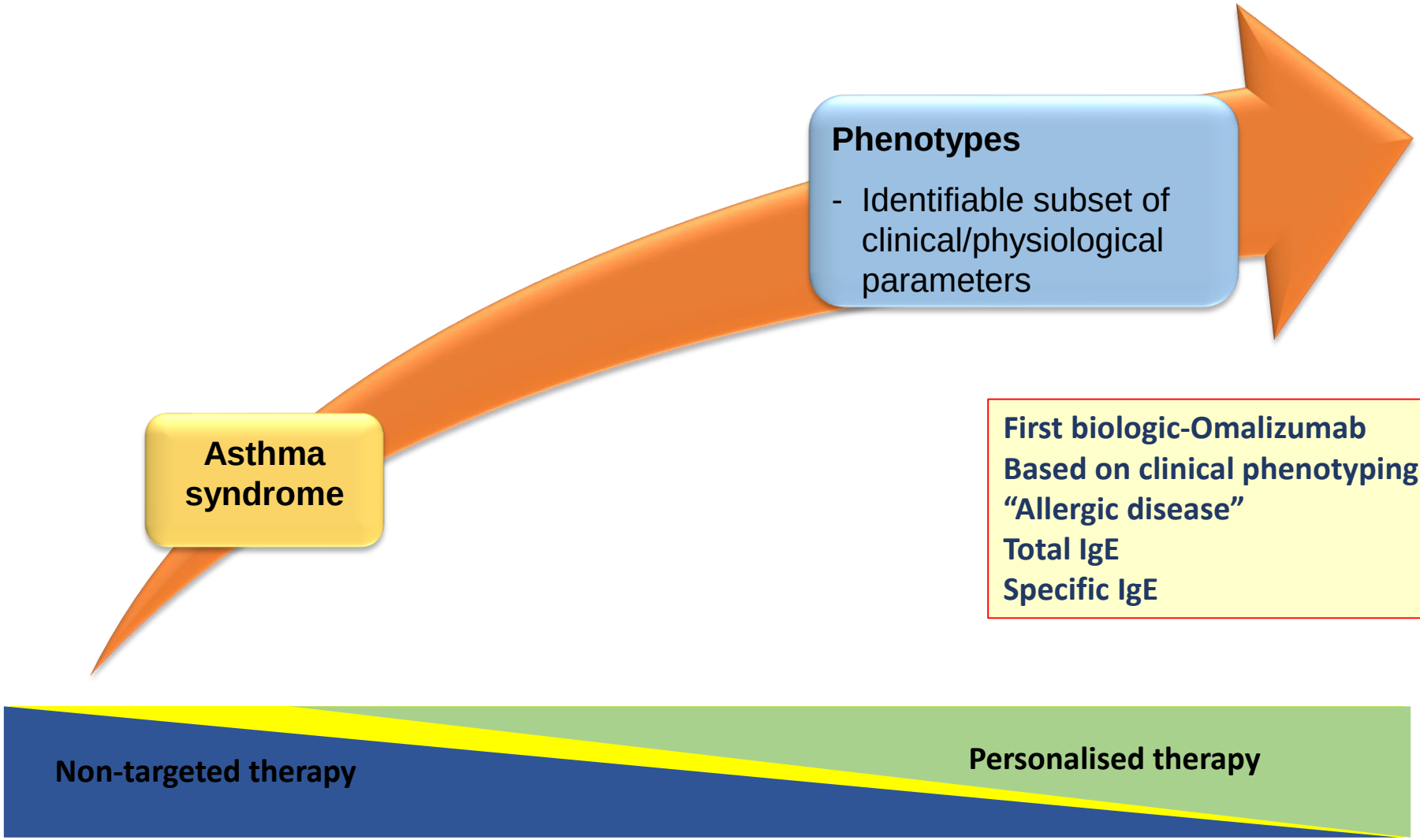
Xolair is indicated as add-on therapy to improve asthma control in adult and adolescent patients with severe persistent allergic asthma



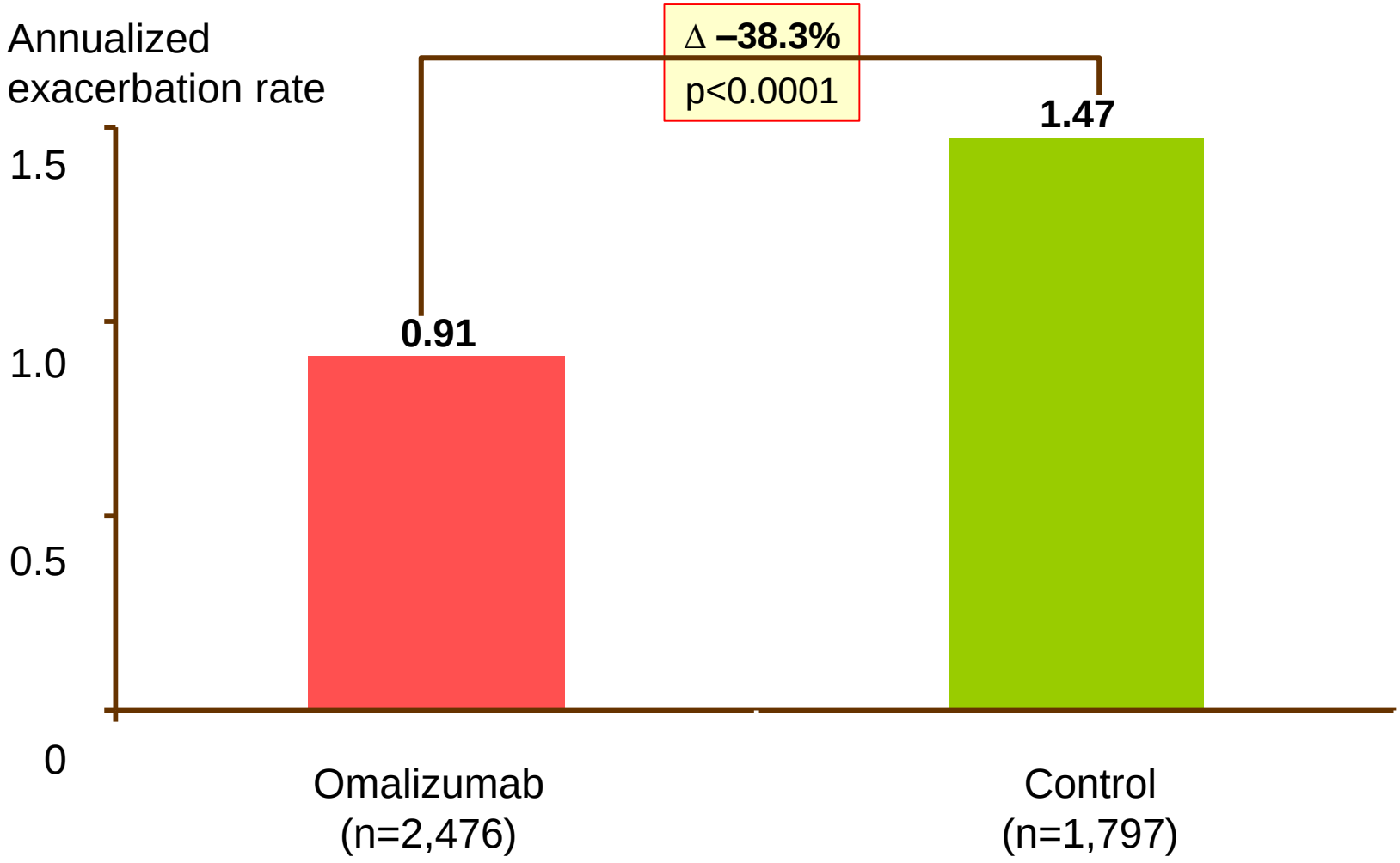
Biologic with the longest use –since October 2005

Binds to long chain of IgE and prevents IgE binding to Fc-Epsilon-R1 on cells

Severe asthma is a heterogeneous condition and biologic therapy has to be stratified

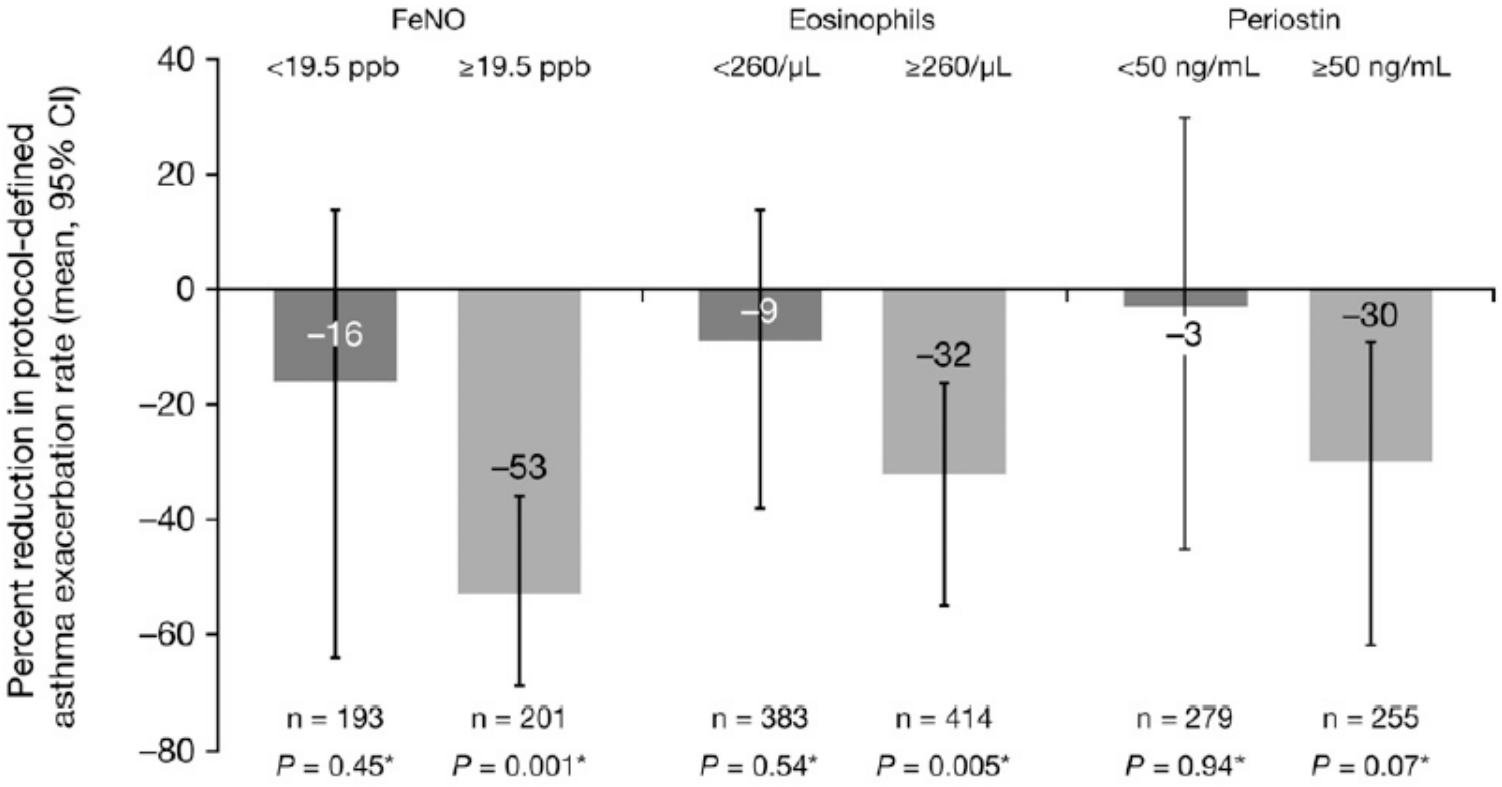


Omalizumab significantly reduces asthma exacerbation rate: pooled data



Bousquet J, et al. Allergy 2005

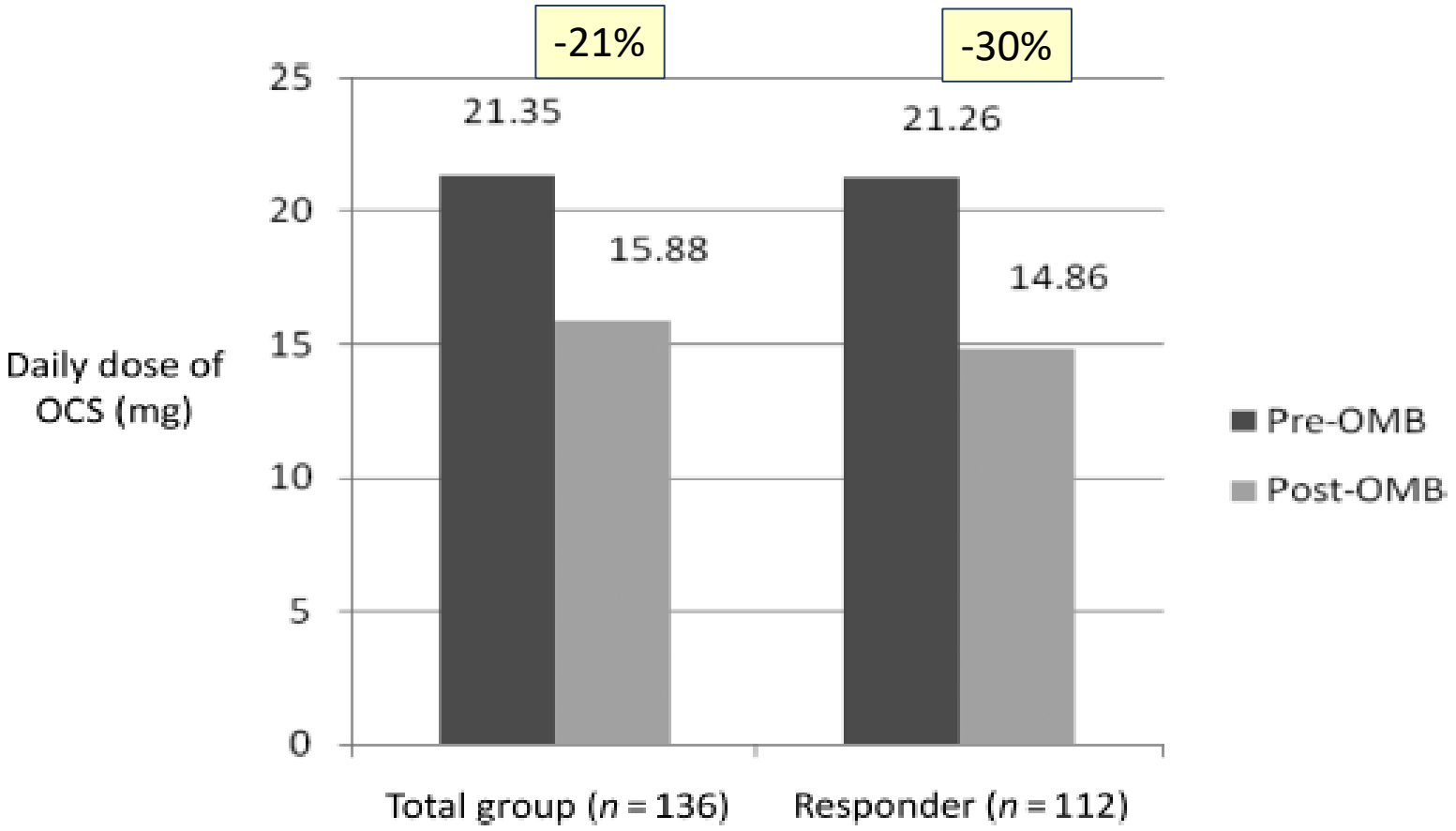
Omalizumab exacerbation reduction: Improved response with Th2 High Profiles



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 N et al AJRCCM 2013; 187: 804-11

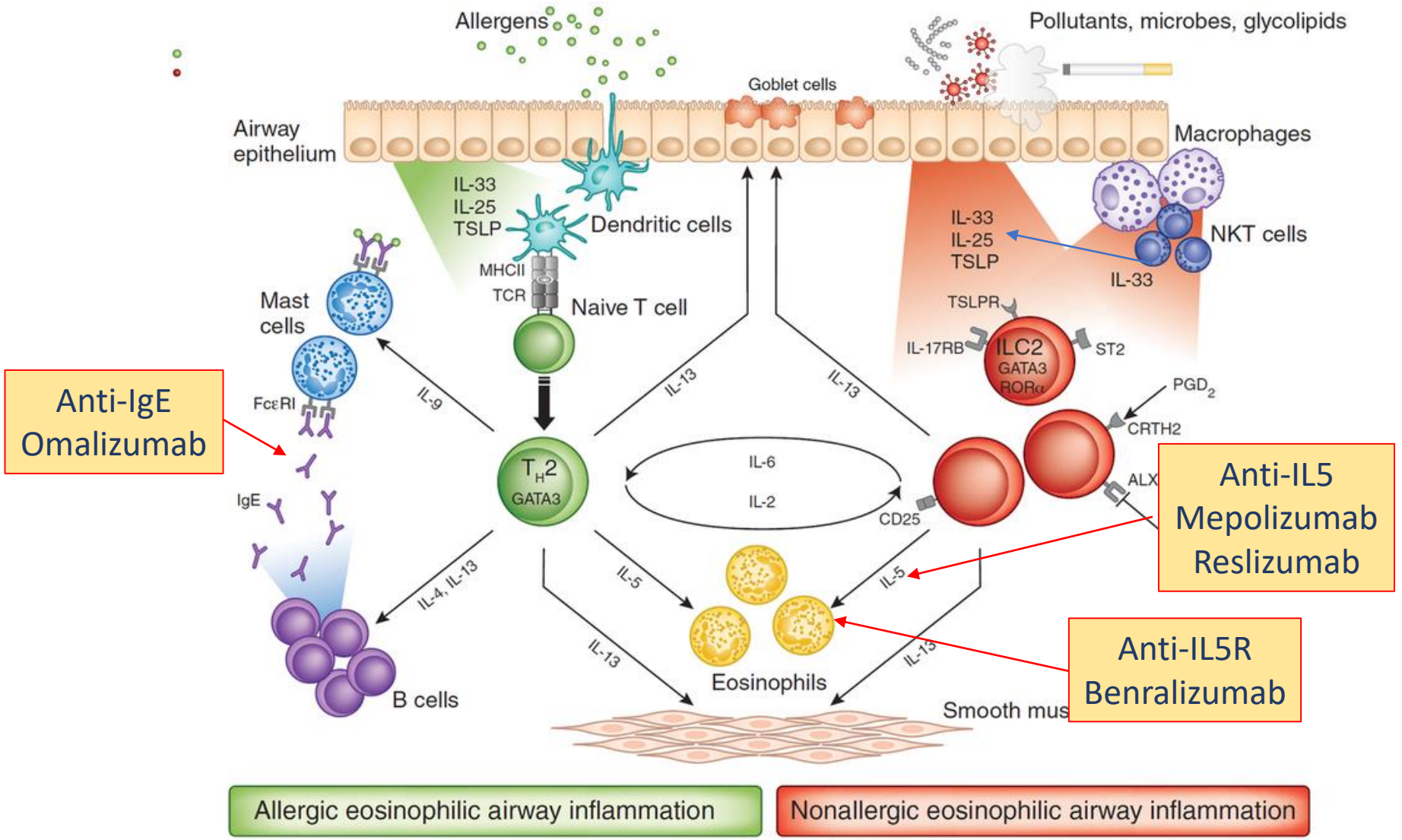
UK Apex study oral steroid sparing effect of Omalizumab



Daily dose of OCS (mg) in the 1 year pre- and post-OMB.

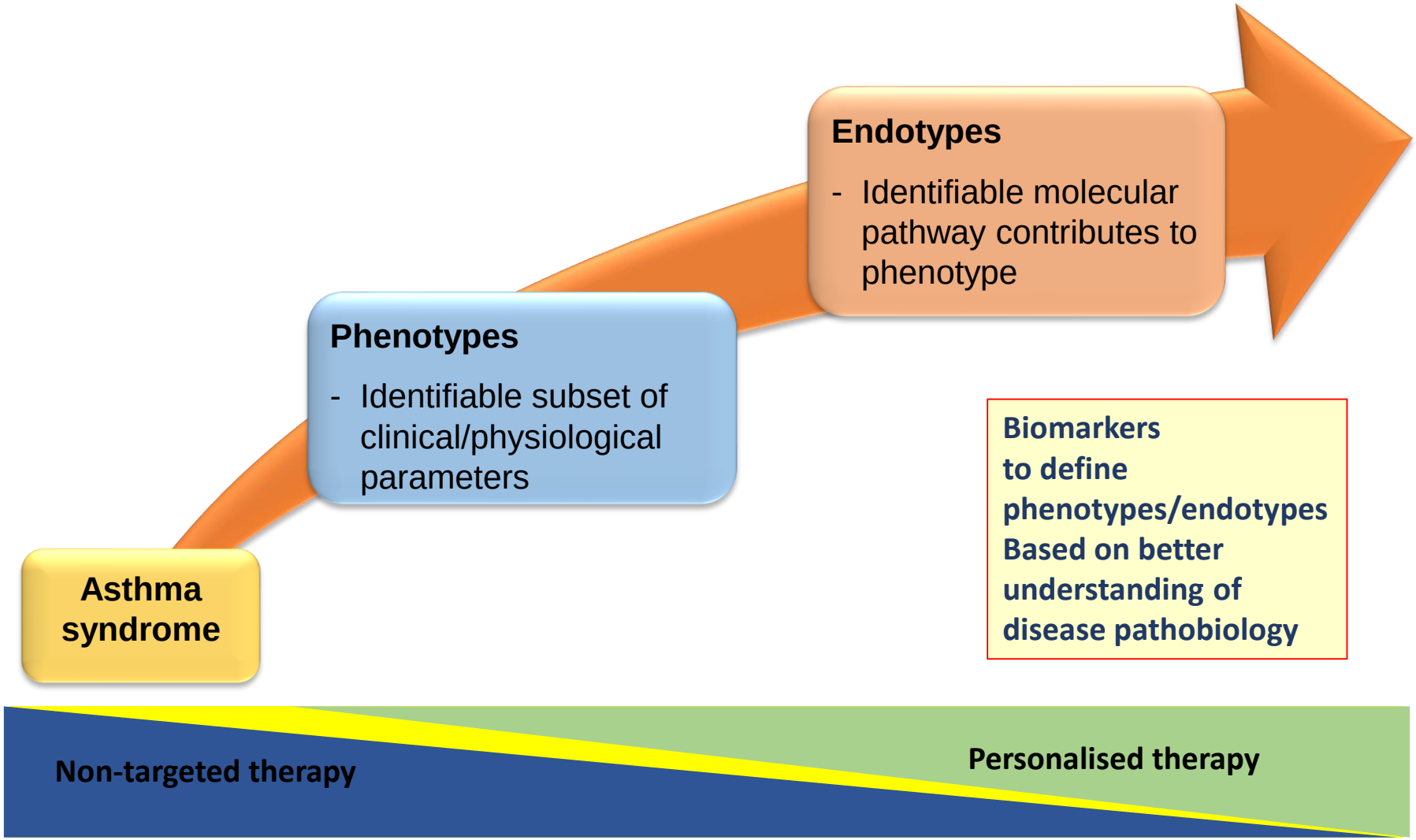
Barnes et al J Asthma 2013

Type 2 airway inflammation and biologic directed targets

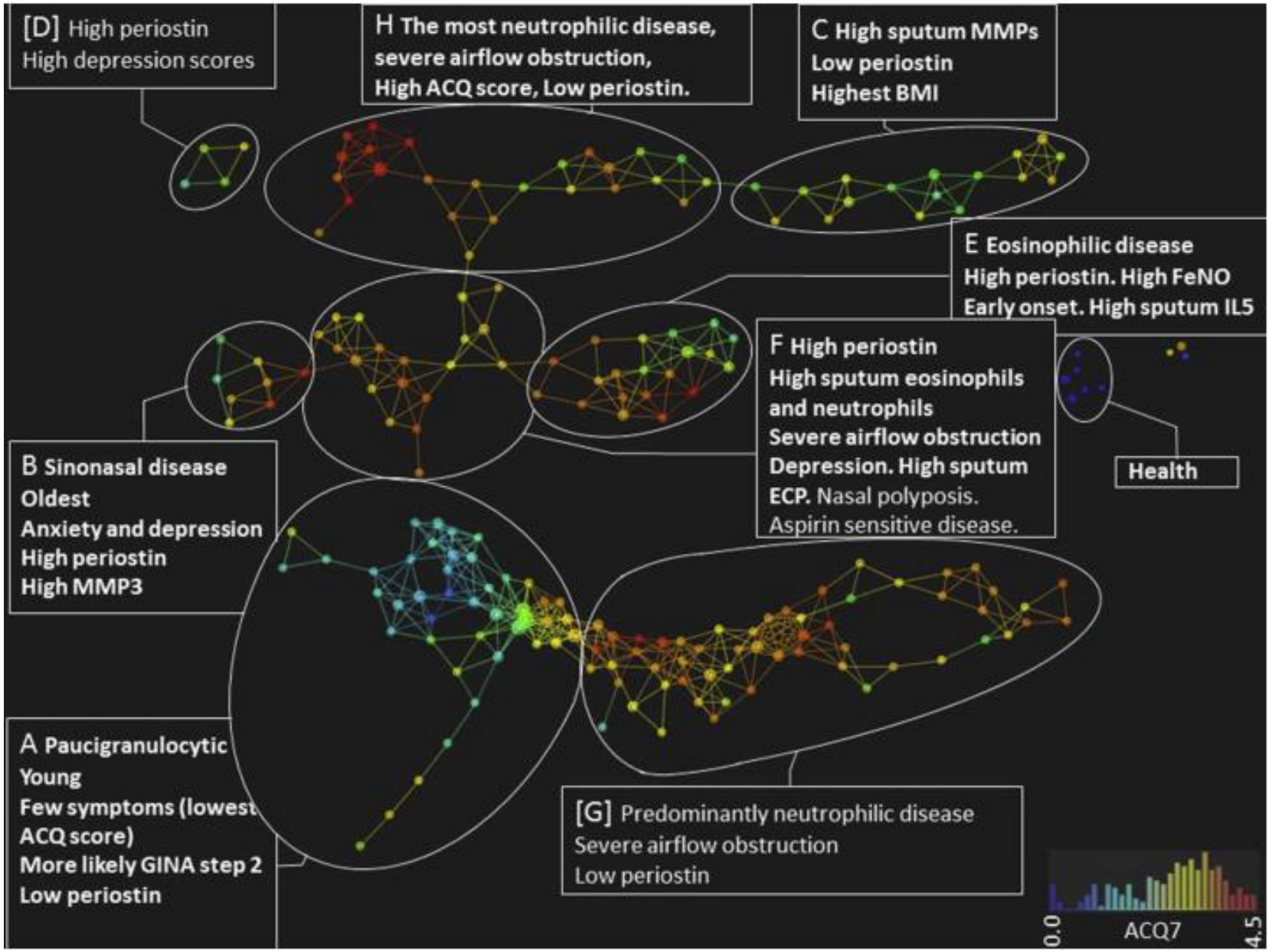


Brusselle et al. Ann Am Thorac Soc 2014:11(5);322-8

Severe asthma is a heterogeneous condition and biologic therapy has to be stratified



TDA endotyping of severe asthma



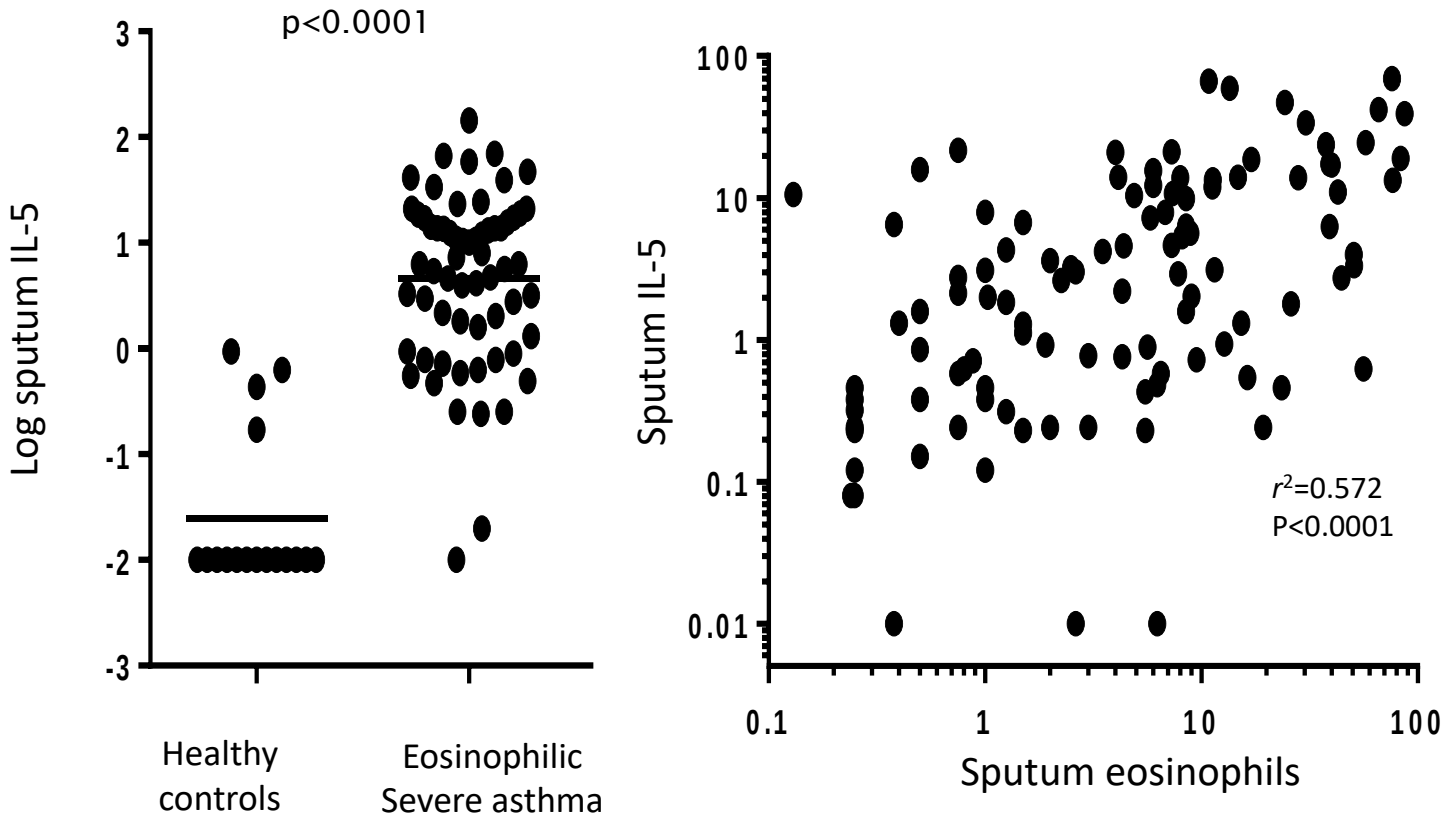
n=145
SA=121
HC=8
MA=9
ModA=7

74 Variables

- Clinical
- Physiological
- Questionnaire
- Sputum
- blood

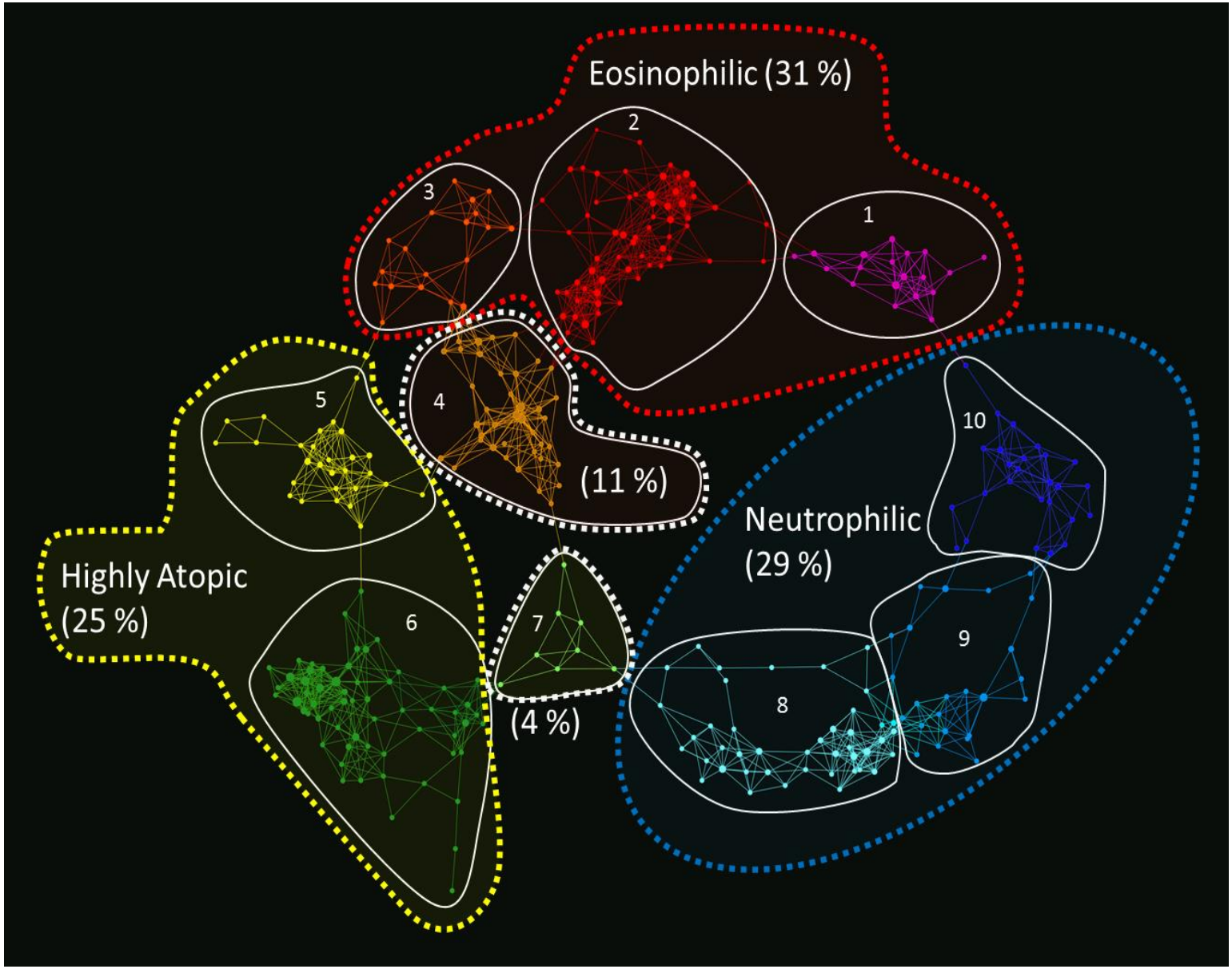
Hinks et al JACI 2016; 138: 61-75

Sputum IL-5 in severe asthma



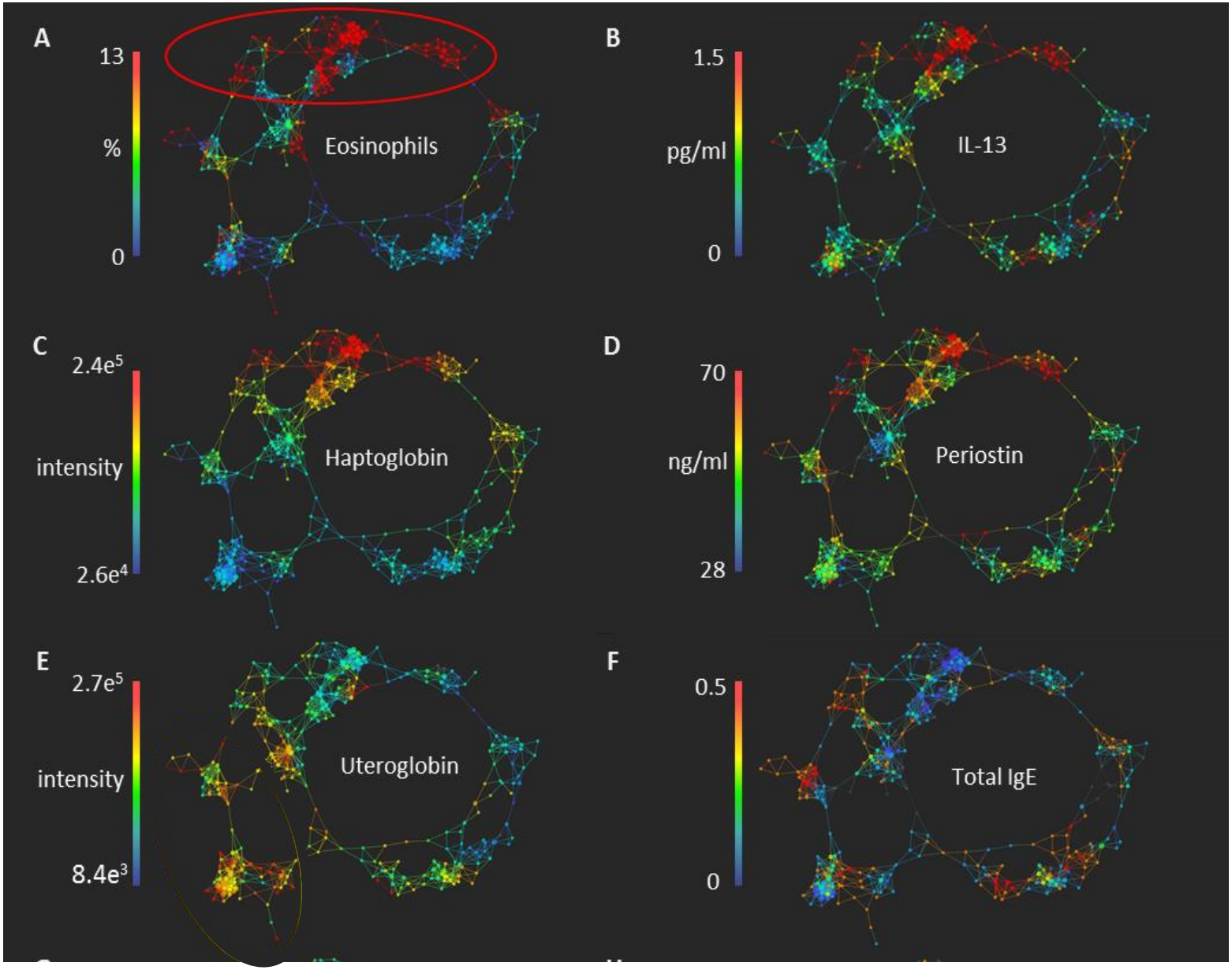
Hinks *et al*. JACI 2016; 138 (1): 61-75

Sputum proteomics sub-phenotyping in asthma



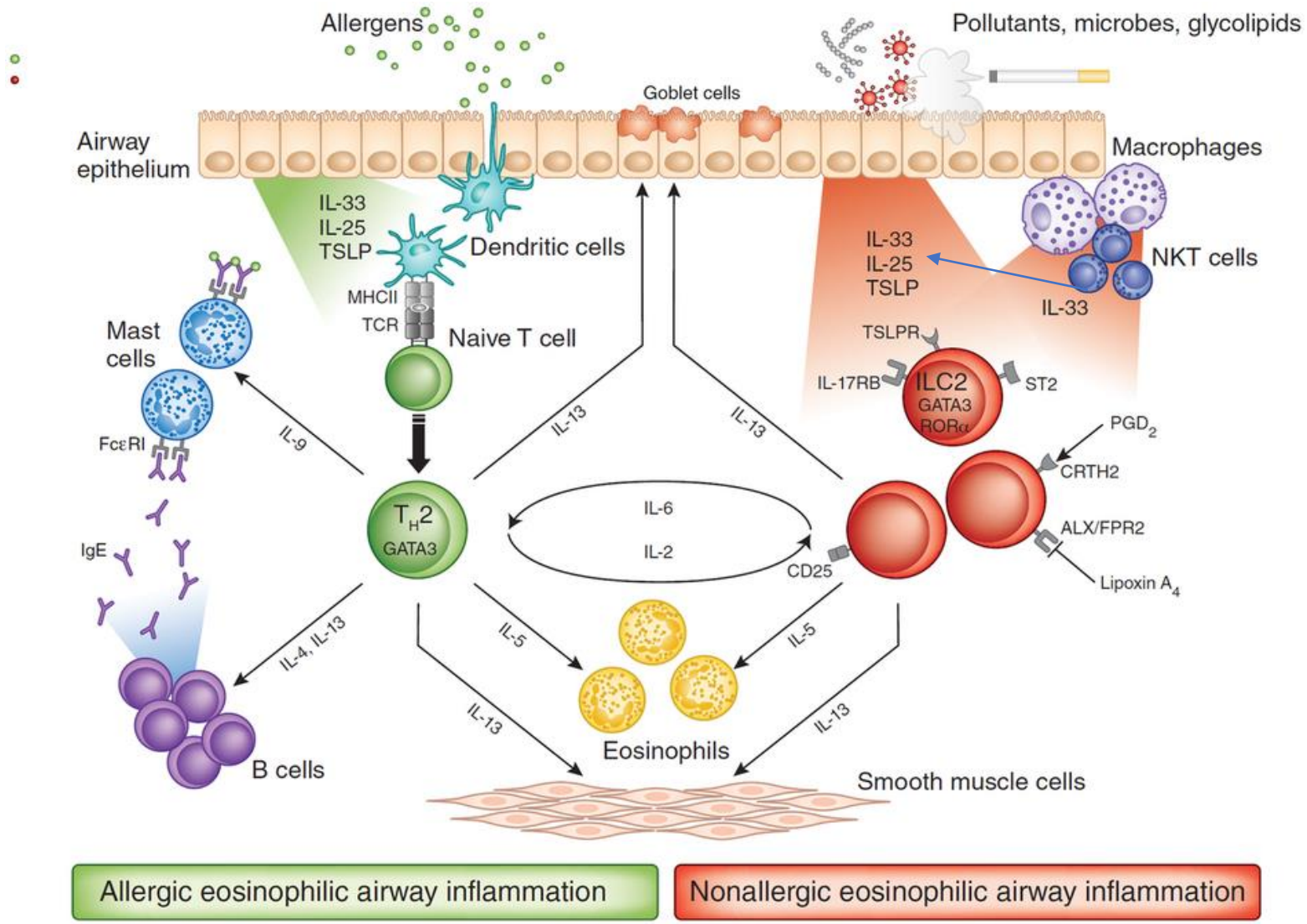
Schofield et al JACI 2019

Sputum proteomics sub-phenotyping in asthma



Schofield et al JACI 2019

Type 2 airway inflammation and biologic directed targets



Brusselle et al. Ann Am Thorac Soc 2014:11(5);322-8

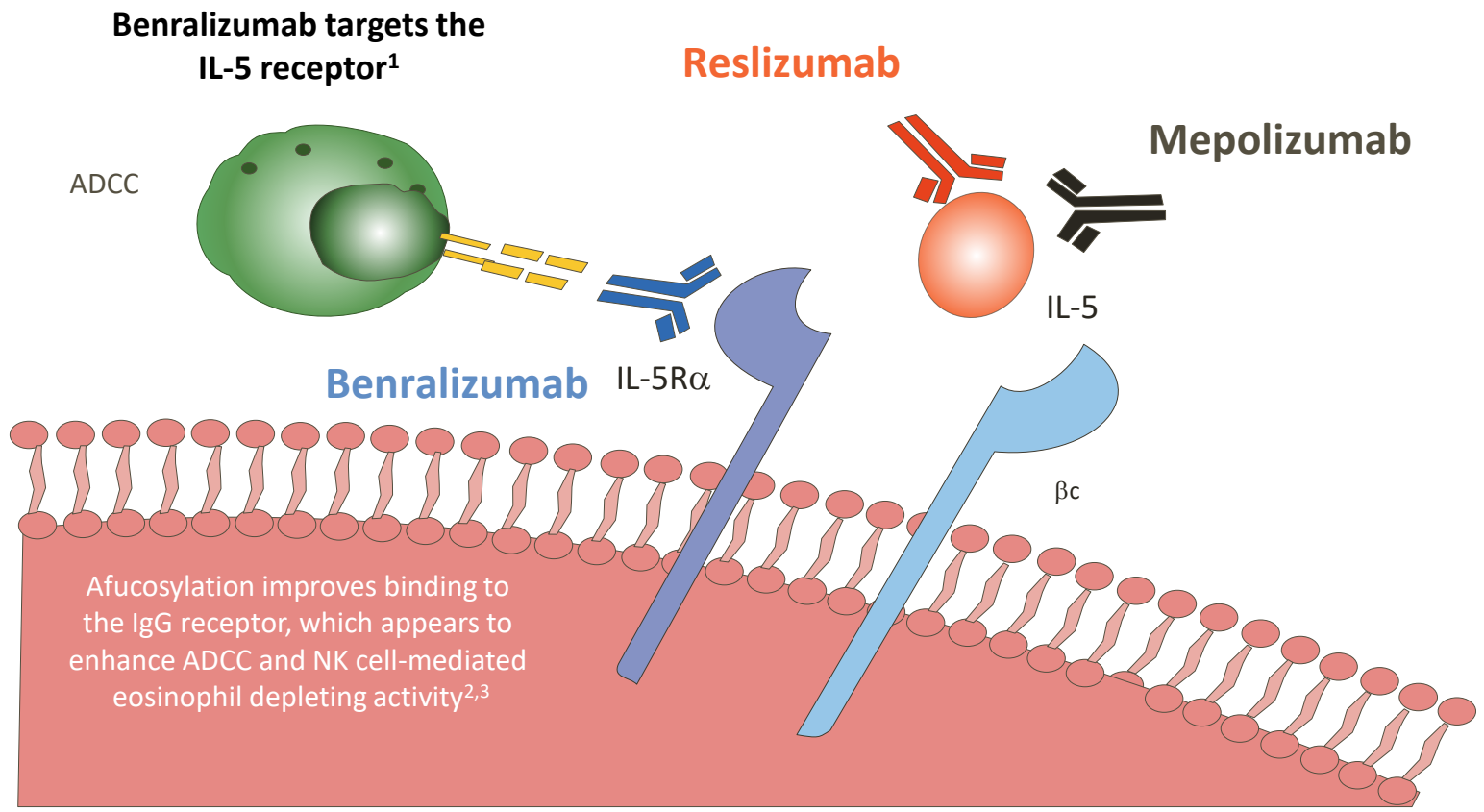
U-BIOPRED study transcriptome-associated clusters of severe asthma from sputum analysis

	TAC 1 (29%)	TAC 2 (21%)	TAC 3 (50%)
'Mechanisms'	**'T-2 associated'**	**'Inflammasome'**	**Mitochondrial oxidative stress**
Affymetrix microarray	IL33R, TSLPR, CCR3, IL3RA	IFN & TNF superfamily, CASP4	Metabolic genes
Gene set variation analysis	ILC2	NLPR3/DAMP-associated	Th17; OXPHOS; ageing
Protein (somalogic)	IL-16, periostin, serpin peptidase inhibitor 1, adiponectin, PAPPA	TNFAIP6, MIF, tyrosine kinase src	Cathepsin B, G
Blood eosinophils (/microL)	430	250	200
Sputum eosinophils (%)	30.9	0.6	1.0
FeNO (ppb)	29.5	22.0	27.5
Clinical features	Severe asthma Highest nasal polyps Oral OCS dependent Severe airflow obstruction	Moderate-to-severe asthma Moderate airflow obstruction High blood CRP levels More eczema	Moderate-to-severe asthma Mild airflow obstruction Lowest oral prednisolone Less frequent exacerbations

BIOPRED: BIOmarkers in PREDiction of respiratory disease outcomes; FeNO: exhaled nitric oxide fraction.

Kuo C-HS *et al. Eur Respir J* 2017;49:1602135.

Monoclonal antibody therapies licenced for severe eosinophilic asthma



ADCC= Antibody dependent cell cytotoxicity, NKK = natural killer cells, IL-5 = interleukin 5

1. Varricchi G, et al. *Curr Opin Allergy Clin Immunol*. 2016;16:186–200; 2. Ghazi A, et al. *Expert Opin Biol Ther.* 2012;12:113–118; 3. Kolbeck R, et al. *J Allergy Clin Immunol* 2010;125:1344–1353.

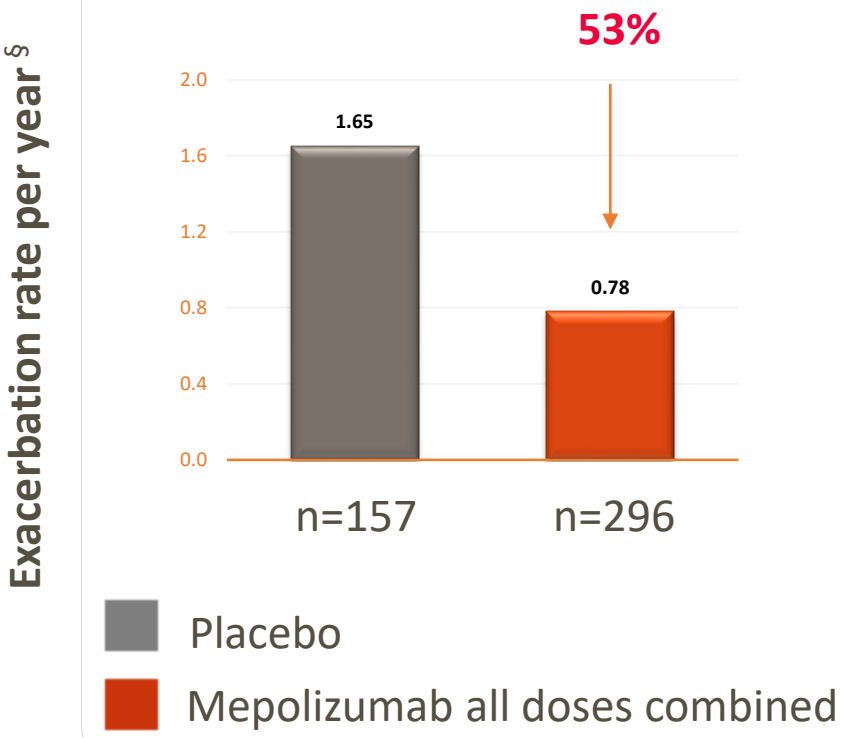
Mepolizumab: impact on asthma exacerbations

Eosinophilic asthma criteria: Peripheral blood eosinophil count of 150 cells/µl on entry or 300 cells/ µl in last year

MENSA[1]

≥ 150 cells/µL
≥ 2 exacerbations

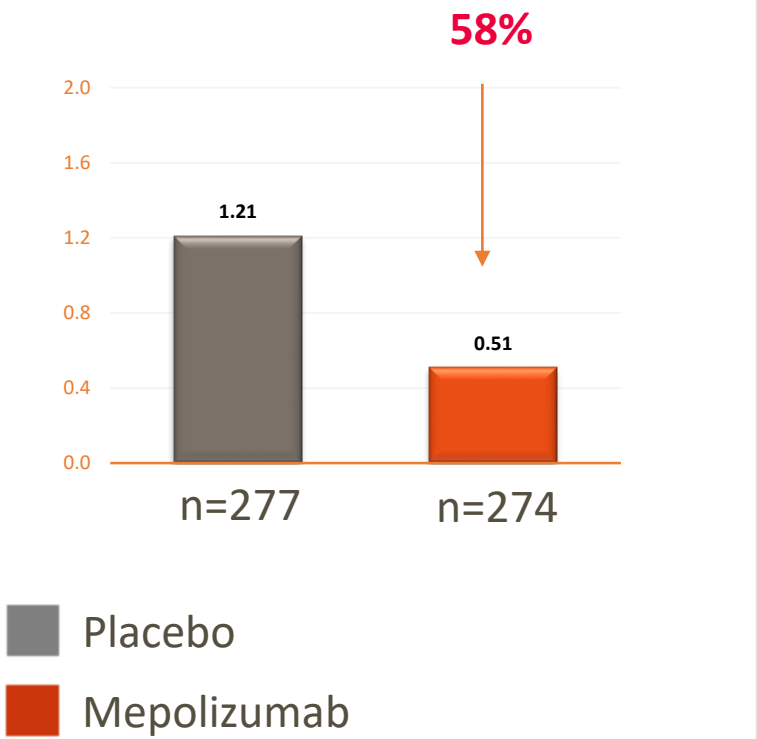
Reduction vs placebo at **32 weeks**



MUSCA[2]

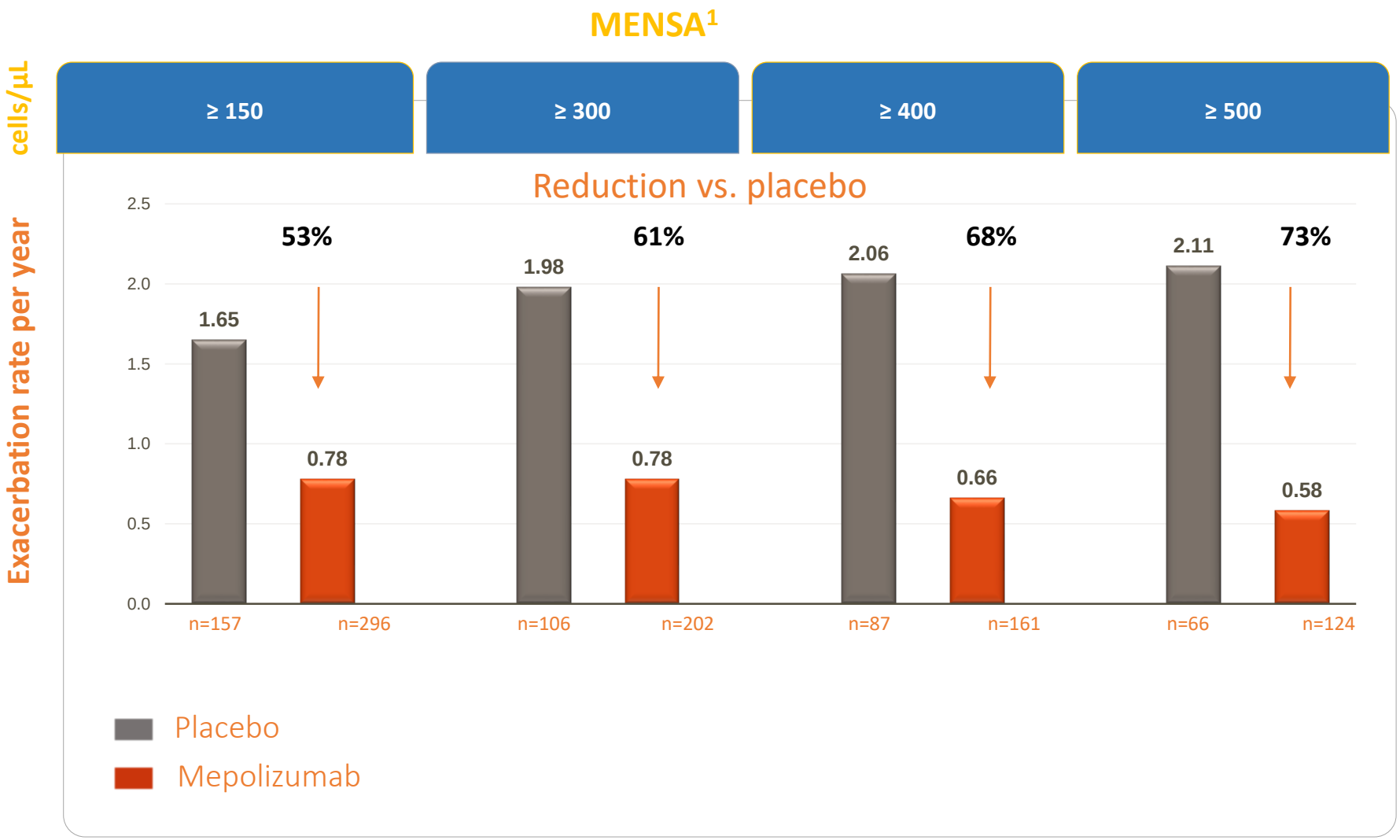
≥ 150 cells/µL
≥ 2 exacerbations

Reduction vs placebo at **24 weeks**



1. Ortega HG et al. Lancet Respir Med. 2016; 4(7): 549-556, 2. Chupp GL et al. Lancet Respir Med. 2017; 5(5): 390-400.

Blood eosinophils a predictive biomarker of response to Mepolizumab



1. Ortega HG, Yancey SW, Mayer B, et al. Lancet Respir Med. 2016;4(7):549-556

Consistency of influence of Mepolizumab in severe eosinophilic asthma

Eosinophilic asthma criteria: Peripheral blood eosinophil count of 150 cells/µl on entry or 300 cells/ µl in last year

Decrease in Exacerbations

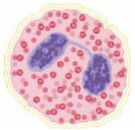
Study	Subjects on mepolizumab (n)	Dose and duration	Severe exacerbation reduction*
MENSA[1]	194	100mg SC for 32 weeks	53% *
MUSCA[2]	274	100mg SC for 24 weeks	58% *

*Improvement in quality of life **

MUSCA STUDY[2]: SGRQ
Treatment difference
(mepolizumab–placebo) 95% CI
–7.7 (–10.5, –4.9)
Responder analysis
Odds ratio (95% CI)
2.2 (1.6 to 3.2)

Severe eosinophilic asthma

MENSA STUDY[1]: SGRQ
Treatment difference
(mepolizumab–placebo) 95% CI
–7.0 (–10.2, –3.8)
Responder analysis
Odds ratio (95% CI)
2.1 (1.3 to 3.2)



*Improvement in FEV_1**

MENSA study[1]: 98 ml
MUSCA study[2]: 120ml

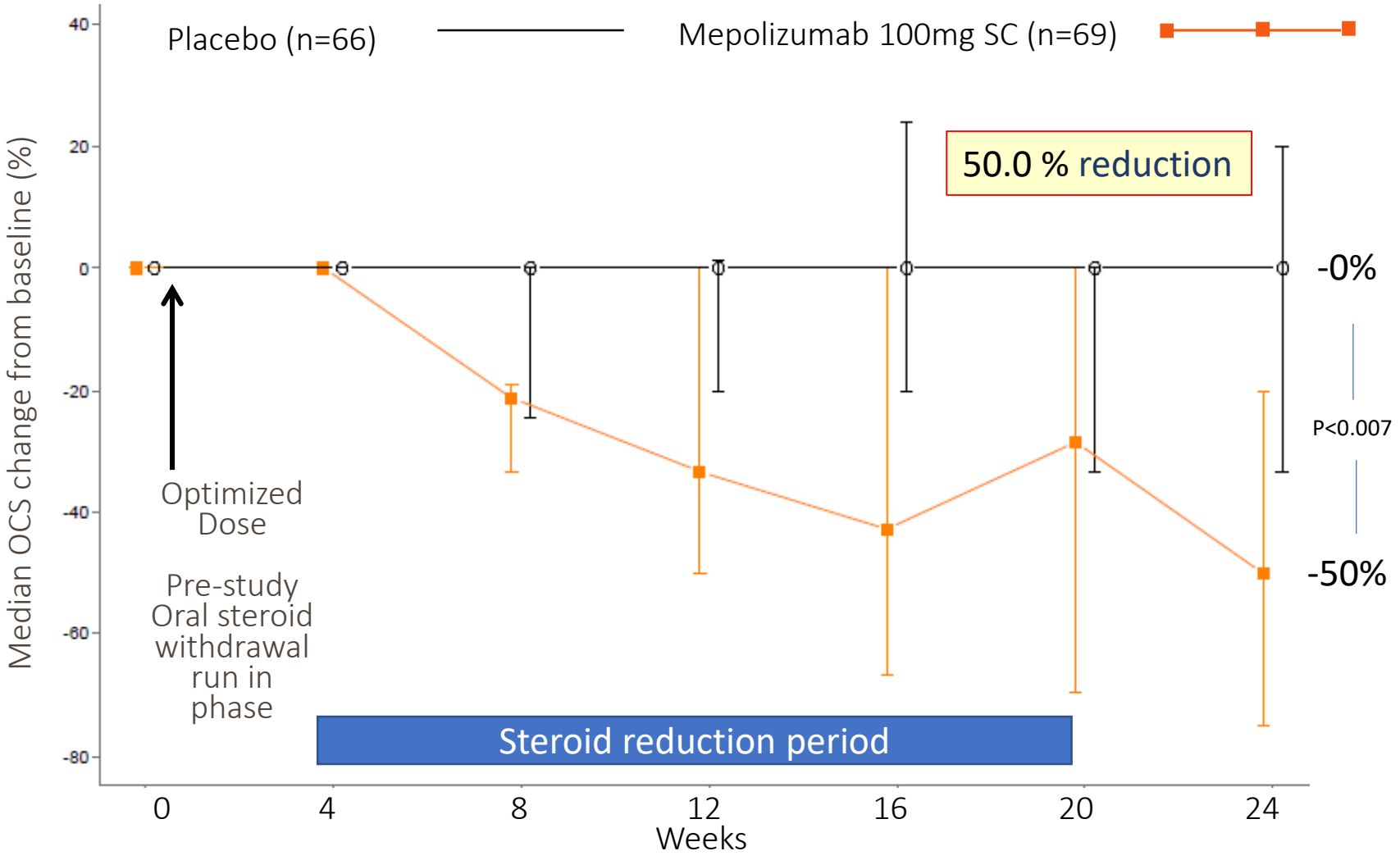
*Improvement in ACQ**

MENSA study[1]: - 0.44
MUSCA study[2]: - 0.40

* All impacts over and above that of placebo in randomised, placebo-controlled, double-blind trials

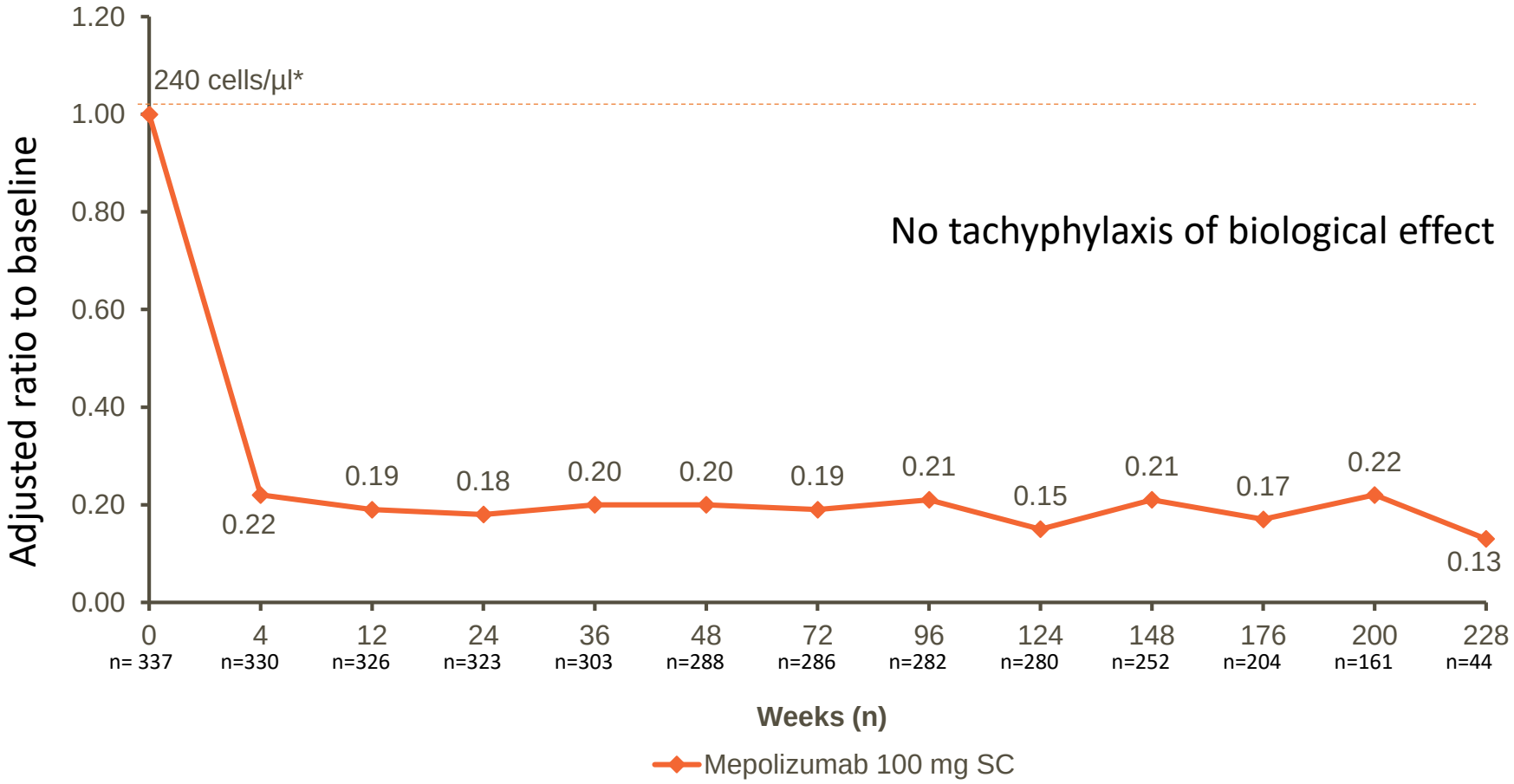
1. Ortega HG, et al. *N Engl J Med*. 2014;371:1198–207; 2. Chupp GL, et al. *Lancet Respir Med*. 2017;5:390–400;

Influence of Mepolizumab on oral steroid reduction in severe asthma



Bel et al. N Engl J Med. 2014;371:1189-1197.

Sustained biological effect of Mepolizumab in supressing but not completely depleting blood eosinophils



*Geometric Mean at baseline

Note: Where a result of Zero was recorded, a small value (i.e., minimum all non-missing results/2) was added prior to log transformation

SC: Subcutaneous

Khatri et al J Allergy Clin Immunol. 2018 2019 May;143(5):1742-1751

Real World Evidence

RWE for anti-eosinophil biologics in SEA

Mepolizumab

- **30 RWE studies** reported up to April 2019†
- Includes the **Temporary Authorisation for Utilisation** (ATU) study, the **Australian Mepolizumab Registry** and the ongoing global **REALITI-A** study[1–3]

Benralizumab

- One RWE study reporting on 13 patients[4]

Reslizumab

- Several small, single-centre RWE studies have been presented[5,6]

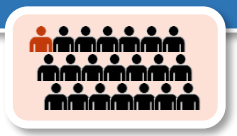
* As of the 26 September 2019 – studies identified from a top-level search of PubMed and published abstracts only; † Based on a GSK-initiated search of studies of mepolizumab at licensed doses in PubMed and abstracts from key respiratory congresses. SEA= severe eosinophilic asthma, RWE= Real world evidence

1. Taillé C, et al. ERS 2019. #PA1654; 2. Harvey ES, et al. ERS 2019. #PA541; 3. Harrison T, et al. ERS 2019. #OA2104; 4. Pealia C, et al. *Pulm Pharmacol Ther.* 2019;58:101830; 6. ClinicalTrials.gov. NCT04022447 Dupilumab for Severe Asthma in a Real Life Setting (DUPI-France). 6 August 2019. Available at: www.clinicaltrials.gov/ct2/show/NCT04022447 [accessed October 2019]; 5. Marth K, et al. ERS 2018. #OA3568; 6. Pinilla KAO, et al. *J Allergy Clin Immunol*. 2019;143:AB99

Efficacy vs effectiveness

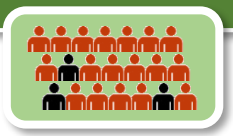
Clinical Trials

Efficacy RCTs[1]
Double-blind
Double-dummy
Strict inclusion criteria
Exclusions
Adherence encouraged
Frequent reviews
Drugs provided



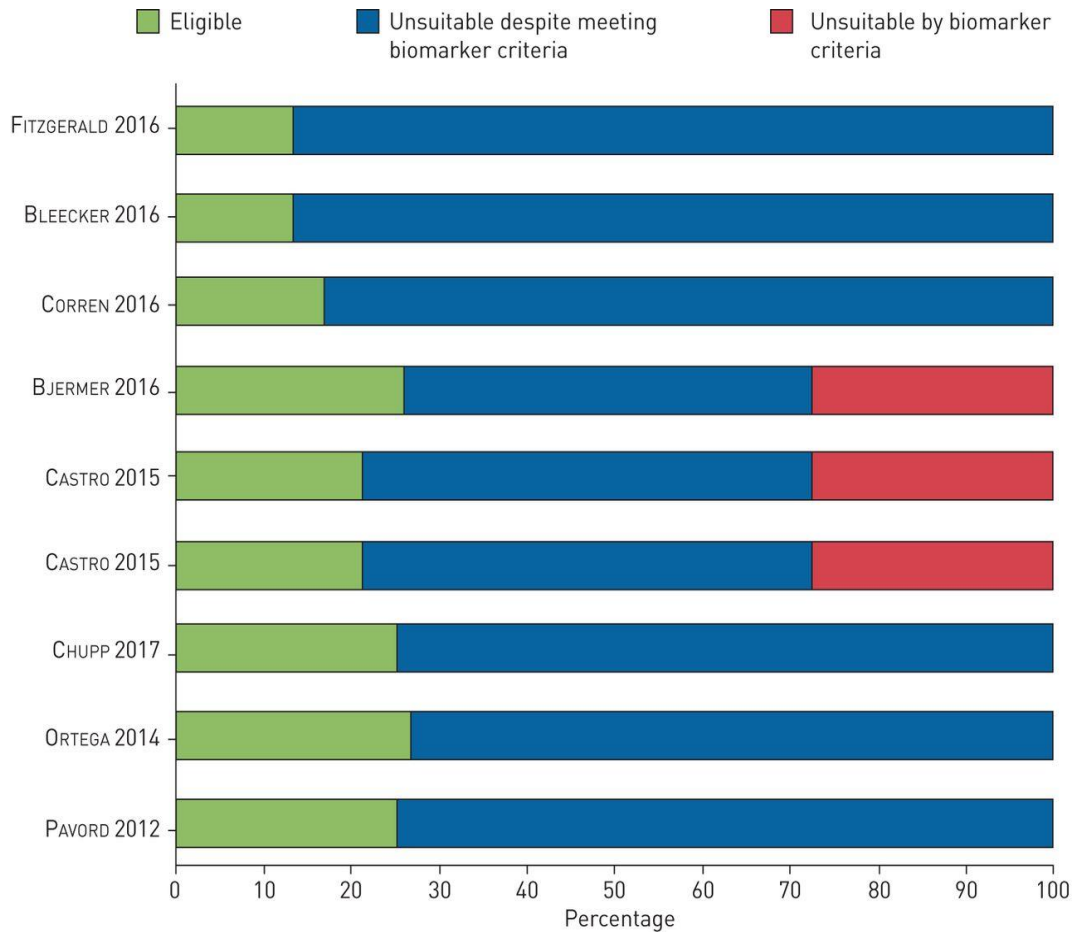
Real world studies

Clinical Effectiveness[2,3]
Open-label
Broad population
All comers
Co-morbid included
Set in normal care
No extra review
Drugs prescribed and collected in usual way



1. The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH harmonised tripartite guideline: Statistical principles for clinical trials E9. 5 February 1998. Available at: www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf [accessed May 2018]; 2. Godwin M, et al. *BMC Med Res Methodol.* 2003;3:28; 3. Singal AG, et al. *Clin Transl Gastroenterol.* 2014;5:e45.

Trial eligibility for phase III interleukin IL-5/5R biologics in severe eosinophilic asthma

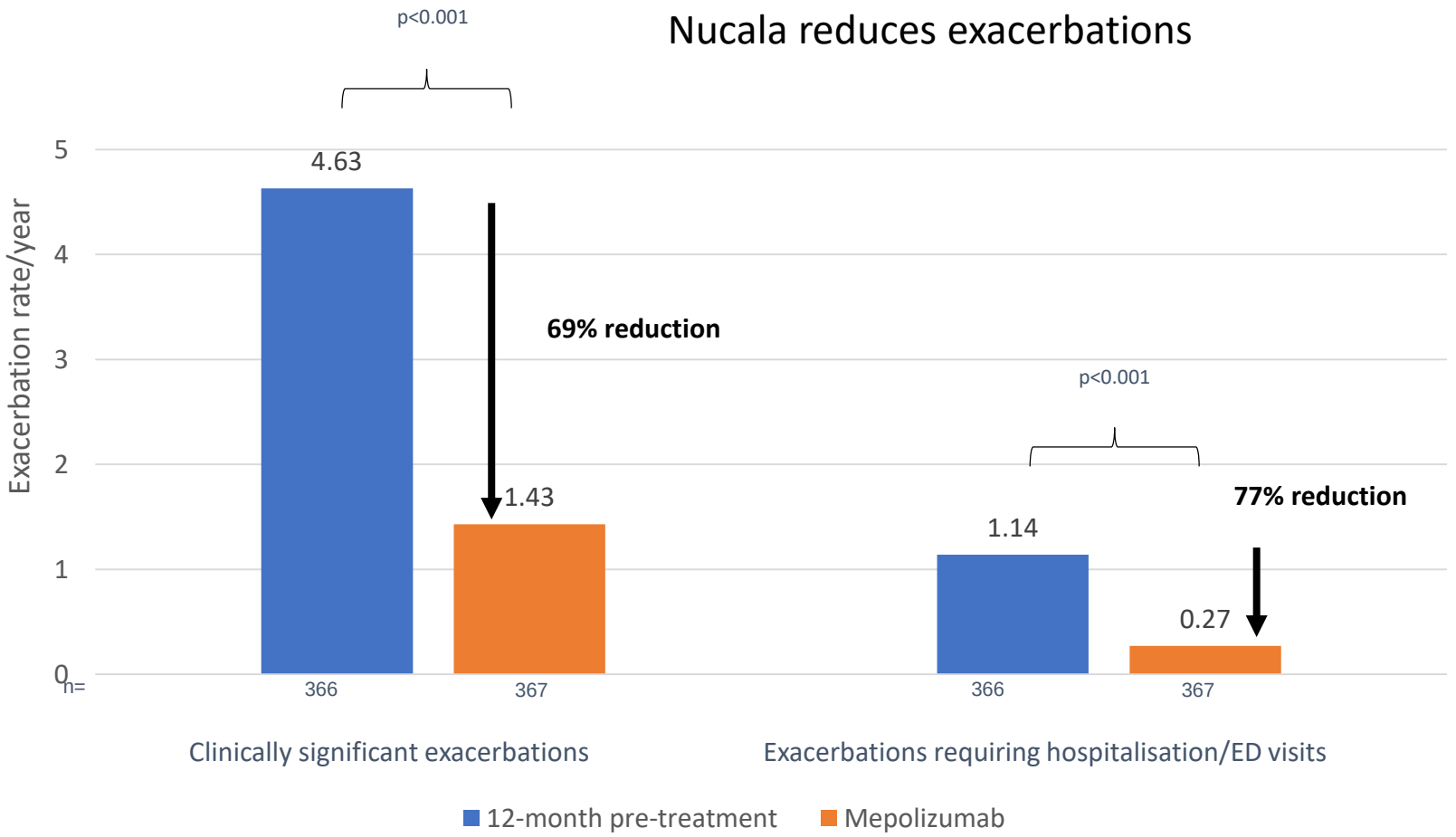


78.9% (73.2–86.6%) of patients with severe eosinophilic asthma would have been excluded from participation in the phase III licensing trials of IL-5/5R targeted treatments

Similar effect with an eosinophilic population defined by ≥2% or ≥3% sputum or by blood eosinophil counts of ≥150 cells/µL

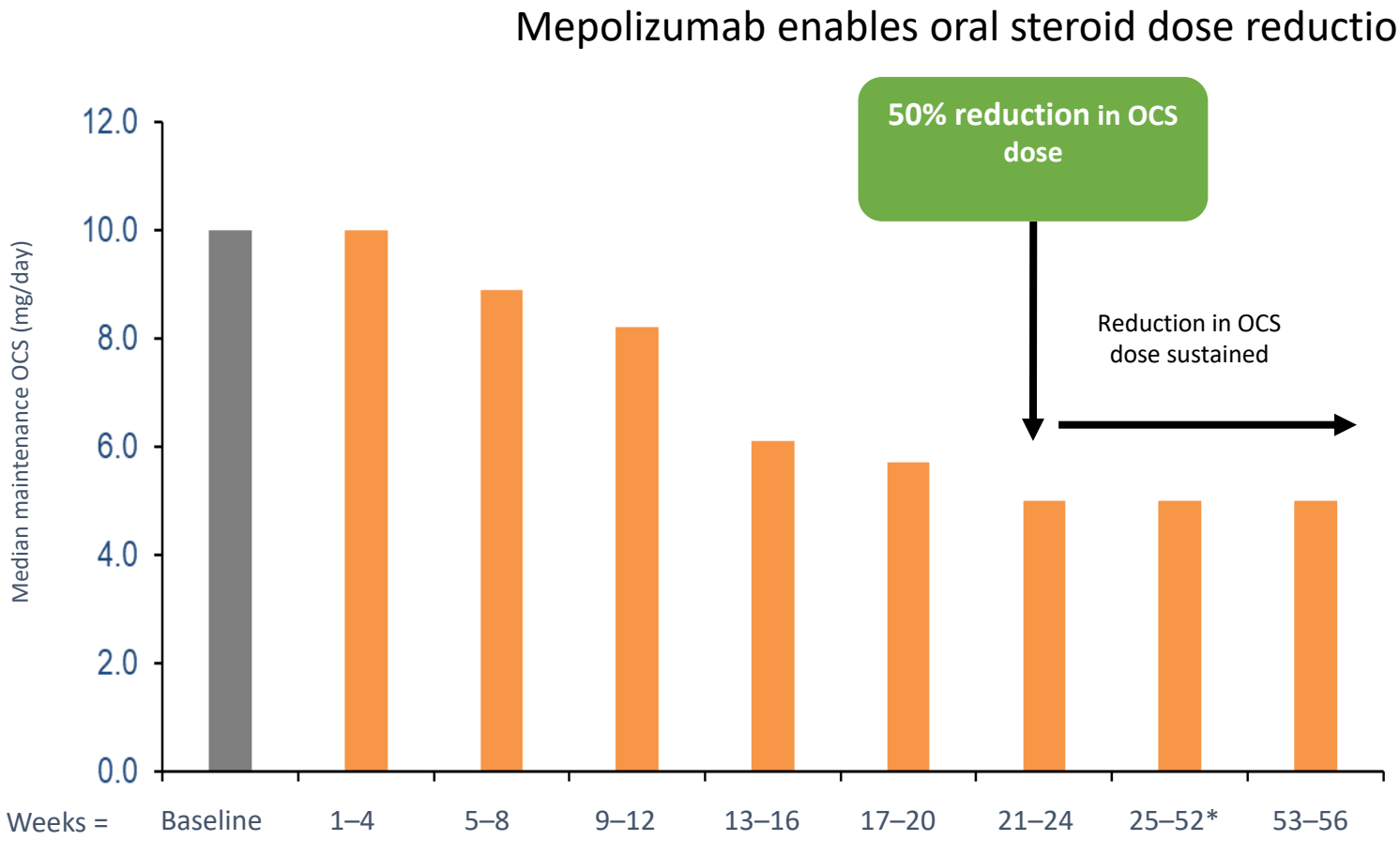
Brown T et al. ERJ 2018

Real world evidence: REALITI-A (n=368)



Harrison T, Canonica GW, Gemzoe K, et al. Effectiveness and safety of mepolizumab in real-world clinical practice: The REALITI-A study. ERS 2019. #OA2104.

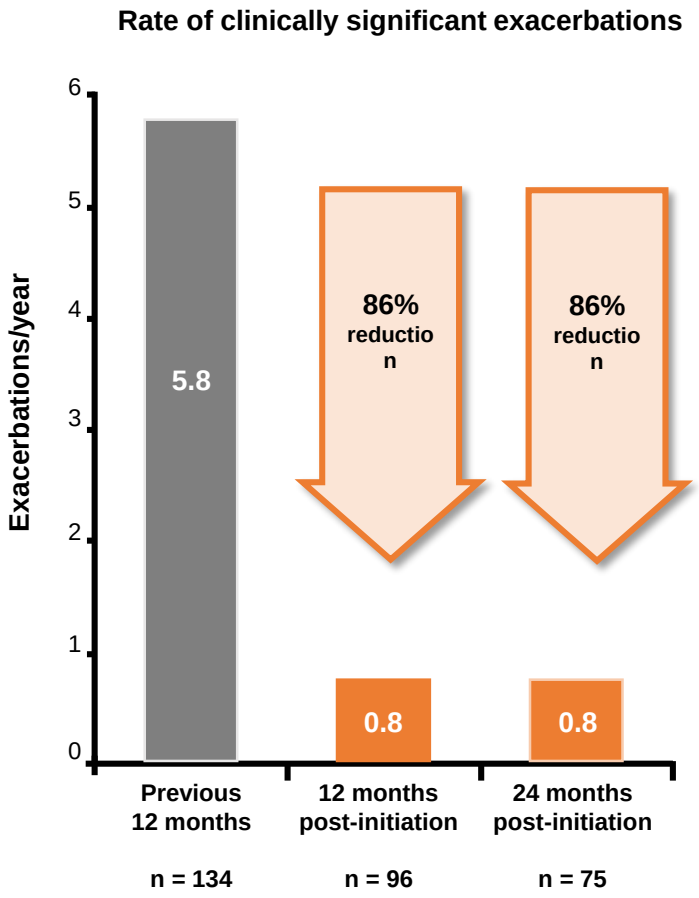
Real world evidence: REALITI-A (n=159)

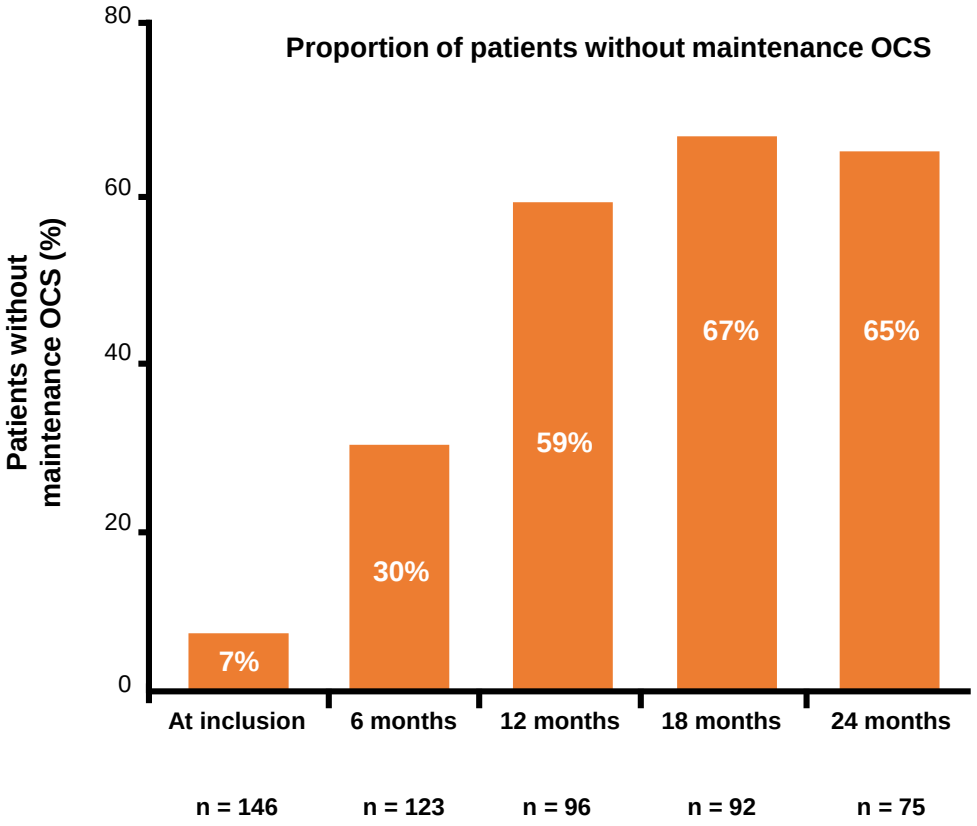


* Median OCS remained at 5.0 mg/day for all assessment time periods from weeks 25 to 52.

Harrison T, Canonica GW, Gemzoe K, et al. Effectiveness and safety of mepolizumab in real-world clinical practice: The REALITI-A study. ERS 2019. #OA2104.

Real world evidence: French Temporary Authorisation for Utilisation (ATU) Exacerbation and OCS use reduction

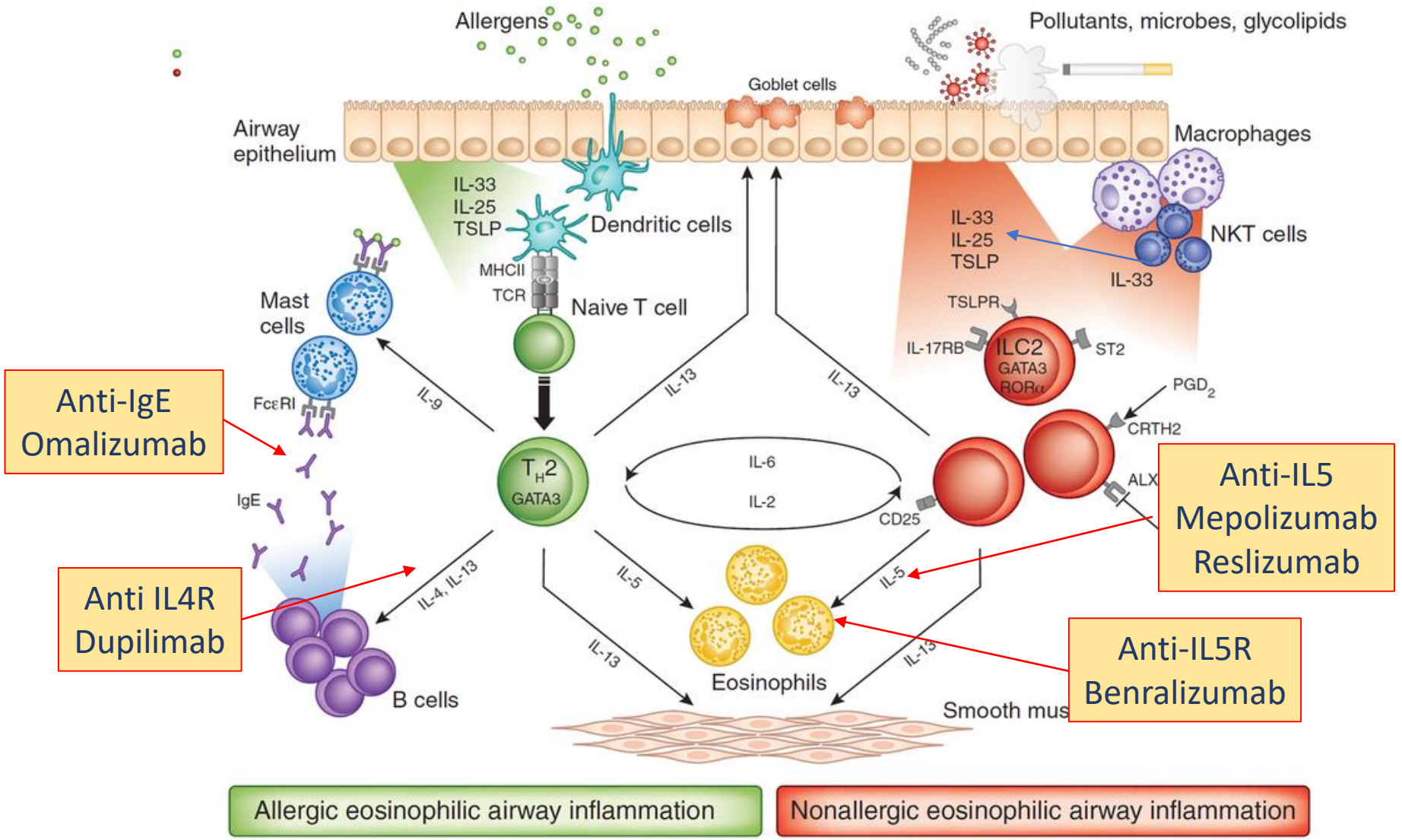




.

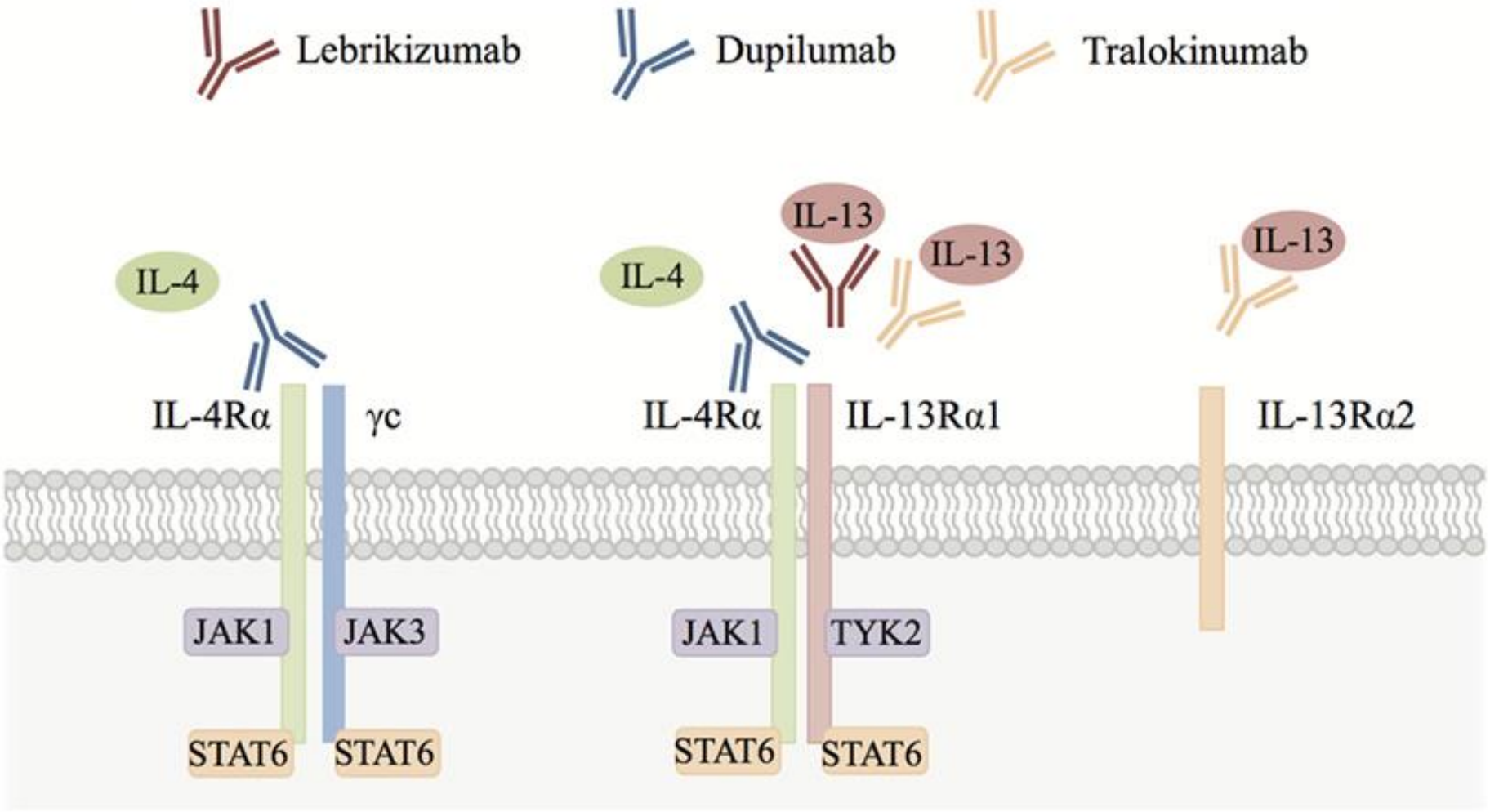
Taillé C, Chanez P, Devouassoux G, et al. Real-life experience with mepolizumab in the French early access program for severe eosinophilic asthma. ERS 2019. #PA1654.

Type 2 airway inflammation and biologic directed targets

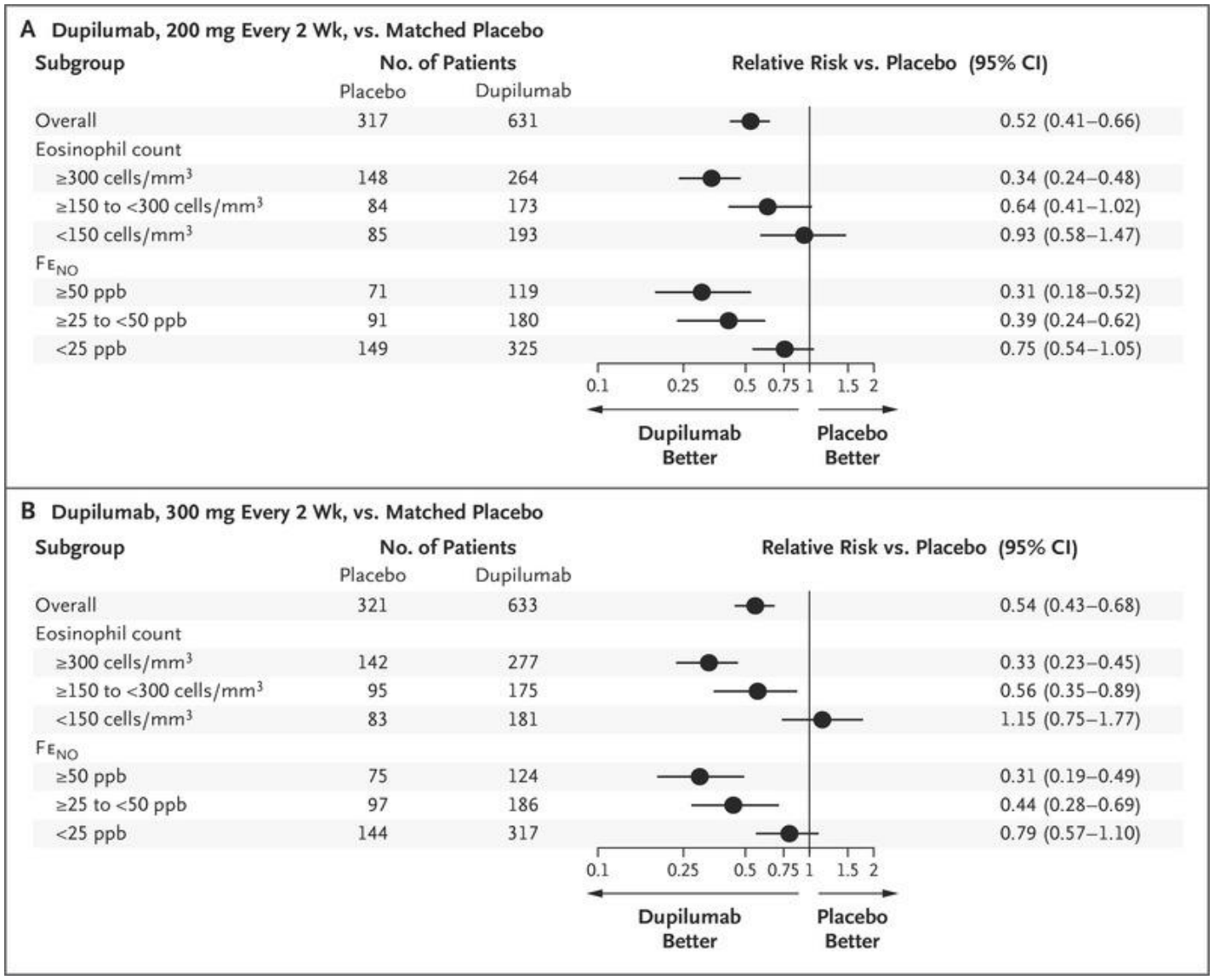


Brusselle et al. Ann Am Thorac Soc 2014:11(5);322-8

Biologics against IL-4 and IL-13 in severe asthma



Influence of Dupilimab on disease exacerbation in asthma according to baseline type 2 inflammatory severity



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

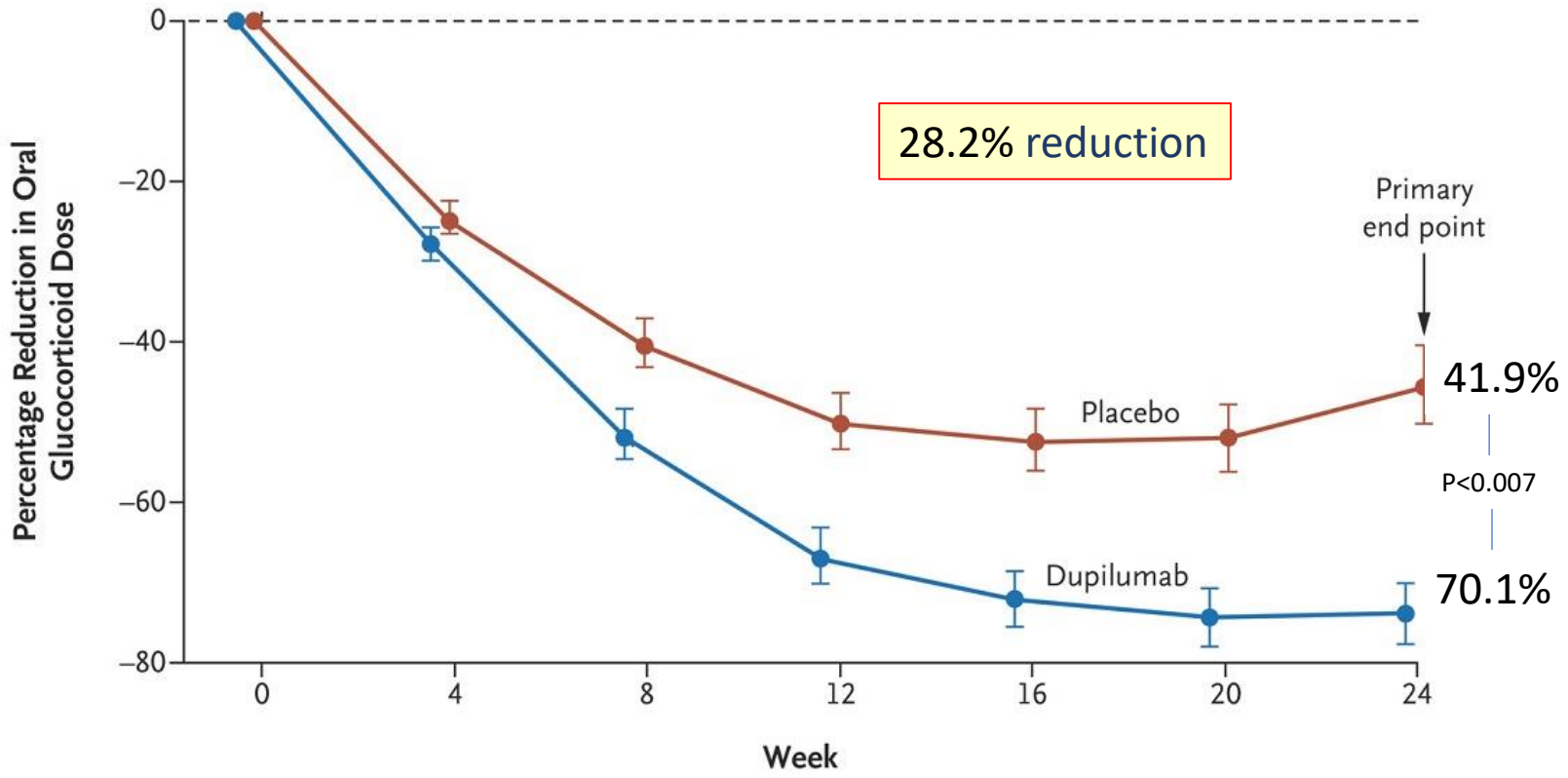
Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	317	631	0.52 (0.41–0.66)
Eosinophil count			
≥300 cells/mm³	148	264	0.34 (0.24–0.48)
≥150 to <300 cells/mm³	84	173	0.64 (0.41–1.02)
<150 cells/mm³	85	193	0.93 (0.58–1.47)
Fe_{NO}			
≥50 ppb	71	119	0.31 (0.18–0.52)
≥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 et al NEJM 2018; 378:2486-2496

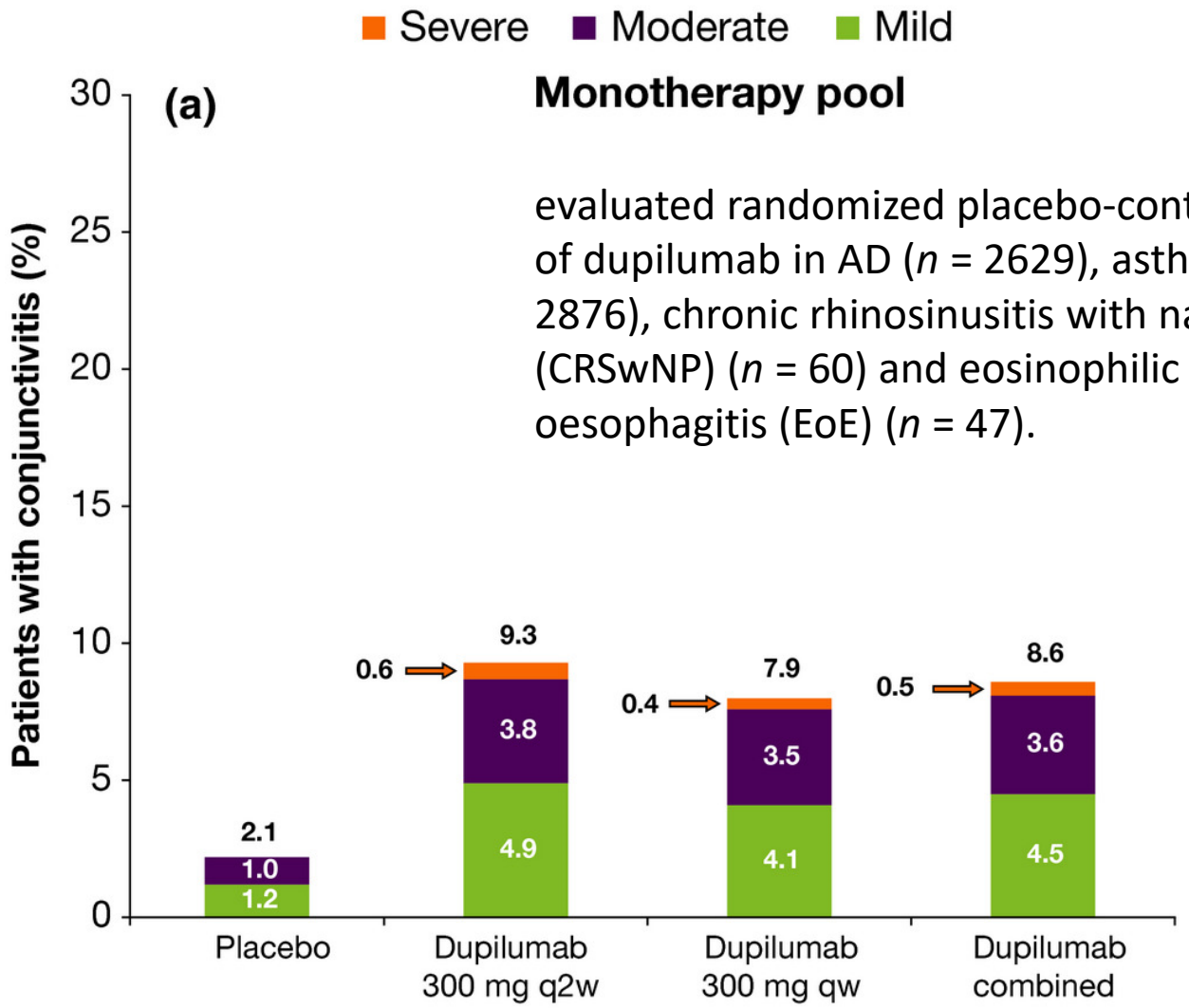
Influence of Dupilimab on oral steroid reduction in severe asthma



No. of Patients							
Placebo	107	107	107	107	107	107	106
Dupilumab	103	103	102	101	101	101	101

Rabe et al N Engl J Med 2018; 378:2475-2485

Dupilimab increases incidence of conjunctivitis



evaluated randomized placebo-controlled trials of dupilumab in AD (*n* = 2629), asthma (*n* = 2876), chronic rhinosinusitis with nasal polyps (CRSwNP) (*n* = 60) and eosinophilic oesophagitis (EoE) (*n* = 47).

Akinlade et al Brit J Dermatol 2019; 181: 459-473

Hypereosinophilia may be a feature of Dupilimab therapy

3000 asthma patients

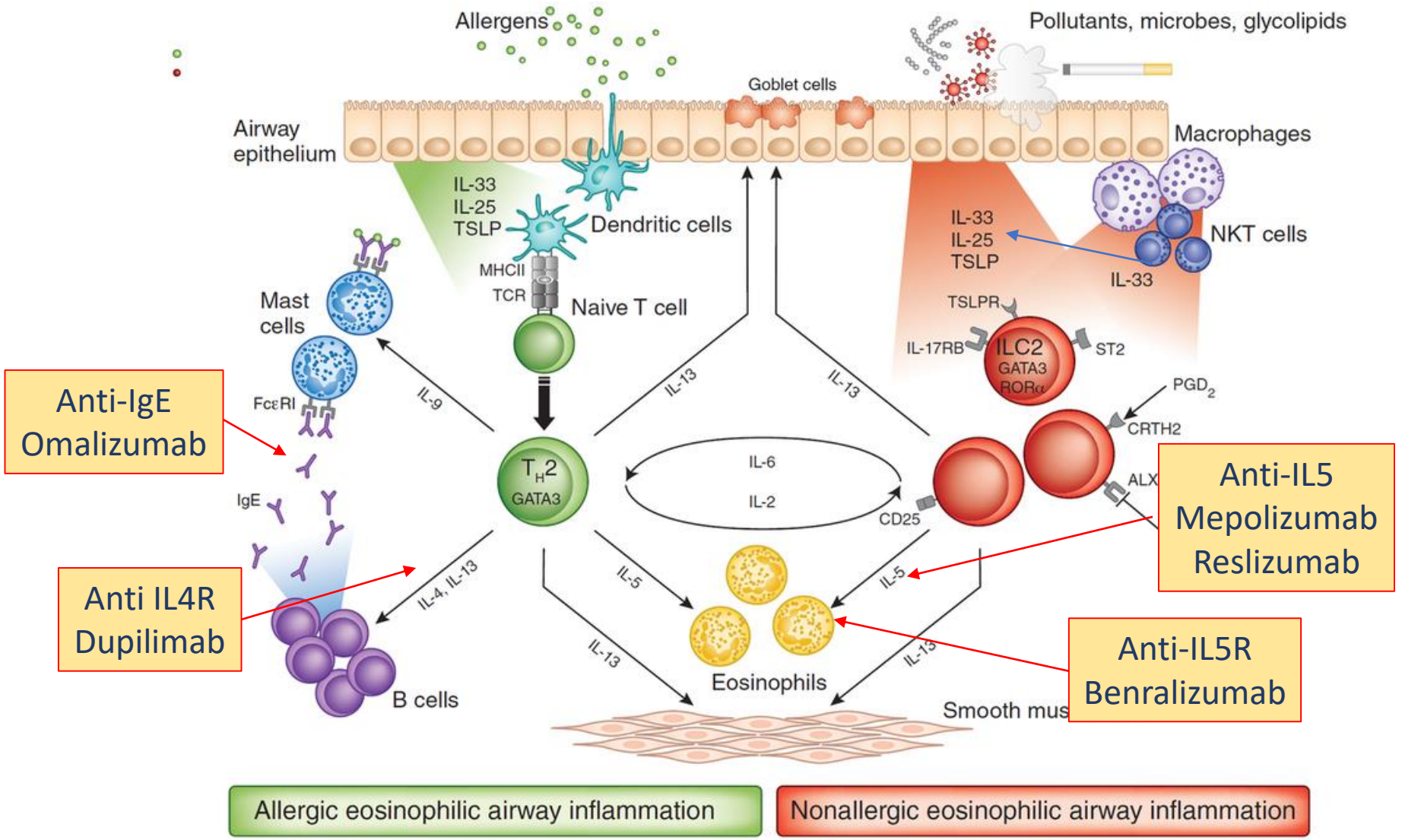
Adverse reactions occurring in ≥1% of DUPIXENT + SOC patients
and at a higher rate than placebo + SOC in Trials 1 and 2 (6-month safety pool)

Adverse Reaction	**DUPIXENT 200 mg Q2W + SOC** n=779 n (%)	**DUPIXENT 300 mg Q2W + SOC** n=788 n (%)	**Placebo + SOC** n=792 n (%)
Injection site reactions	111 (14)	144 (18)	50 (6)
Oropharyngeal pain	13 (2)	19 (2)	7 (<1)
Eosinophilia	17 (2)	16 (2)	2 (<1)

Anaphylaxis has been reported

https://www.dupixenthcp.com/asthma/safety-data

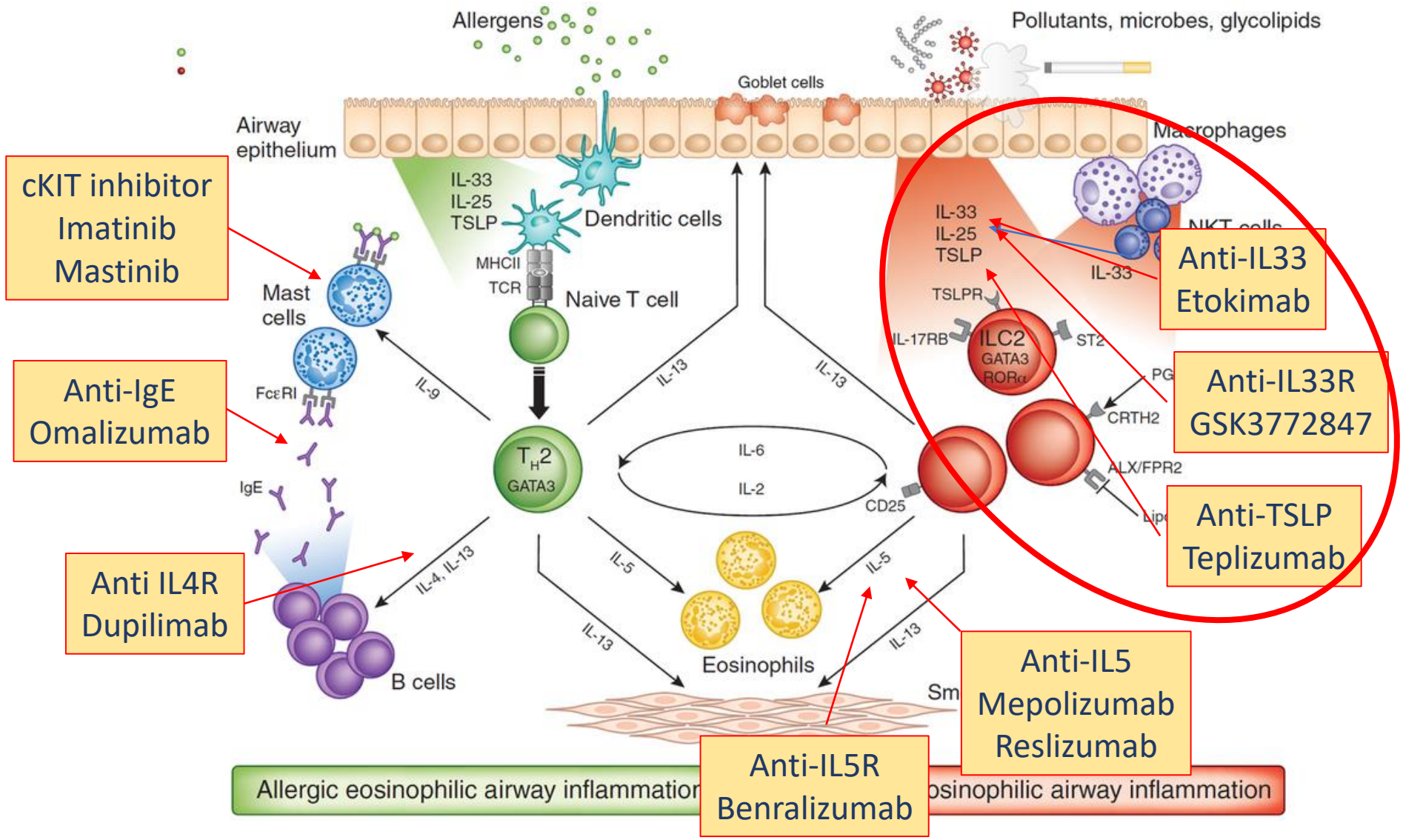
Type 2 airway inflammation and biologic directed targets



Brusselle et al. Ann Am Thorac Soc 2014:11(5);322-8

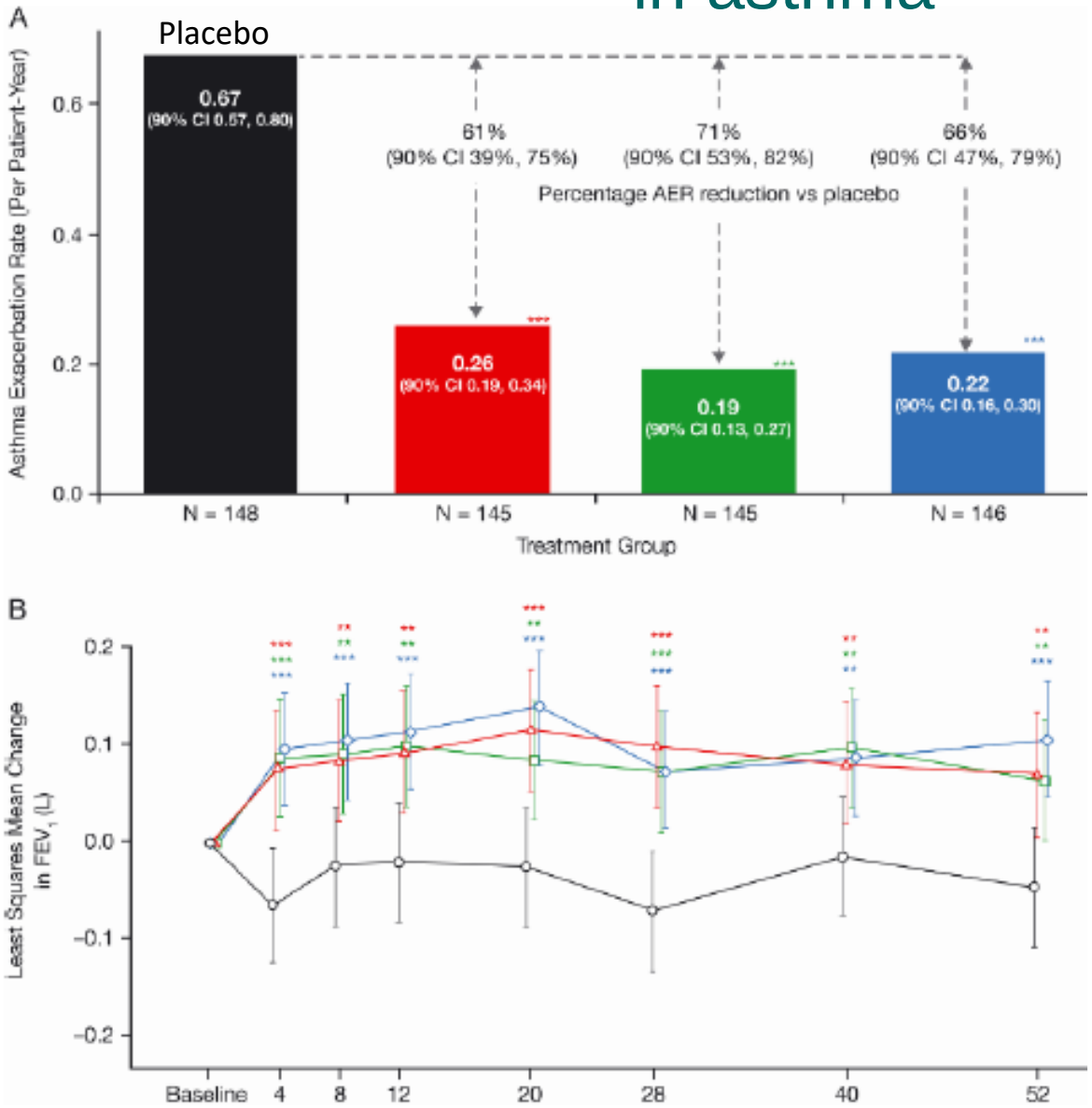
Where to in the future

Type 2 airway inflammation and biologic directed targets



Brusselle et al. Ann Am Thorac Soc 2014:11(5);322-8

Influence of Tezepelumab on clinical outcomes in asthma



R,D-B,P-C,P-G study

Three Tezepelumab Subcutaneous doses:

- Low – 70mg Q4W
- Medium 210 mg Q4W
- High – 280mg Q2W

52 week study

~50% low dose IS
(median 400µg FP)

~50% high dose IS
(median 1000 µg FP)

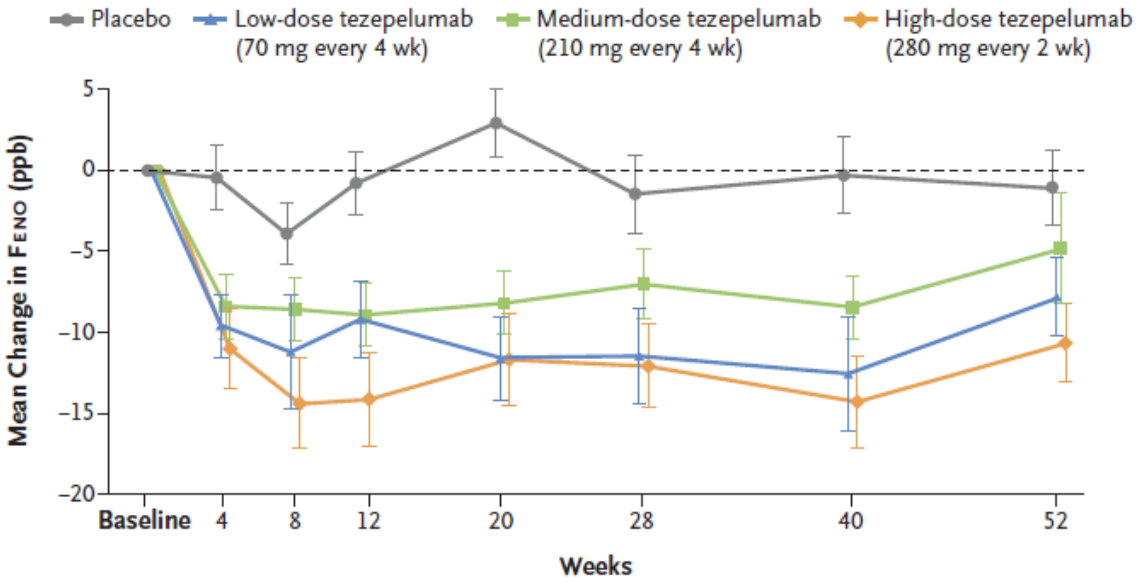
ACQ 2.63-2.76
FeNO* 19.7-21.5ppb
Pb eos* 255-275 /µl

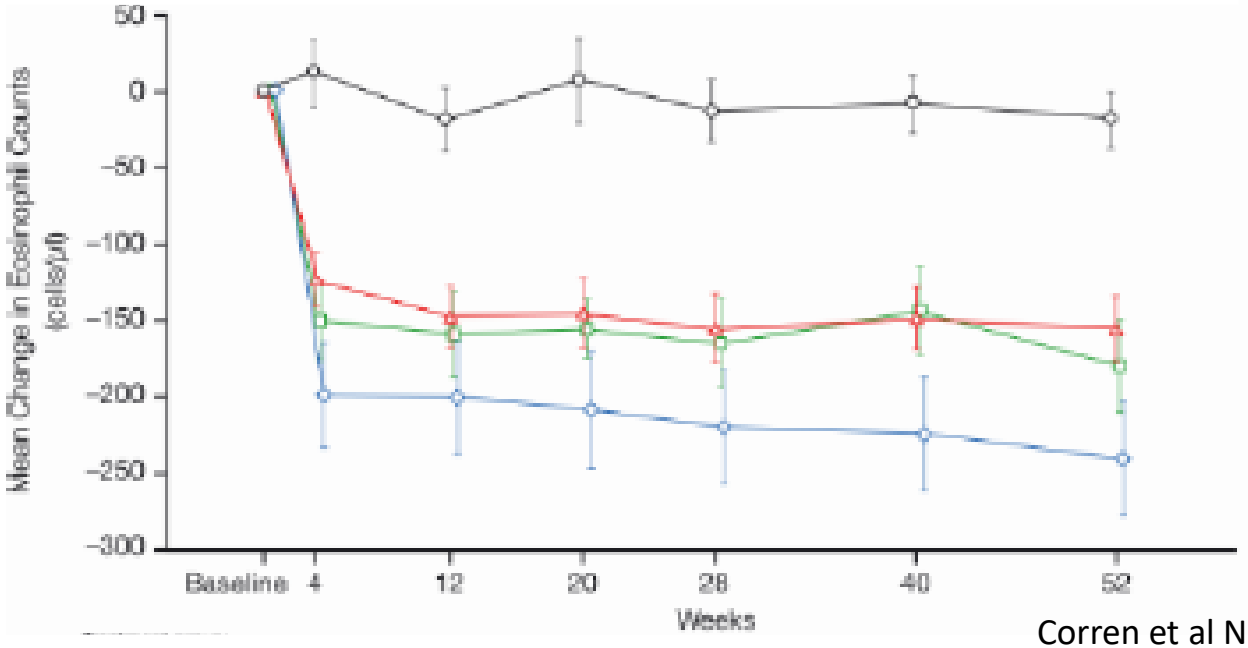
* median

Corren et al NEJM 2017: 377: 936-946

Influence of Tezepelumab on clinical biomarkers in asthma

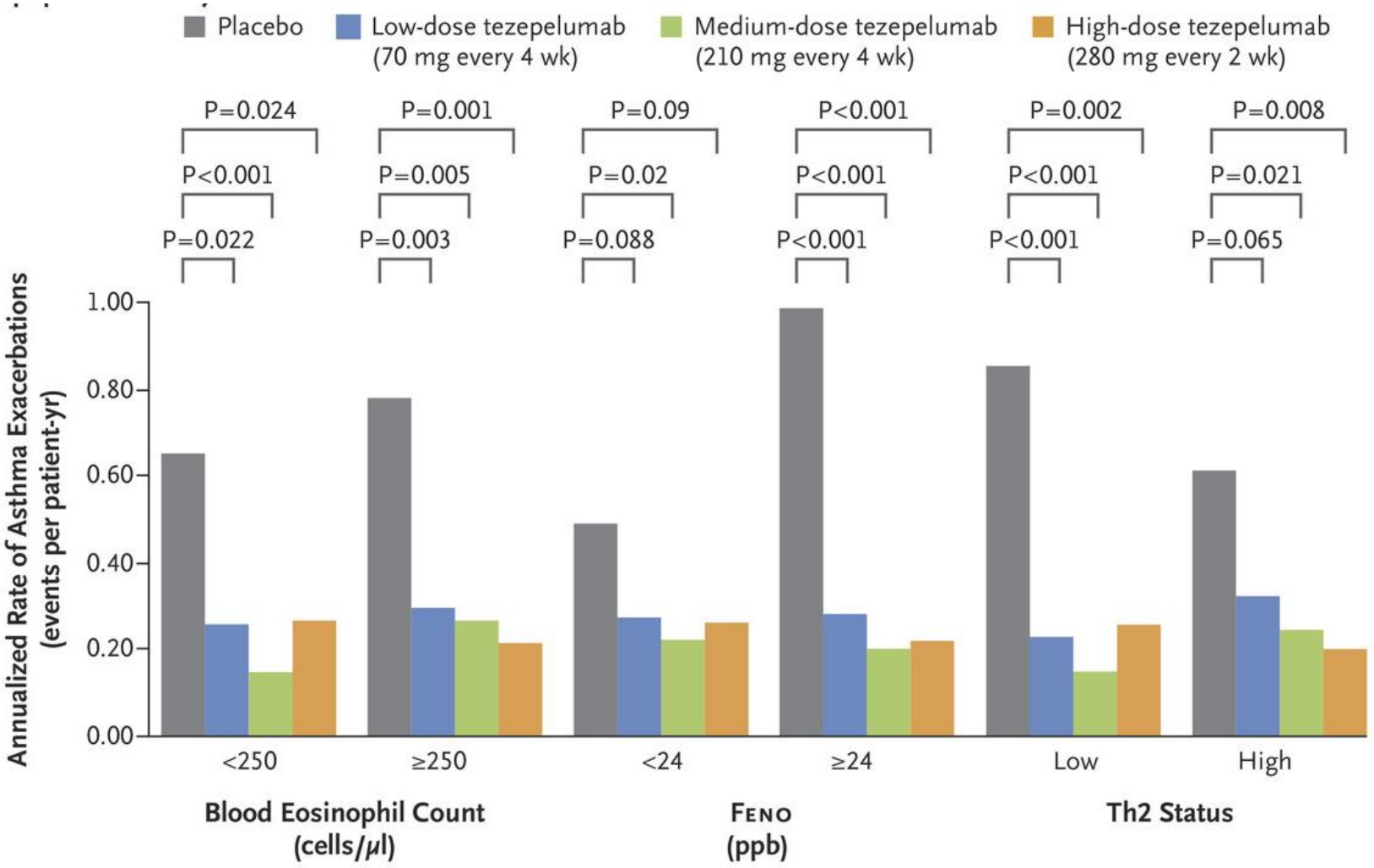
Change in FENO





Corren et al NEJM 2017: 377: 936-946

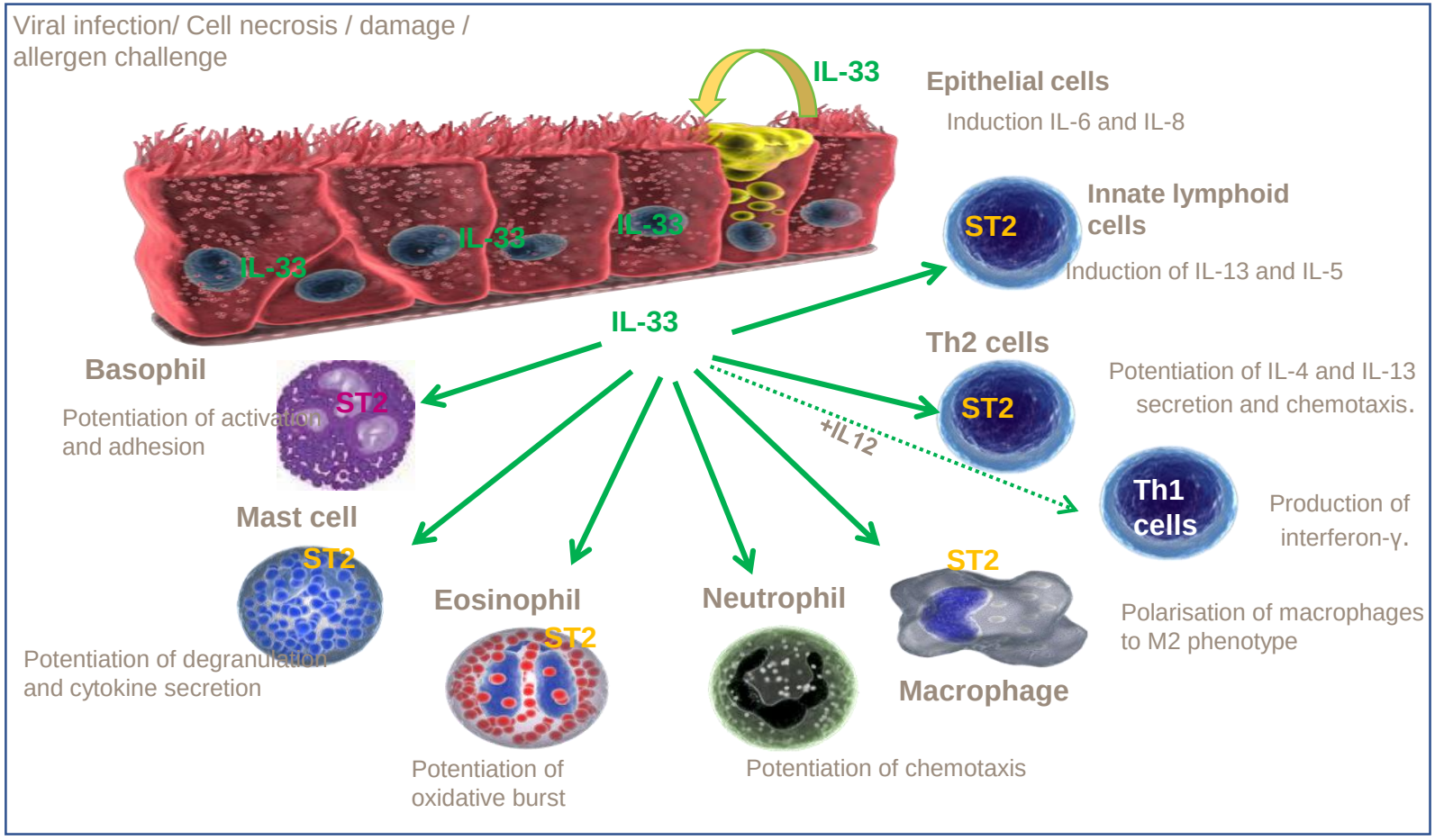
Influence of Tezepelumab on exacerbation rates in asthma independant of type 2 inflammation?



Corren et al NEJM 2017: 377: 936-946

IL-33 pathway : Biology

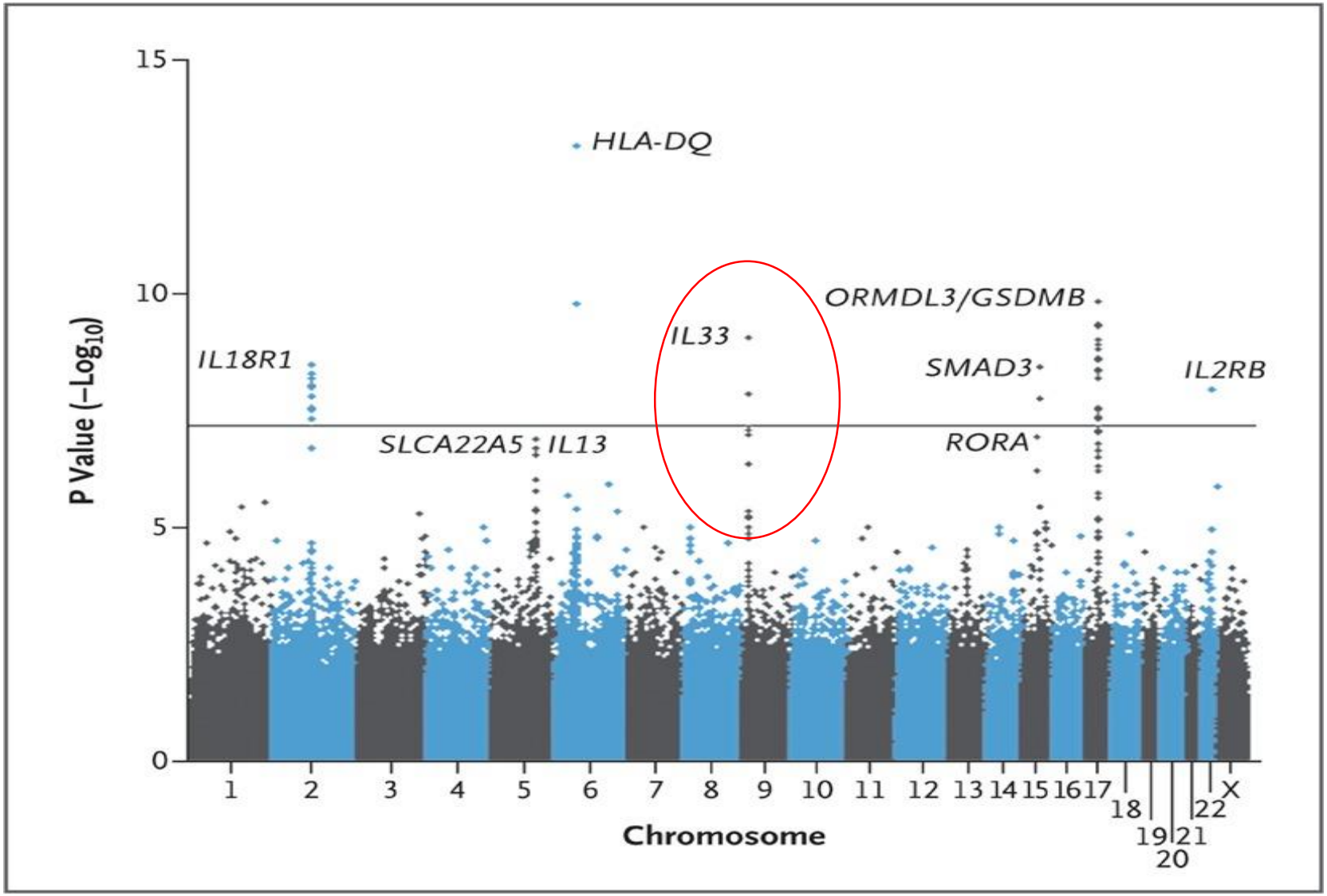
IL-33 engages a wide range of immune cells amplifying a mixed inflammatory response



- IL-33 can drive a mixed inflammatory and activates many cell types thought to be key in driving the inflammation in asthmatic lung.
- The IL-33R is a heterodimer of ST2 and IL-1RAcP, which forms a high affinity unit with the IL-33 ligand and its signalling is dependent on MyD-88.

Cayrol and Girard Current Opinion Immunology 2014; 31:31–37

A Large-Scale, Consortium-Based Genomewide Association Study of Asthma



Moffatt et al N Engl J Med 2010; 363:1211-1221

A rare IL33 loss-of-function mutation reduces blood eosinophil counts and protects from asthma

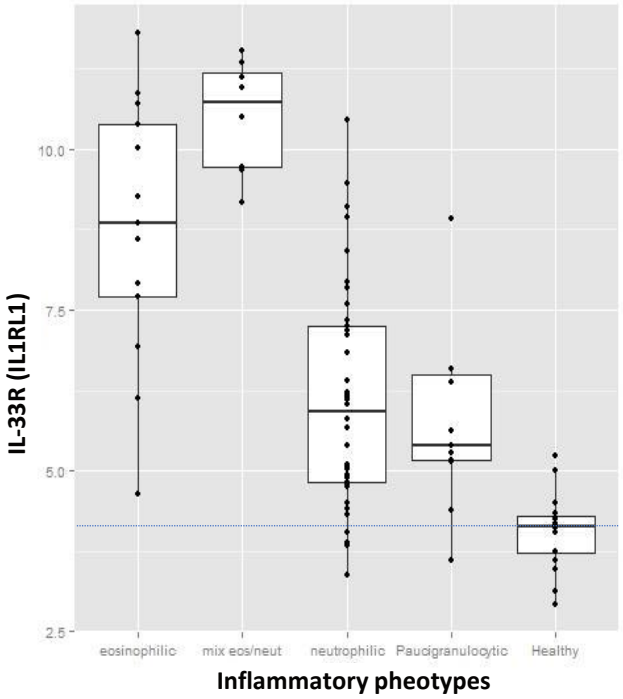
Eosinophil counts	**AF**	**β (SD)**	**(95%CI)**	***P***	**N individuals**		**P_{het}, I^2**
Iceland	0.65%	-0.21	(-0.27, -0.16)	2.5×10^{-16}	103,104		
The Netherlands	0.69%	-0.48	(-0.93, -0.03)	0.036	1,370		
Combined		-0.22	(-0.27, -0.17)	5.3×10^{-17}	104,474		0.25, 25.0
Asthma	**AF**	**OR**	**(95%CI)**	***P***	**N cases**	**N controls**	
Iceland:	0.65%	0.36	(0.21, 0.61)	1.2×10^{-4}	3,512	298,026	
The Netherlands	0.53%	1.08	(0.36, 3.21)	0.89	351	2,830	
Germany	0.40%	0.89	(0.14, 5.48)	0.90	284	252	
Denmark-1	0.50%	0.72	(0.29, 1.79)	0.48	1,121	1,004	
Denmark-2 (COPSAC)	0.45%	0.24	(0.06, 0.94)	0.04	1,197	865	
Combined		0.47	(0.32, 0.70)	1.8×10^{-4}	6,465	302,977	0.24, 26.8

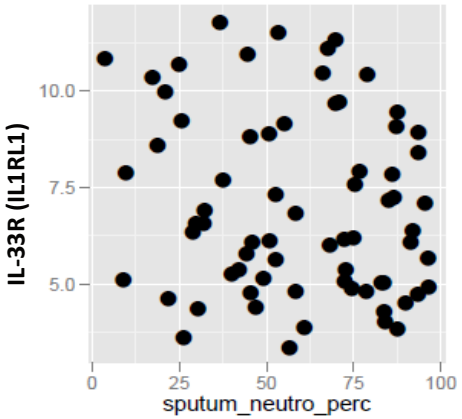
Allele frequency (AF) of rs146597587[C], the effect (β (SD)) on eosinophil counts and odds ratio (OR) for asthma and the corresponding *P*-values are provided, in addition to the number of individuals, or cases and controls tested. All the asthma sample sets include children and/or young adults: Iceland 45 years age or younger[9], The Netherlands younger than 45 years of age[23, 42], Germany 5–18 years of age[24], Denmark-1 14 to 44 years of age[25, 26] and Denmark-2 (COPSAC) children with severe asthma with at least 2 exacerbations leading to hospitalization between 2 and 6 years of age[13] (Materials and methods).

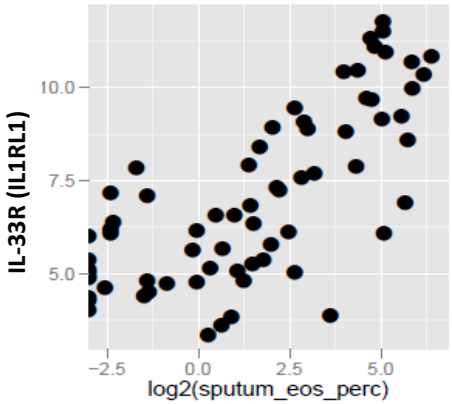
Smith et al PLoS Genet 13(3): e1006659. https://doi.org/10.1371/journal.pgen.1006659

IL-33R relationship to severe asthma phenotypes

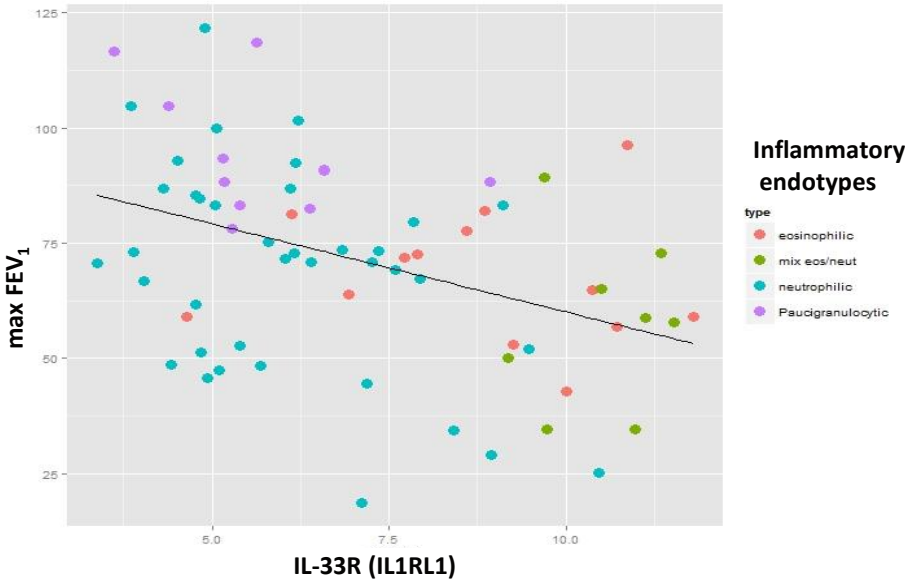
IL-33R expression with sputum cell phenotype stratification







Correlation with max FEV_1



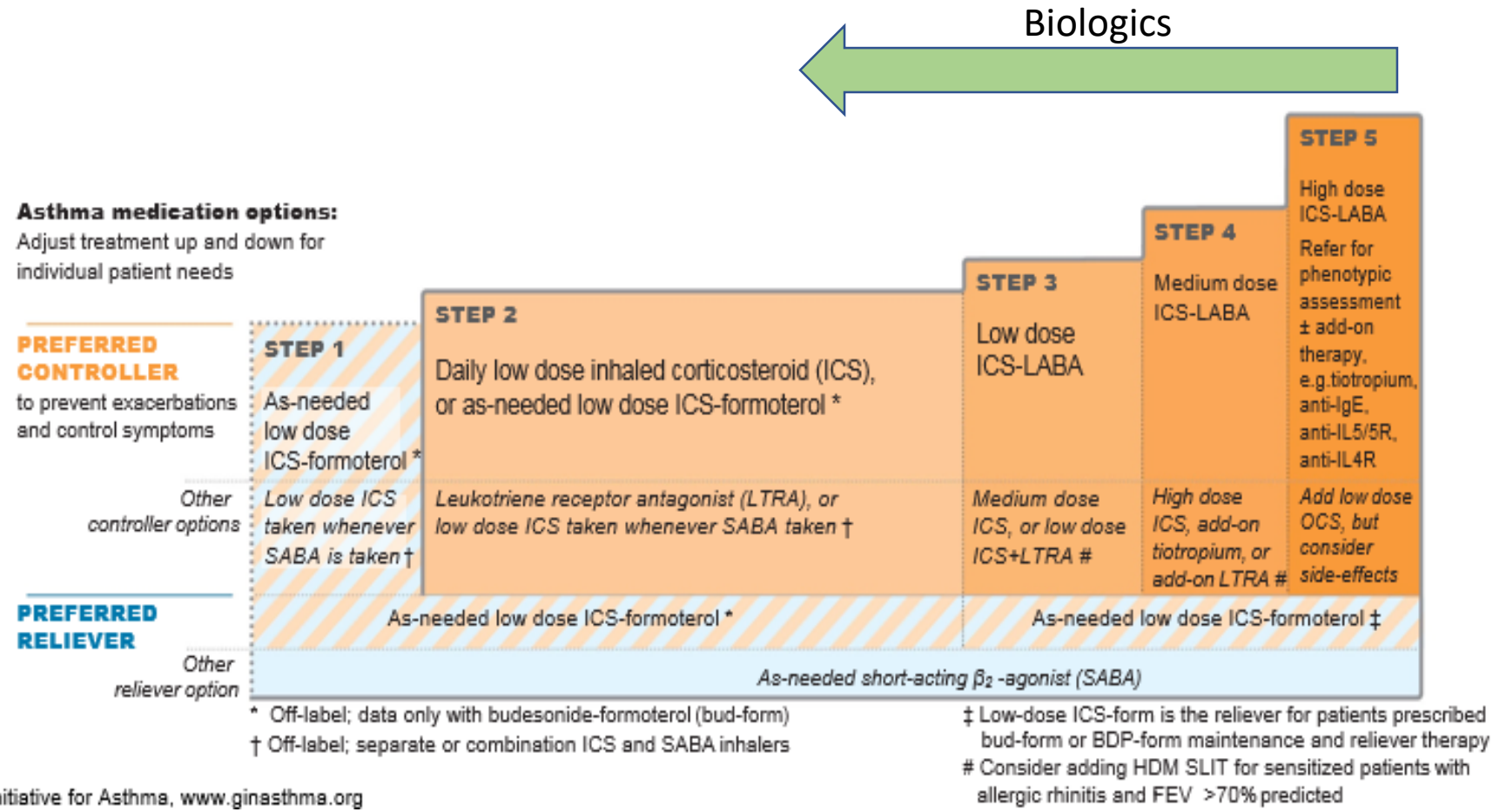
- IL-33R is upregulated in all asthma inflammatory phenotypes, though highest in eosinophil high asthmatics
- IL-33R expression is heterogeneous in neutrophilic asthma
- Negative correlation of IL33R with max FEV_1 across inflammatory phenotypes

Monoclonal antibody therapy severe asthma

1st generation	"anti-IgE" Omalizumab
2nd generation	" more specific anti type 2 cytokine/cytokine receptor therapy" Mepolizumab, Reslizumab, Benralizumab, Dupilimab
3rd generation	" Higher level cascade anti-alarmin therapy" Tezepelumab (anti TSLP), anti-IL33R, anti-IL25

Will 3rd generation monoclonals for severe asthma make others redundant?

Will biologics get introduced earlier in disease management?



* Off-label; data only with budesonide-formoterol (bud-form)

† Off-label; separate or combination ICS and SABA inhalers

‡ Low-dose ICS-form is the reliever for patients prescribed bud-form or BDP-form maintenance and reliever therapy

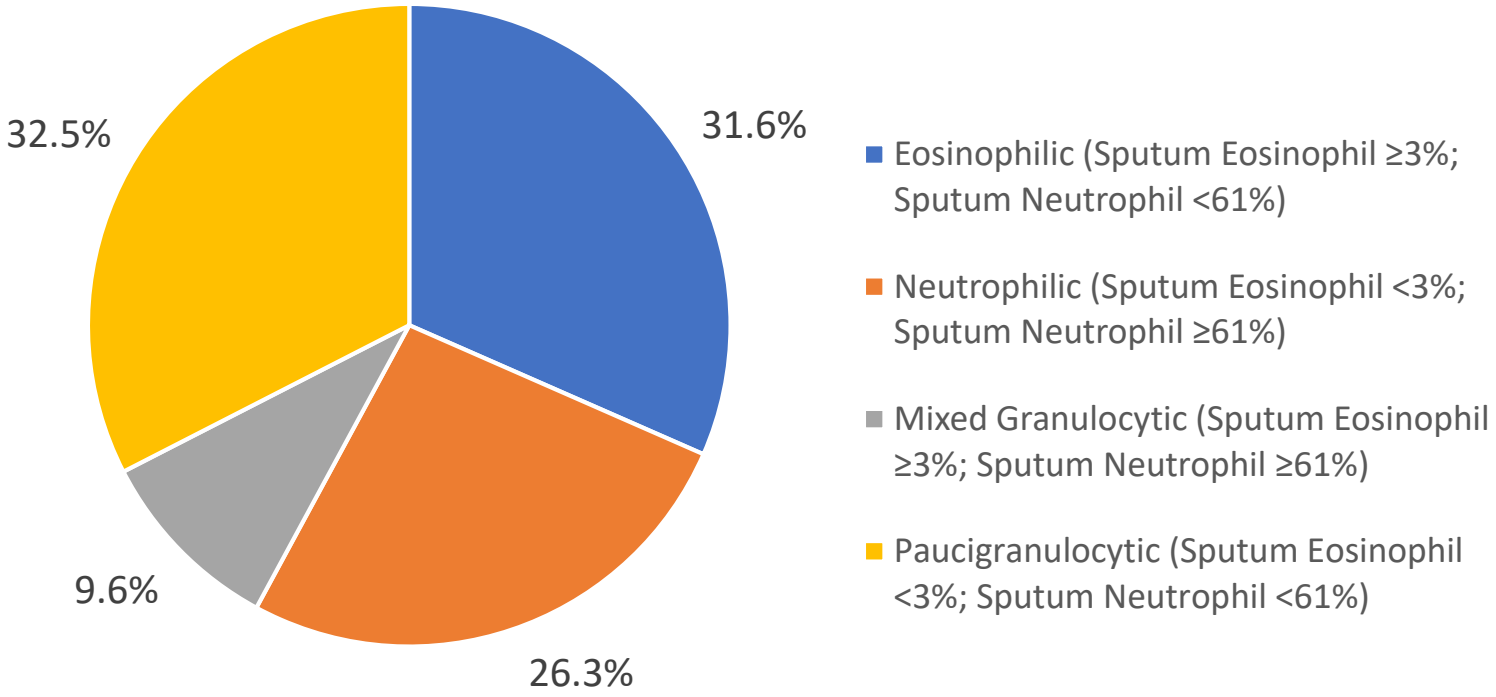
\# Consider adding HDM SLIT for sensitized patients with allergic rhinitis and FEV >70% predicted

ICS, inhaled corticosteroid; LABA, long-acting β-agonist; LTRA, leukotriene receptor antagonists; OCS, oral corticosteroid; SABA, short-acting β2-agonist

Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2019. Available from: www.ginasthma.org (Accessed April 2019).

The Wessex Severe Asthma Cohort inflammatory phenotypes

Severe Asthma Sputum Inflammatory Phenotypes:

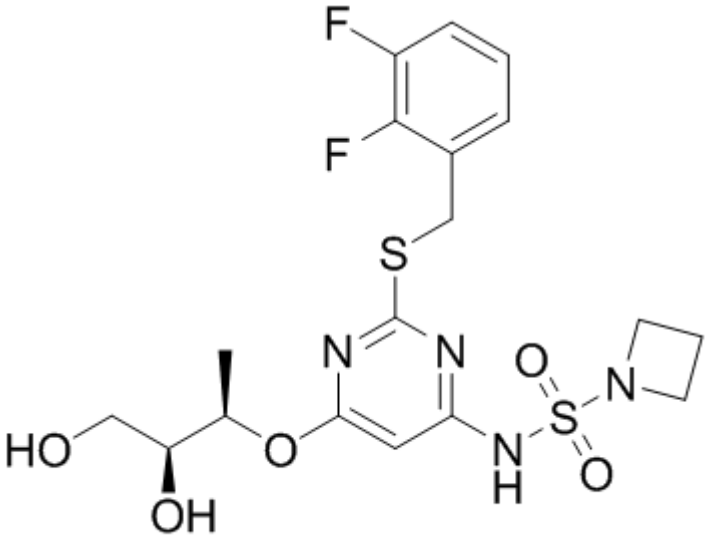


	WSAC	SARP[1]	UBIOPRED[2]	BSAR[3]	BIOAIR[4]
Cohort size (n)	342	204	421	350	93
Successful sputum induction (%)	61.1	60.7	43.0	32.2	24.6

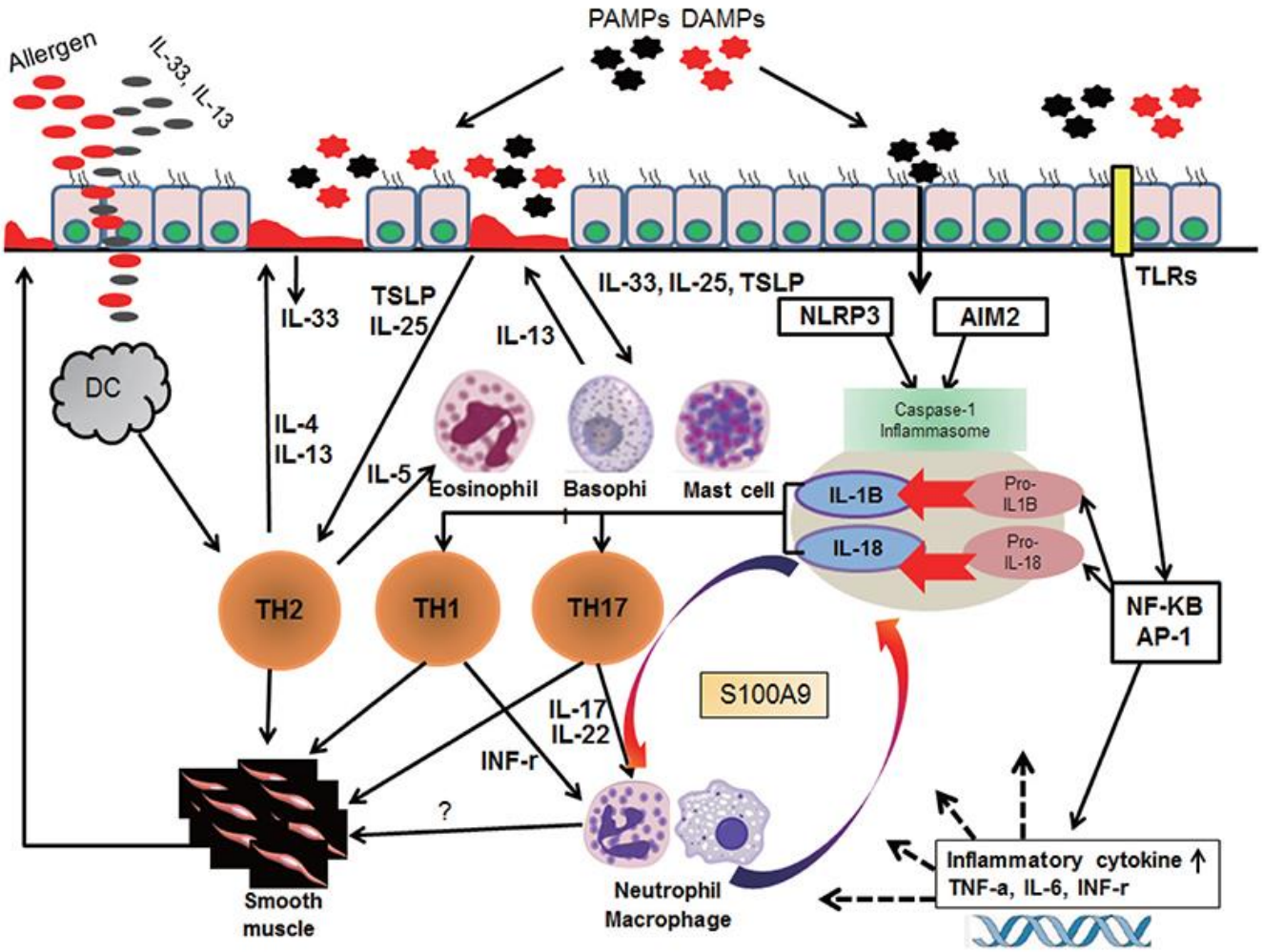
1. Moore et al. AmJRCCM 2010; 2. Shaw et al. ERJ 2015; 3. Schleich et al. Respir Med 2014; 4. Kupczyk et al. Thorax 2013.

CXCR2 antagonists previously in clinical development for asthma

- Two different CXCR2 antagonists have been studied across asthma severities and in a challenge model (Navarixin/MK-7123 and AZD-5069).
- CXCR2 antagonists consistently reduce blood, sputum and mucosal neutrophils and have some impact on neutrophil activation markers
- Does not seem to translate to improvements in bronchial hyperreactivity, exacerbation rates or asthma symptoms
  - —Caveats: 1) only 2/4 studies enrolled patients based on sputum neutrophils; 2) asthma severity varied from mild to severe; 3) dosing duration varied from 10 days to 6 months



Is the airway microbiome a therapeutic target?



Lee et al Asia Pacific Allergy 2014: 4: 187-196

Severe asthma treatment evolution

BIOMARKERS
&
ENDOTYPING

2020

Biologics

2000s

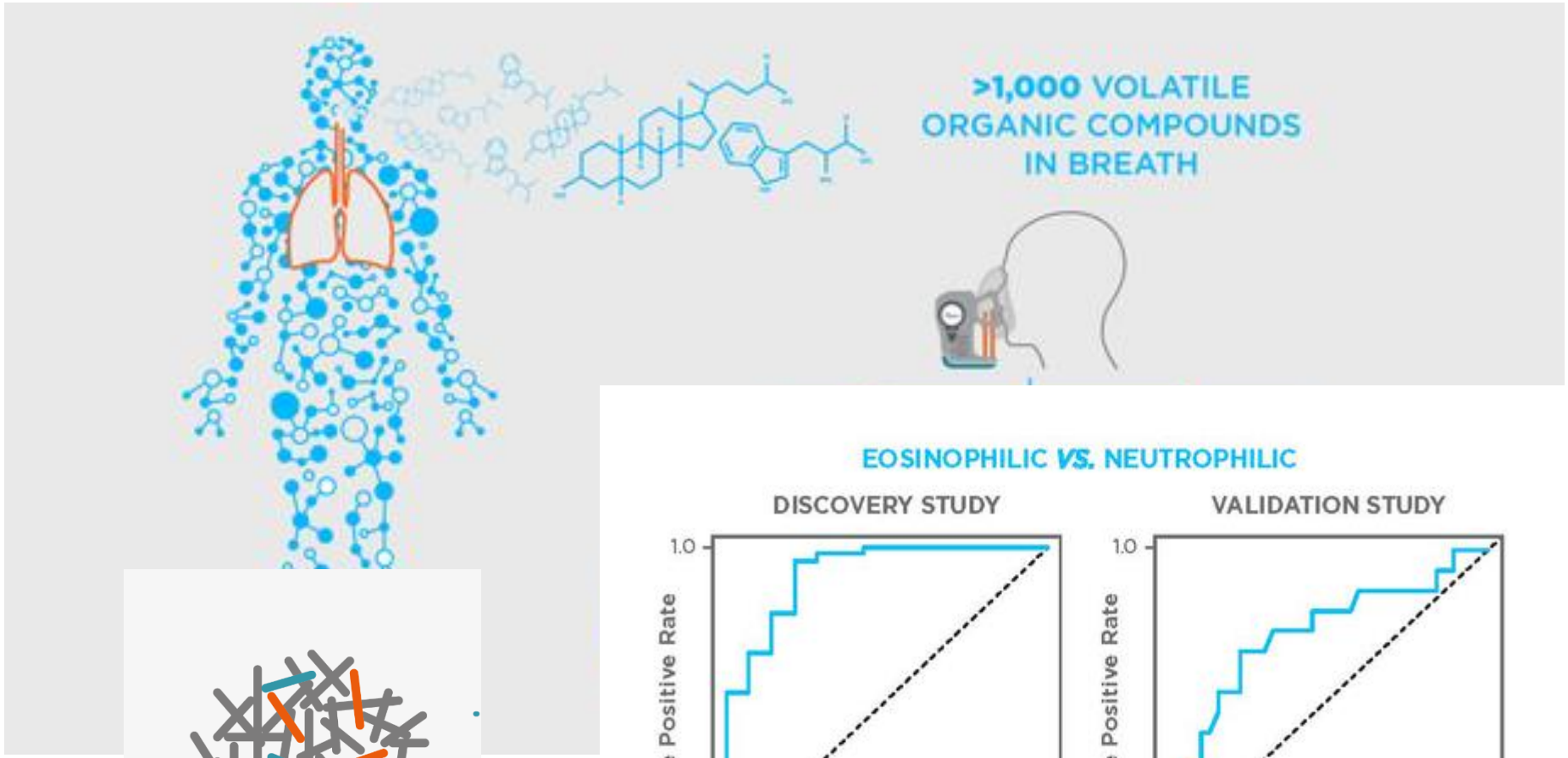
Anti-inflammatory

1970s-80s

1950s

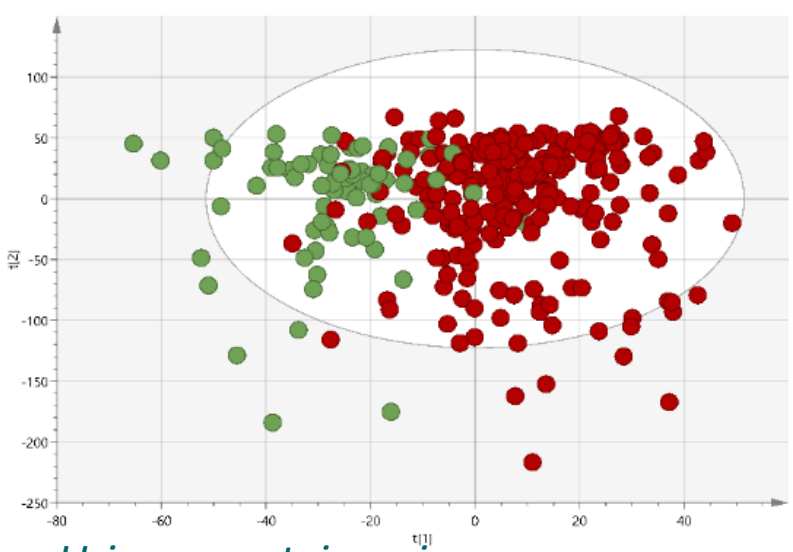
Bronchodilators

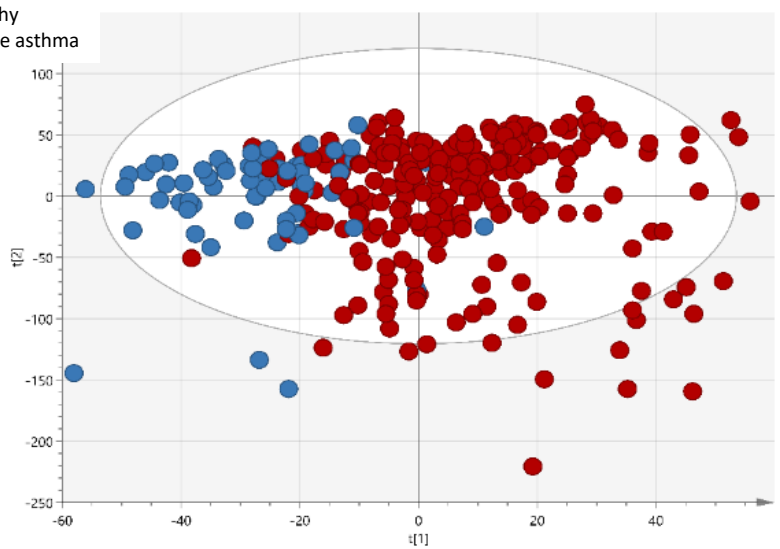
Breathomics



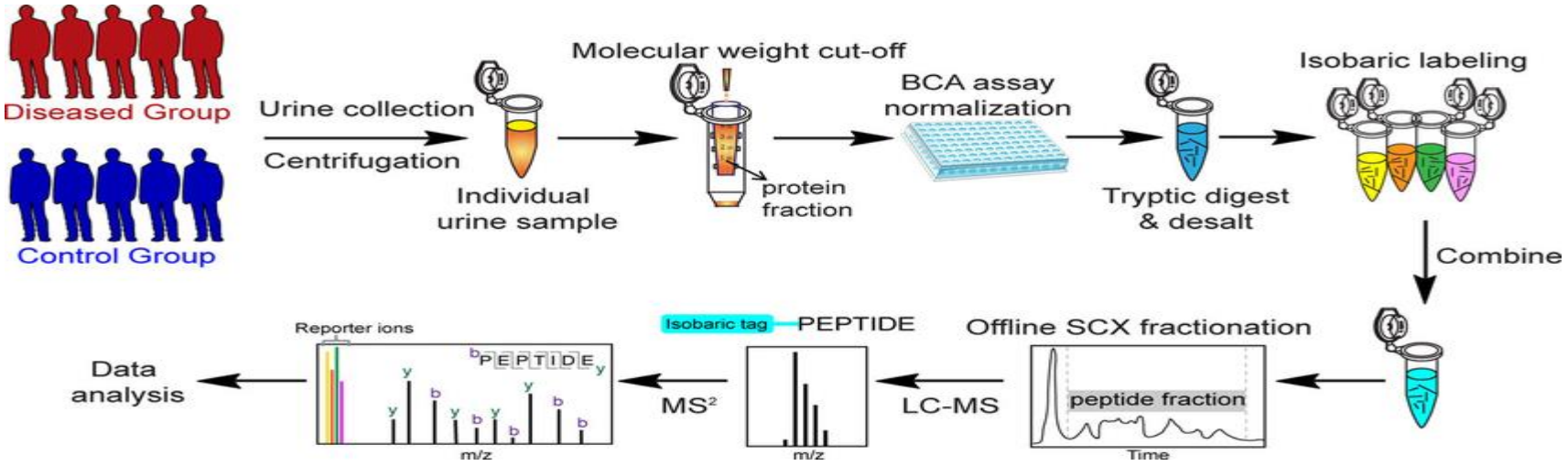
Schlieich et al Am J Respir Crit Care Med 2019,;200:444-453

Urinary metabolomics: Metabolic differences between control individuals, mild to moderate and severe asthmatics in UPLC-MS





Urinary proteinomics



Severe asthma treatment evolution

2020

2000s

1970s-80s

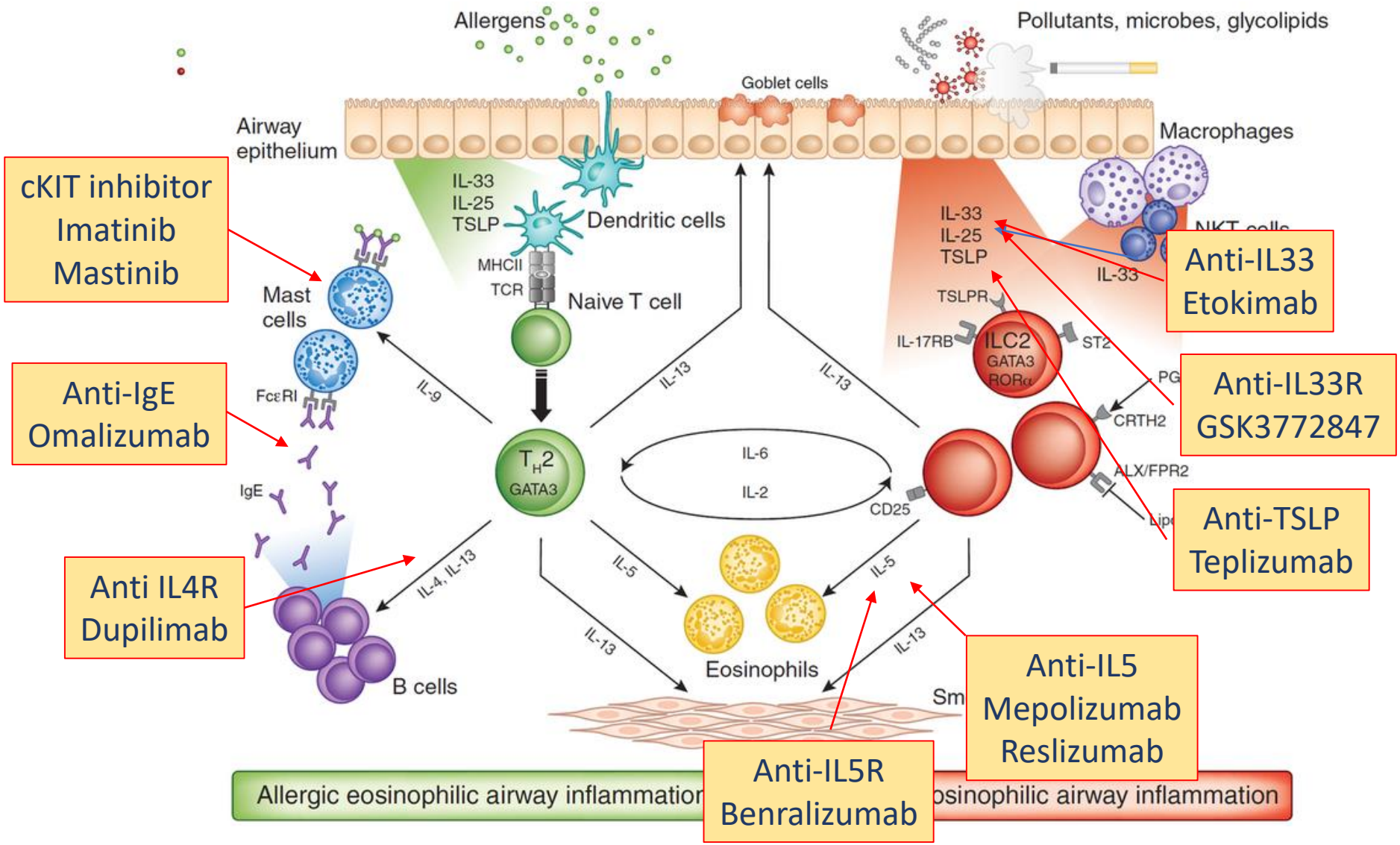
1950s

Biologics

Anti-inflammatory

Bronchodilators

Type 2 airway inflammation and biologic directed targets



Brusselle et al. Ann Am Thorac Soc 2014:11(5);322-8