Severe Asthma Management

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Erasmus MC Rotterdam

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Disclosure: Guy Brusselle

- ERS Science Council Chair

- GINA Scientific Committee Member and Board of Directors

- Member of Advisory boards for AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Novartis, Sanofi and Teva.

- Lecture fees from AstraZeneca, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline, Novartis and Teva.

Severe Asthma Management

- Severe asthma: Diagnosis
  - Definition
  - Difficult-to-control asthma
  - Phenotyping
- Severe asthma: Targeted therapies
  - Uncontrolled severe asthma
  - Corticodependent severe asthma
- Biomarkers
- Conclusion

Treatment of asthma (GINA 2018)
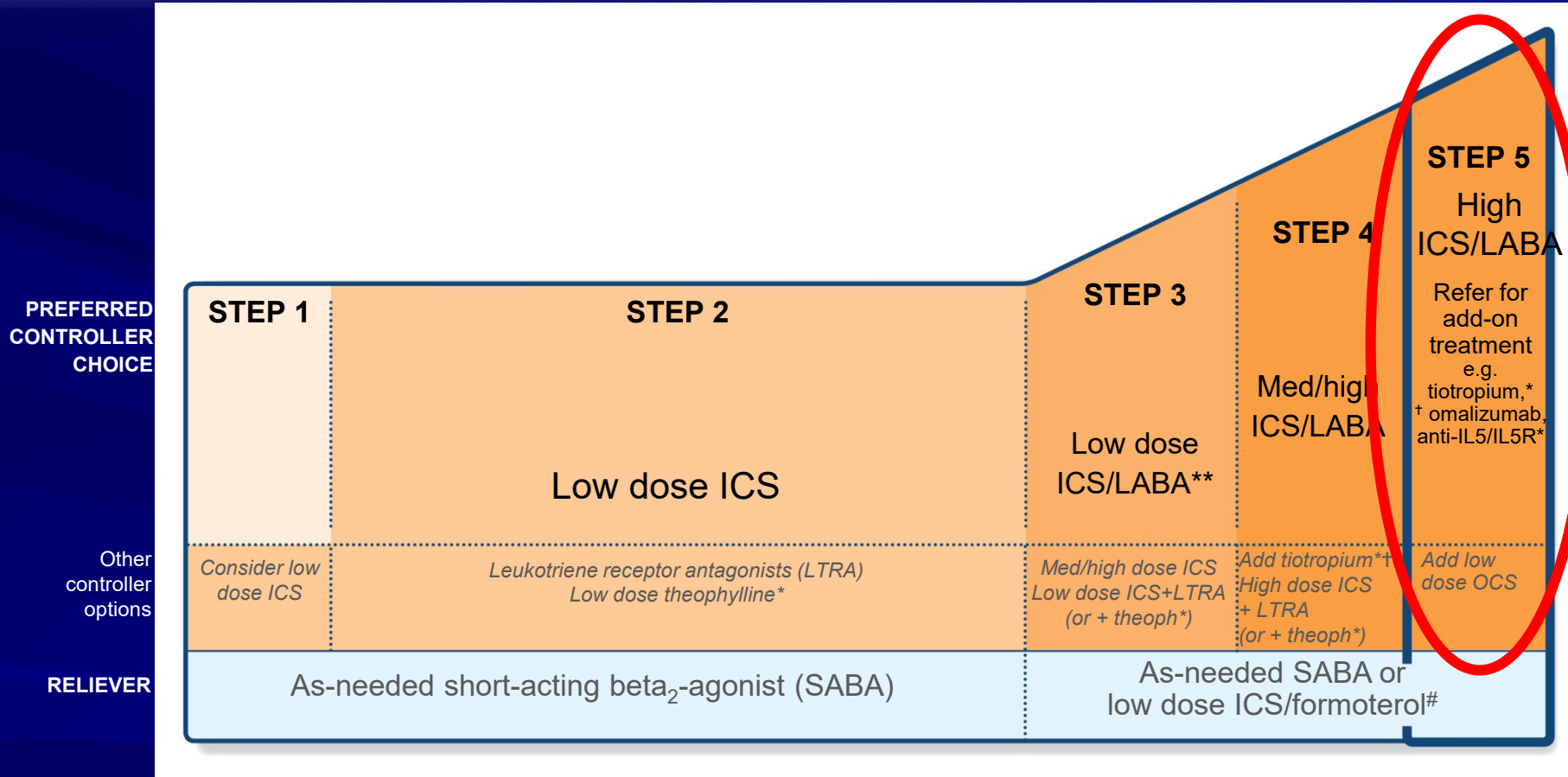
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Erasmus MC
Universitair Medisch Centrum Rotterdam

UNIVERSITEIT GENT

ERS / ATS Guidelines on severe asthma

International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma

Kian Fan Chung[1,2,21], Sally E. Wenzel[3,21], Jan L. Brozek[4], Andrew Bush[1,2], Mario Castro[5], Peter J. Sterk[6], Ian M. Adcock[1], Eric D. Bateman[7], Elisabeth H. Bel[6], Eugene R. Bleecker[8], Louis-Philippe Boulet[9], Christopher Brightling[10], Pascal Chanez[11], Sven-Erik Dahlen[12], Ratko Djukanovic[13], Urs Frey[14], Mina Gaga[15], Peter Gibson[16], Qutayba Hamid[17], Nizar N. Jajour[18], Thais Mauad[19], Ronald L. Sorkness[18] and W. Gerald Teague[20]

F. Chung et al, ERJ 2014.

EUROPEAN RESPIRATORY SOCIETY

AMERICAN THORACIC SOCIETY · 1905 · ATS

Definition of severe asthma

- When the diagnosis of asthma is confirmed and comorbidities addressed,

- **severe asthma** is defined as asthma that requires treatment with high dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy.

Definition of uncontrolled asthma

- At least one of the following:

1. Poor symptom control:
   ACQ consistently > 1.5, ACT < 20

2. Frequent severe exacerbations: two or more bursts of systemic CS in the previous year

3. Serious exacerbations: at least one hospitalisation or ICU stay in the previous year

4. *Airflow limitation: after appropriate bronchodilator withold FEV_1 < 80% predicted*

F. Chung et al, ERJ 2014.

Evaluation of uncontrolled asthma

- Poor compliance (ICS)
- Poor inhaler technique
- Environmental factors:
  - Allergen exposure
  - Smoking
- Incorrect diagnosis
- Significant comorbidities

Evaluation of uncontrolled asthma

TABLE 7 Comorbidities and contributory factors

1) Rhinosinusitis/(adults) nasal polyps
2) Psychological factors: personality trait, symptom perception, anxiety, depression
3) Vocal cord dysfunction
4) Obesity
5) Smoking/smoking related disease
6) Obstructive sleep apnoea
7) Hyperventilation syndrome
8) Hormonal influences: premenstrual, menarche, menopause, thyroid disorders
9) Gastro-oesophageal reflux disease (symptomatic)
10) Drugs: aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), β-adrenergic blockers, angiotensin-converting enzyme inhibitors

GINA

DIFFICULT-TO-TREAT & SEVERE ASTHMA

in adolescent and adult patients

Diagnosis and Management

A GINA Pocket Guide
For Health Professionals

November 2018

Investigate and manage adult and adolescent patients with difficult-to-treat asthma

Consider referring to specialist or severe asthma clinic at any stage

DIAGNOSIS:
"Difficult-to-treat asthma"

For adolescents and adults with symptoms and/or exacerbations despite GINA Step 4 treatment, or taking maintenance OCS

Key

decision, filters

intervention, treatment

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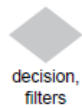
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1 **Confirm** the diagnosis (asthma/differential diagnoses)

2 **Look for factors** contributing to symptoms, exacerbations and poor quality of life:

- Incorrect inhaler technique
- Suboptimal adherence
- Comorbidities including obesity, GERD, chronic rhinosinusitis, OSA
- Modifiable risk factors and triggers at home or work, including smoking, environmental exposures, allergen exposure (if sensitized on skin prick testing or specific IgE); medications such as beta-blockers and NSAIDs
- Overuse of SABA relievers
- Medication side effects
- Anxiety, depression and social difficulties

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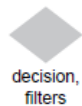
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3 Optimize management, including:

- Asthma education
- Optimize treatment (e.g. check and correct inhaler technique and adherence; switch to ICS-formoterol maintenance and reliever therapy, if available)
- Treat comorbidities and modifiable risk factors
- Consider non-biologic add-on therapy (e.g. LABA, tiotropium, LM/LTRA, if not used)
- Consider non-pharmacological interventions (e.g. smoking cessation, exercise, weight loss, mucus clearance, influenza vaccination)
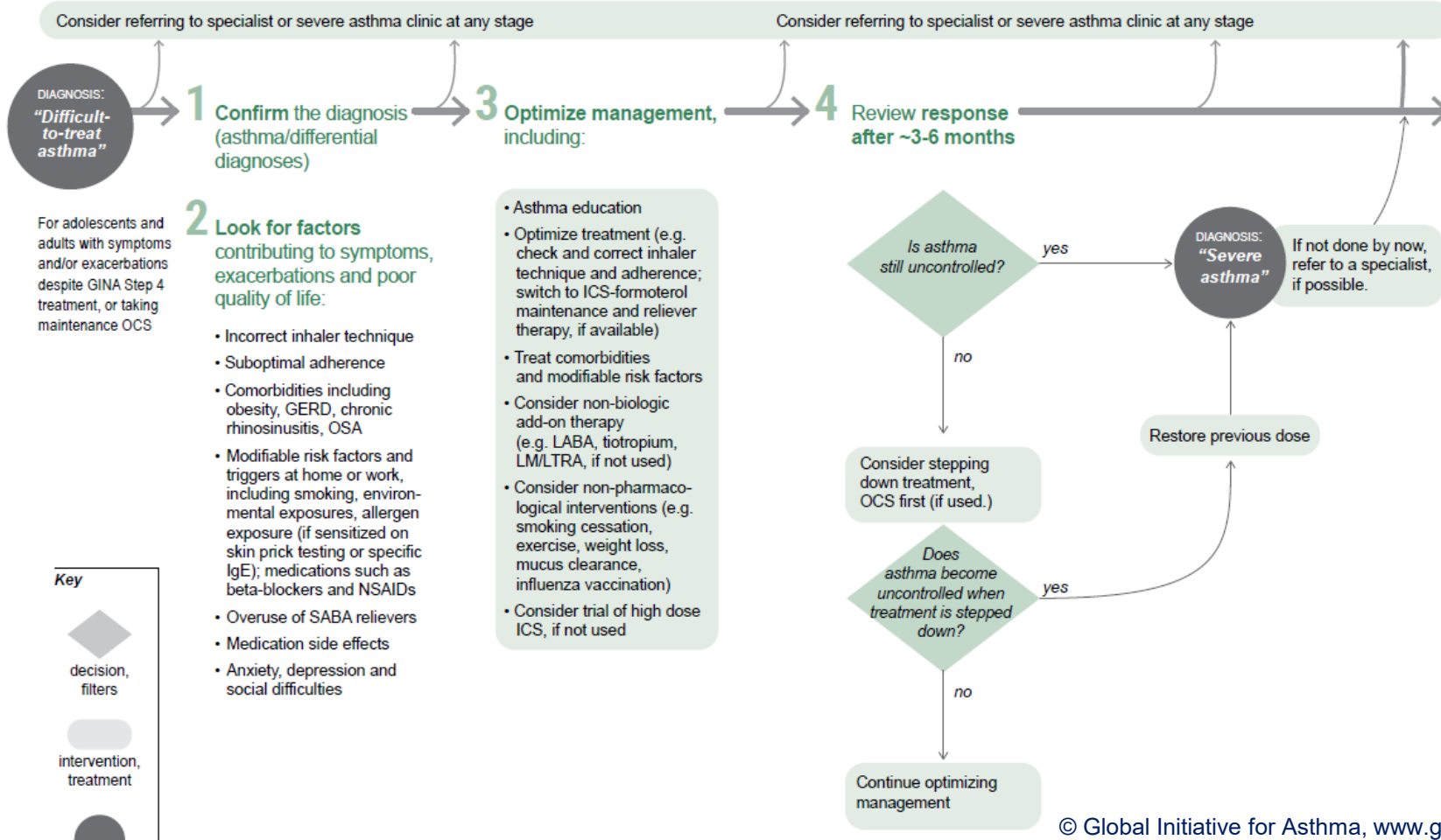- Consider trial of high dose ICS, if not used
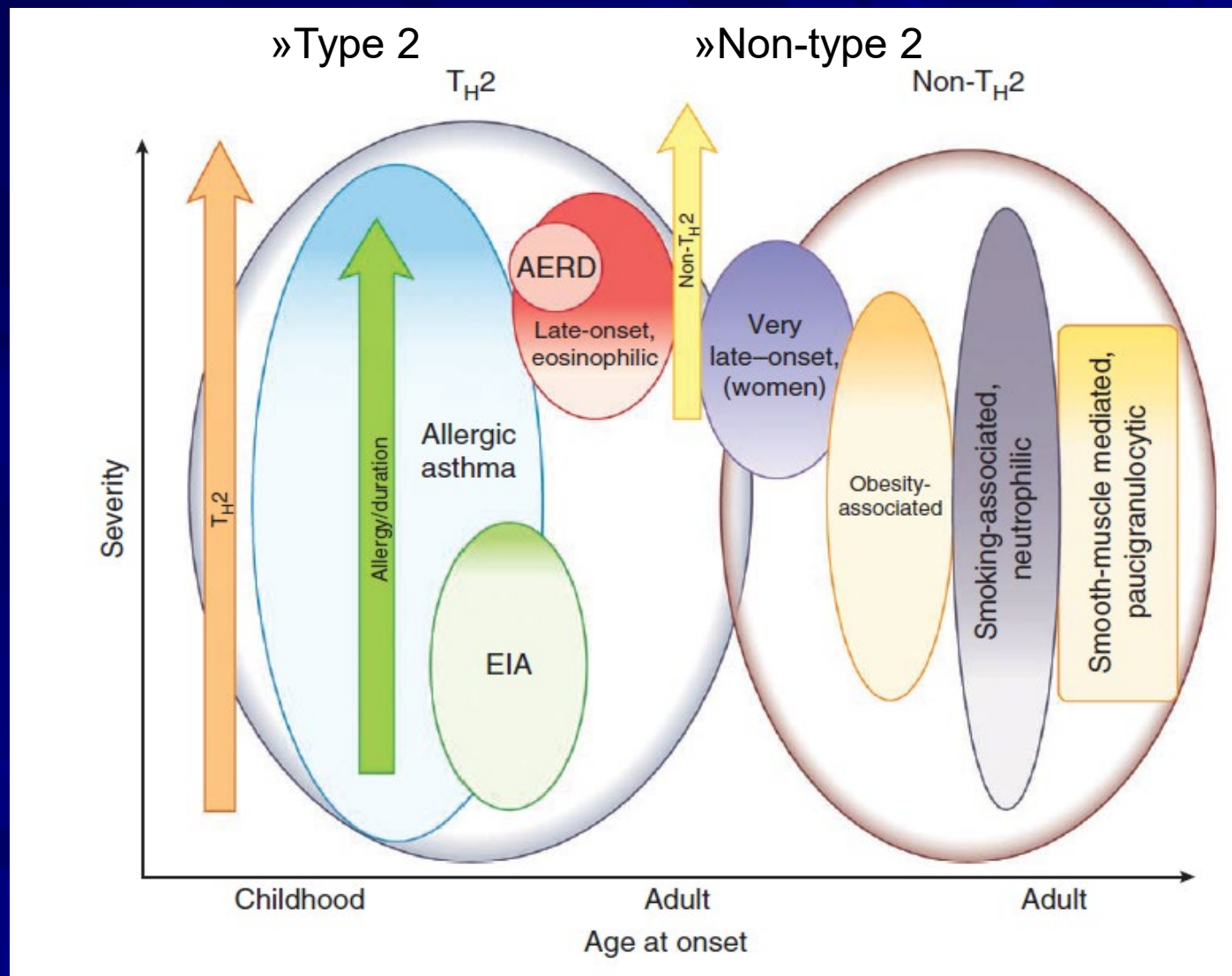
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- Consider non-pharmacological interventions (e.g. smoking cessation, exercise, weight loss, mucus clearance, influenza vaccination)
- Consider trial of high dose ICS, if not used

4 **Review response** after ~3-6 months

Is asthma still uncontrolled? — **yes** →

DIAGNOSIS: *"Severe asthma"*

If not done by now, refer to a specialist, if possible.

no ↓

Consider stepping down treatment, OCS first (if used.)

Does asthma become uncontrolled when treatment is stepped down? — **yes** →

Restore previous dose

no ↓

Continue optimizing management

Key

◇ decision, filters

▢ intervention, treatment

●
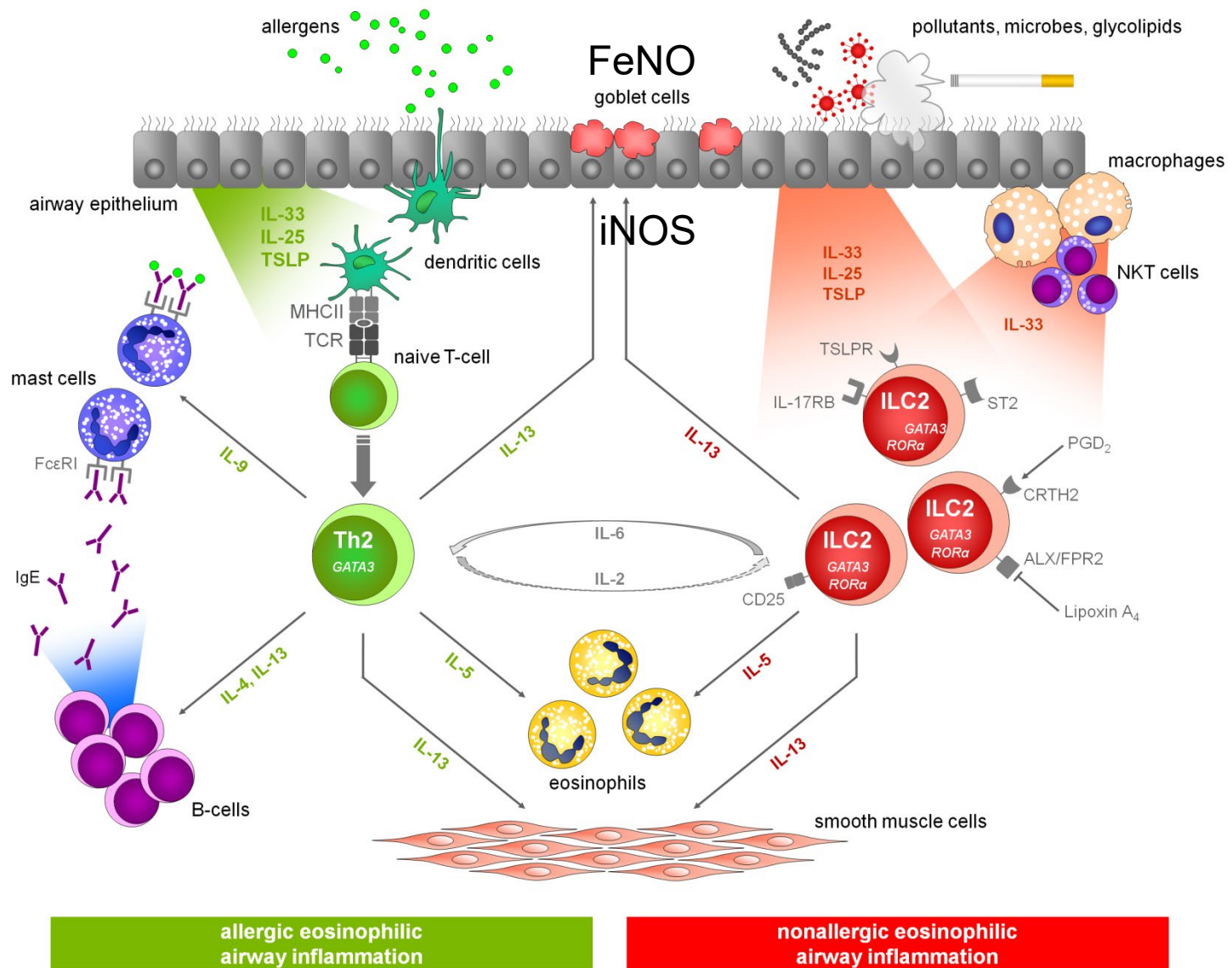
GLOBAL INITIATIVE FOR ASTHMA
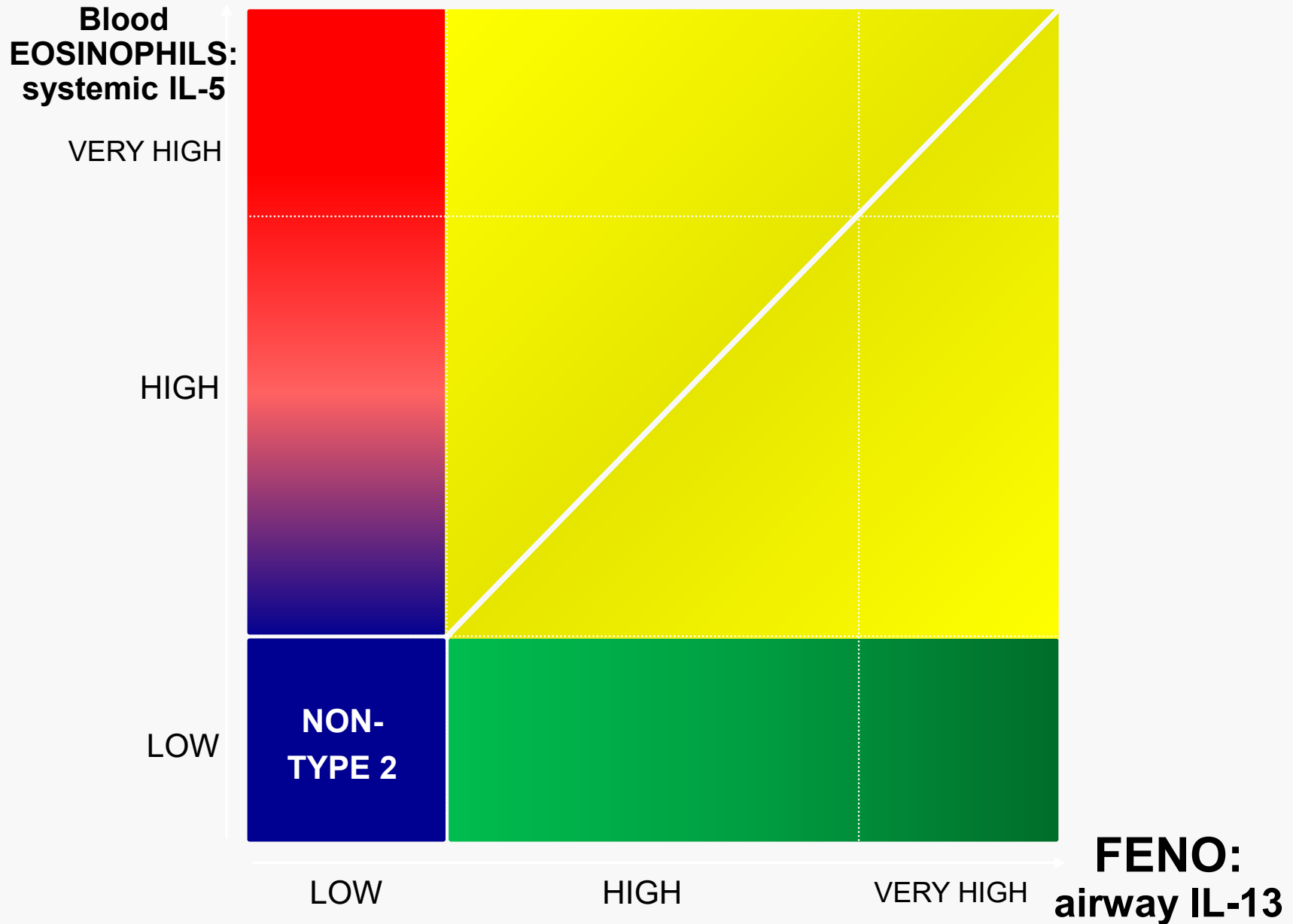
Phenotypes of severe asthma

AERD = aspirin exacerbated respiratory disease;
EIA = exercise-induced asthma

Wenzel SE. Nat Med 2012;18(5):716–25.

Heterogeneity of eosinophilic asthma

allergens

FeNO

goblet cells

pollutants, microbes, glycolipids

airway epithelium

IL-33
IL-25
TSLP

dendritic cells

iNOS

IL-33
IL-25
TSLP

macrophages

NKT cells

IL-33

mast cells

MHCII
TCR

naive T-cell

TSLPR

IL-17RB

ILC2
GATA3
RORα

ST2

FcεRI

IL-9

IL-13

IL-13

PGD$_2$

CRTH2

IgE

Th2
GATA3

IL-6

IL-2

ILC2
GATA3
RORα

ILC2
GATA3
RORα

ALX/FPR2

Lipoxin A$_4$

CD25

IL-4, IL-13

IL-5

IL-5

B-cells

IL-13

eosinophils

IL-13

smooth muscle cells

allergic eosinophilic airway inflammation

nonallergic eosinophilic airway inflammation

Brusselle G. et al. Nat Med 2013.

Asthma: type 2 _versus_ non-type 2 inflammation

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■ Conclusion

Anti-IgE omalizumab in severe allergic asthma
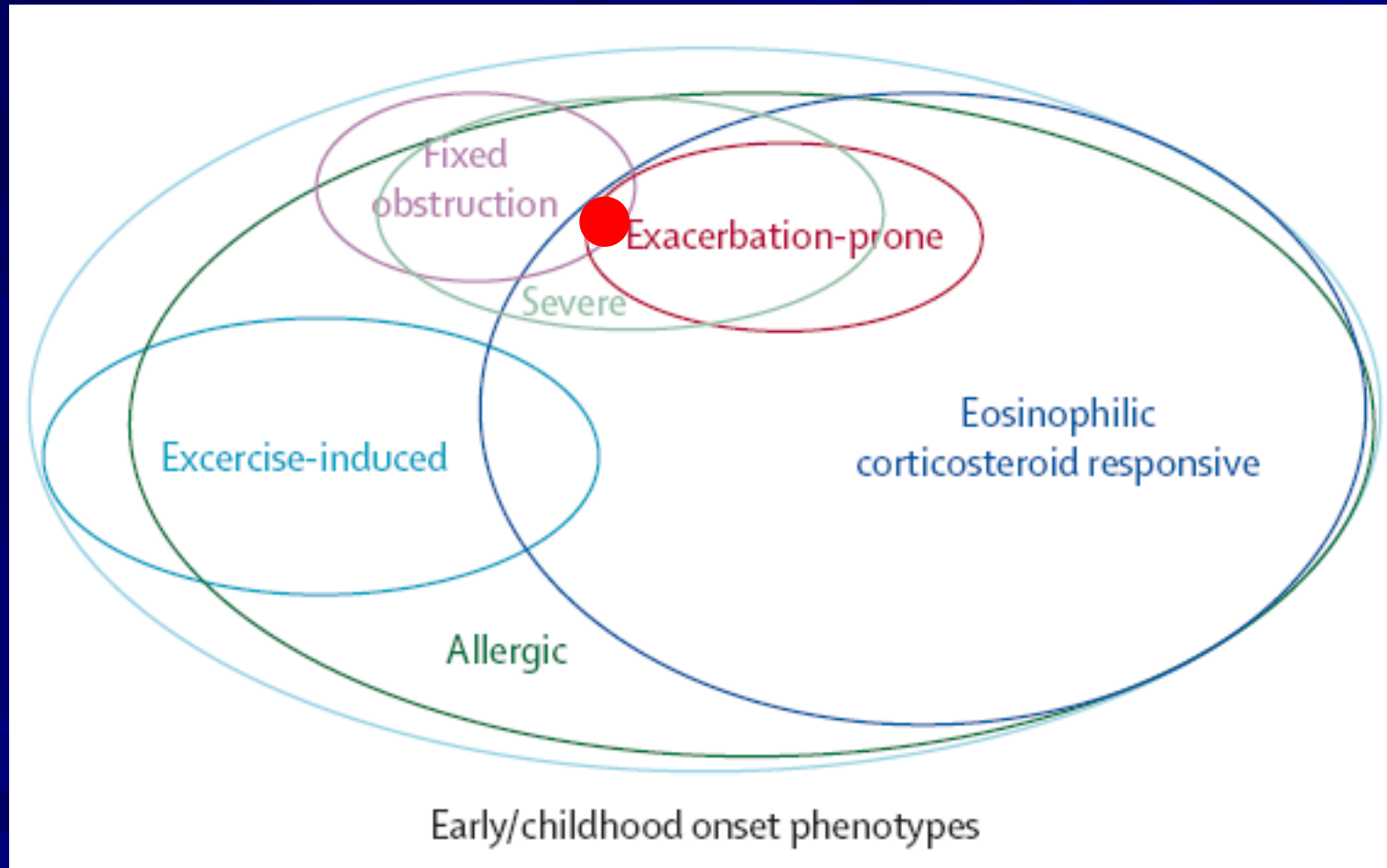
Anti-IL5 monoclonal antibodies mepolizumab and reslizumab in severe eosinophilic asthma

Brusselle G. et al. Nat Med 2013.
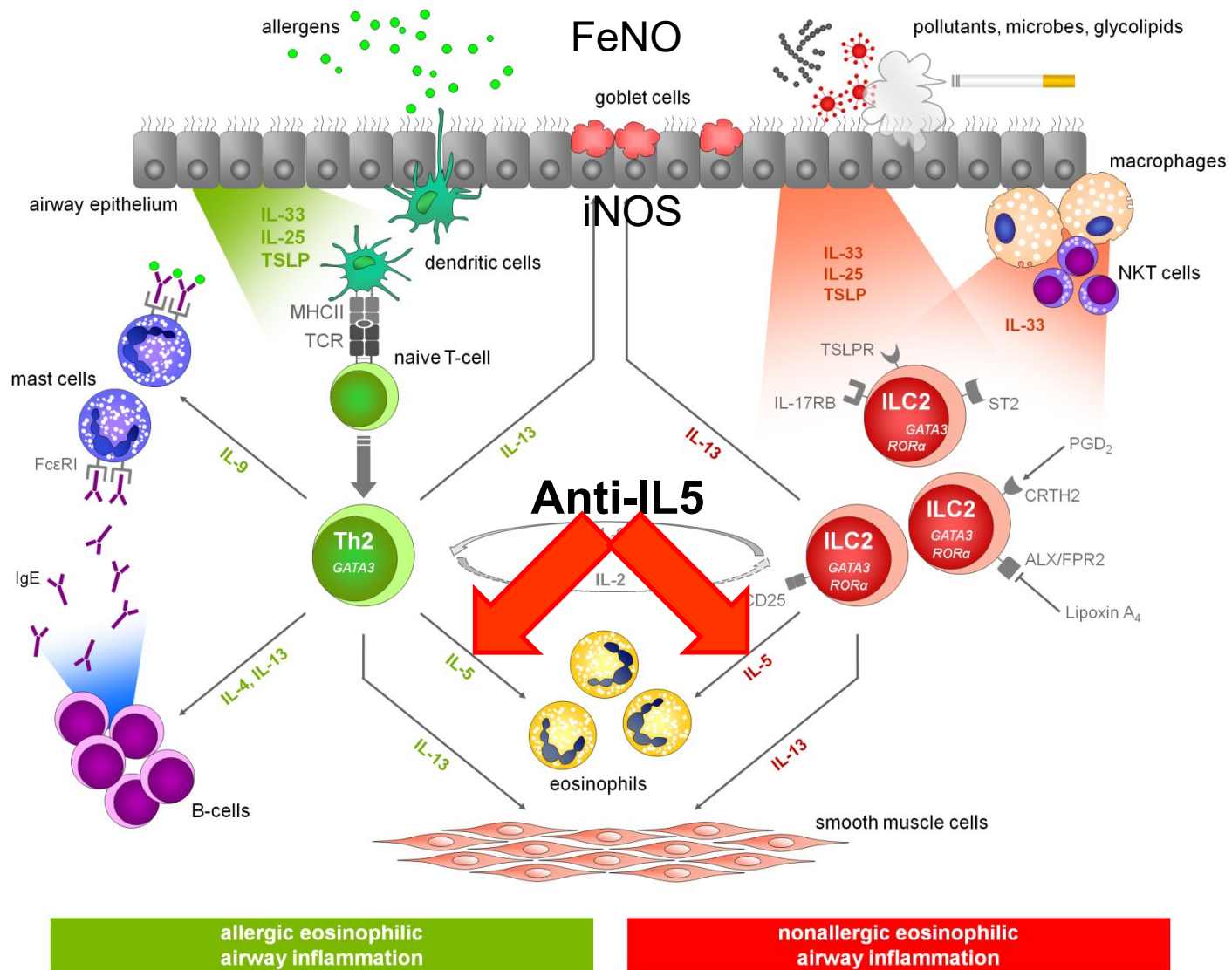
Anti-IL5 mepolizumab reduces exacerbation rate in severe eosinophilic asthma
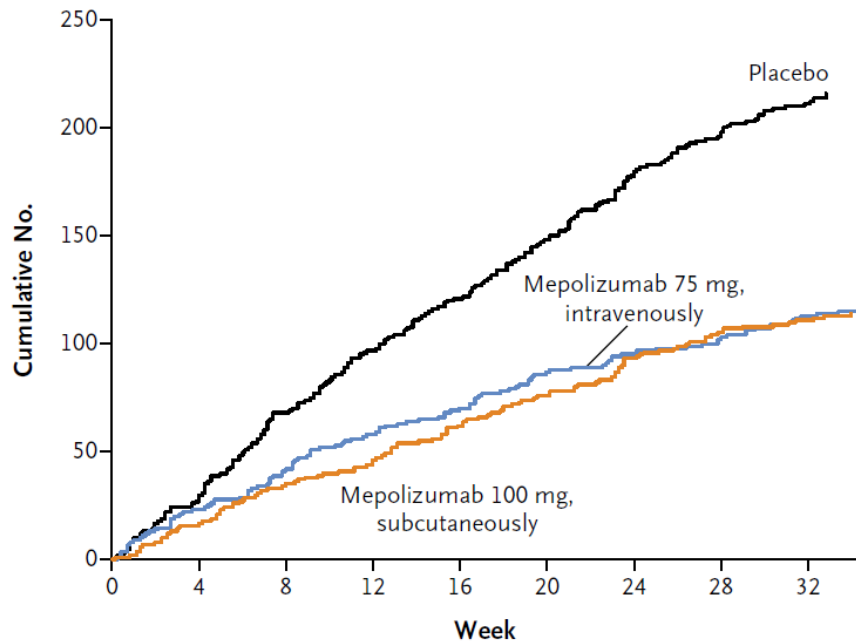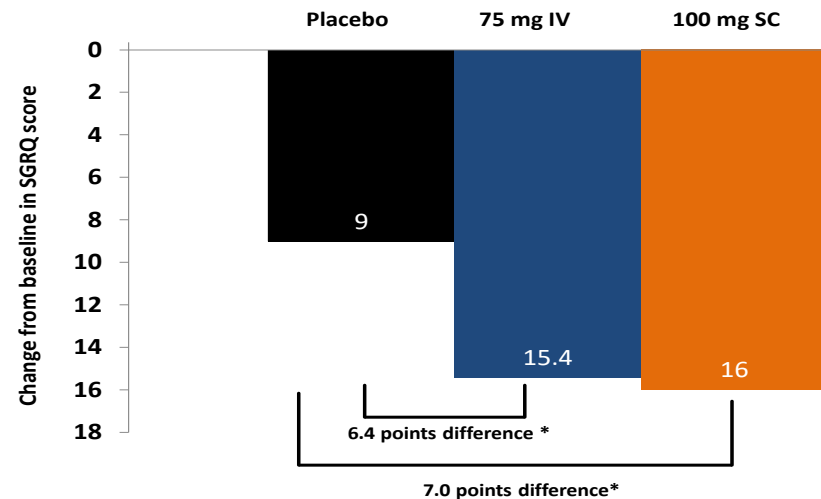
Adolescents and adults on high dose ICS+LABA
with ≥ 2 exacerbations in the past year and
blood eos > 300/μL in the past year or > 150/μL at screening.

MENSA study. Ortega H. et al, NEJM 2014.

Anti-IL5 reslizumab IV reduces exacerbation rate in severe eosinophilic asthma
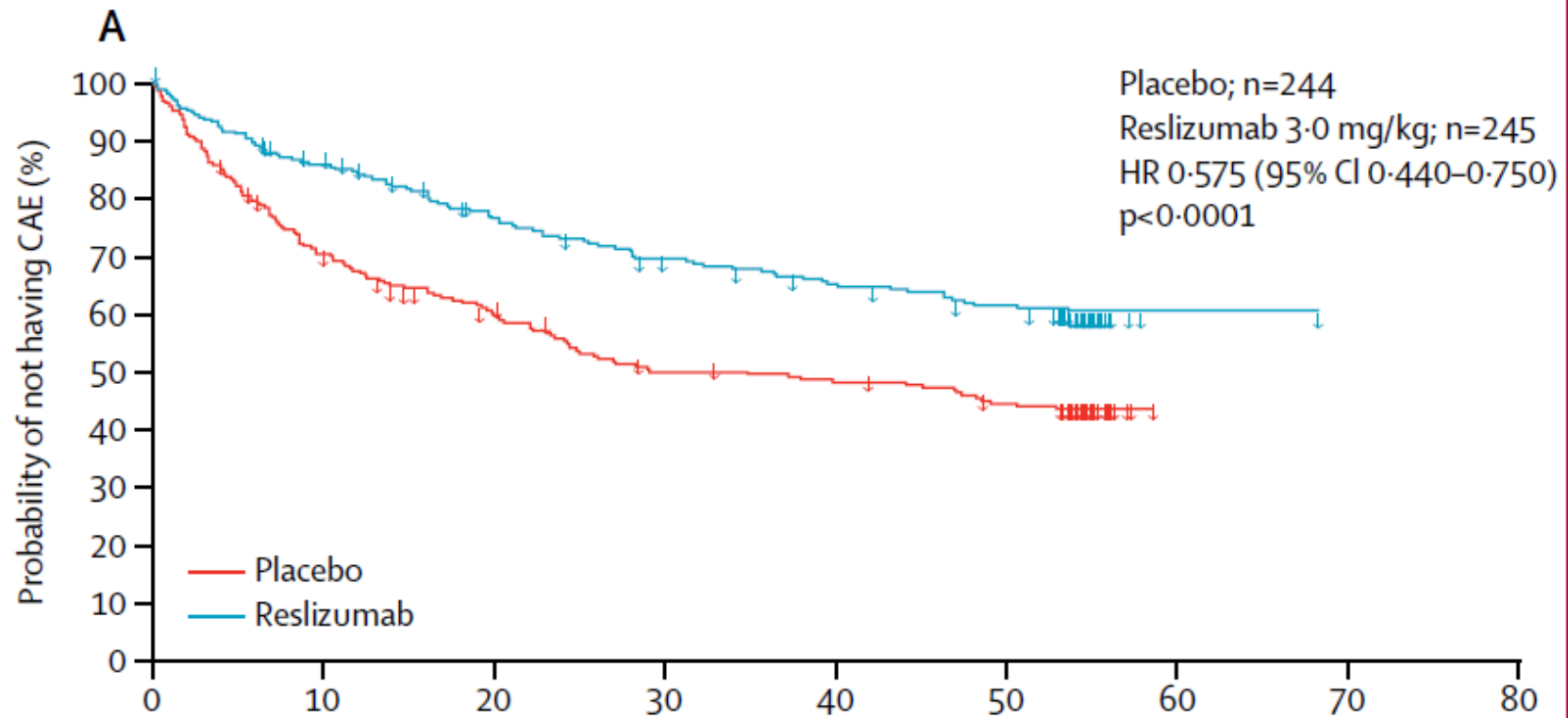
Adolescents and adults on medium to high dose ICS+LABA
with uncontrolled asthma (ACQ > 1.5), ≥ 1 exacerbation in the past year
and blood eos > 400/µL (at screening).

Castro M, et al. Lancet Resp Med 2015.

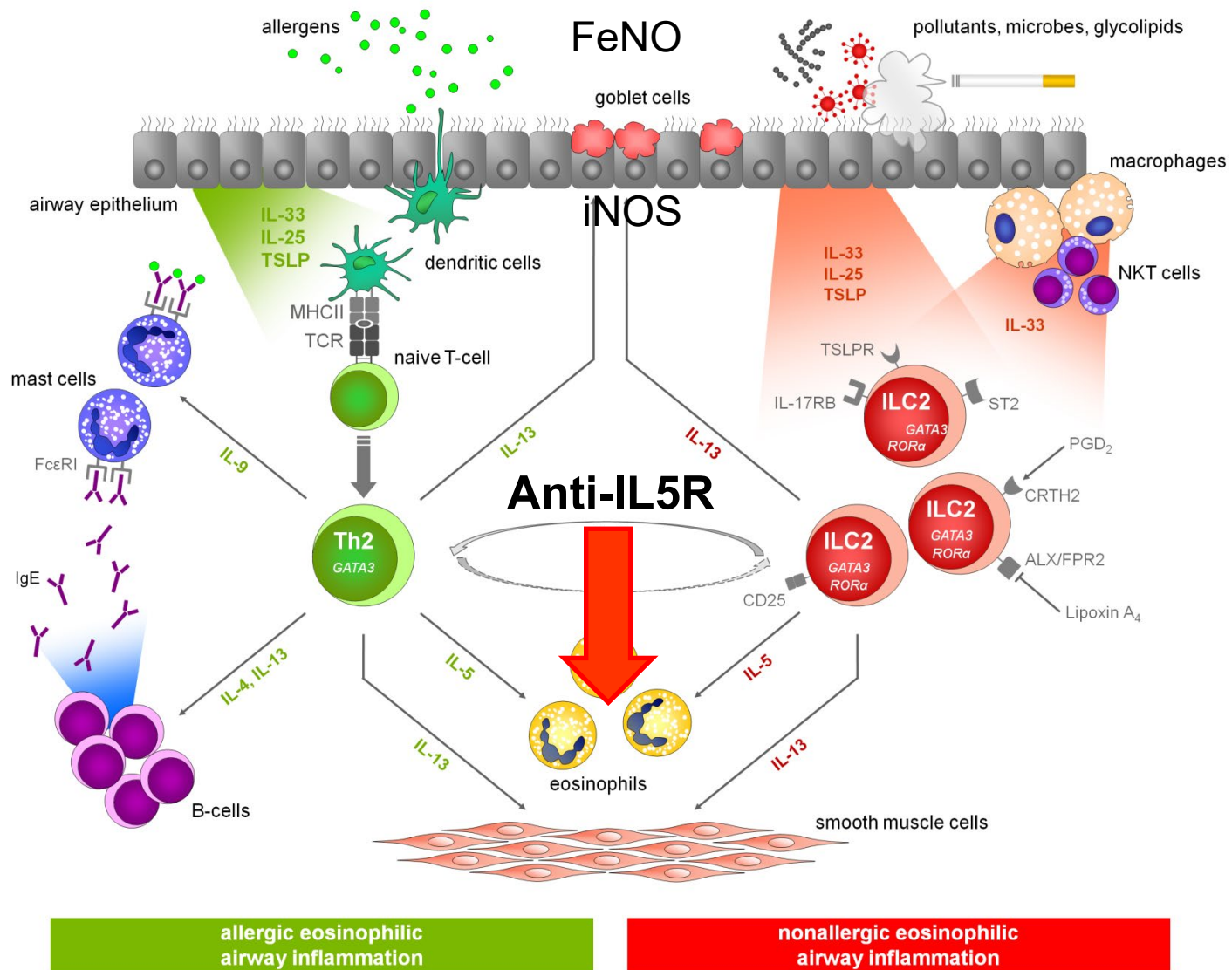# Reduction of exacerbation rates with reslizumab IV in eosinophilic asthma according to clinical characteristics
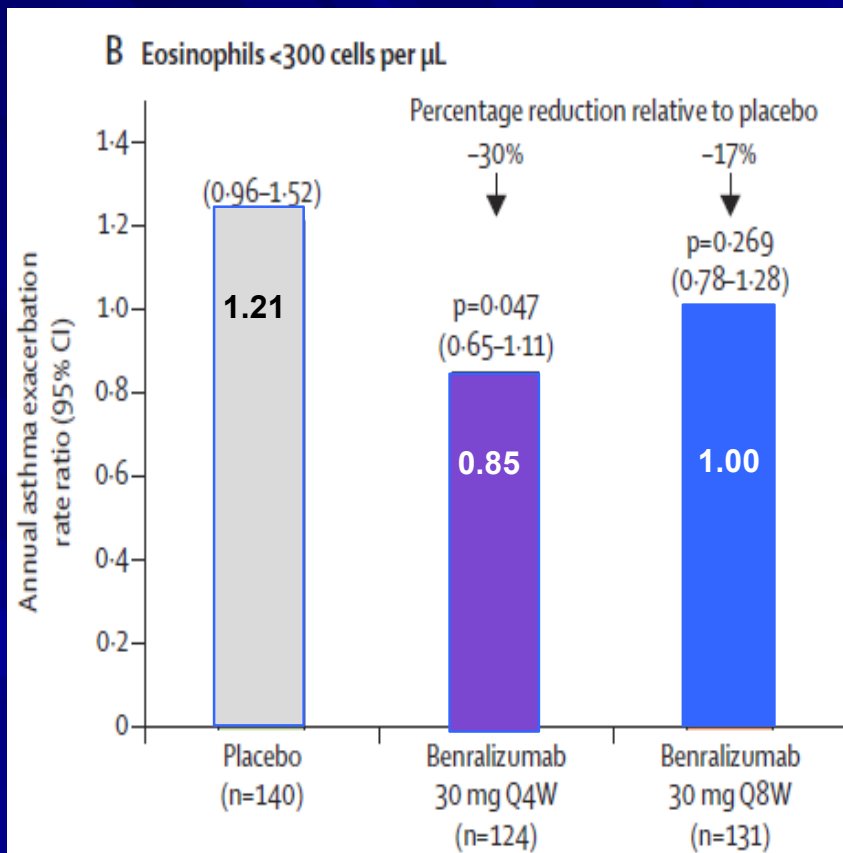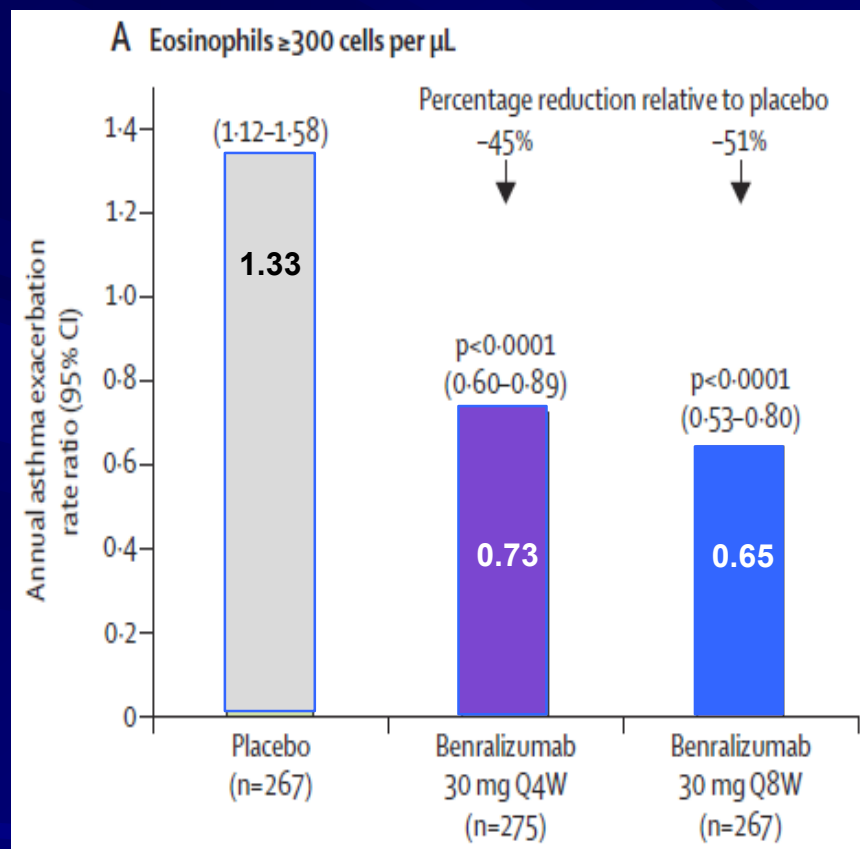
Severe asthma exacerbations (OCS)
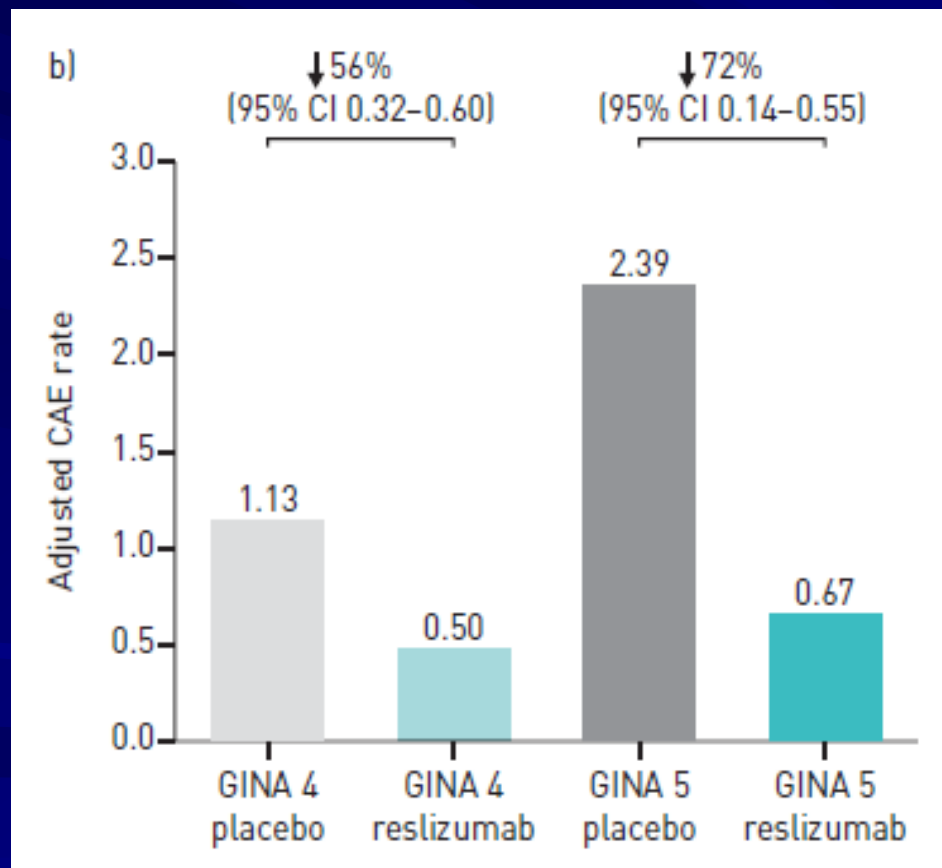
ED visits or hospitalisation
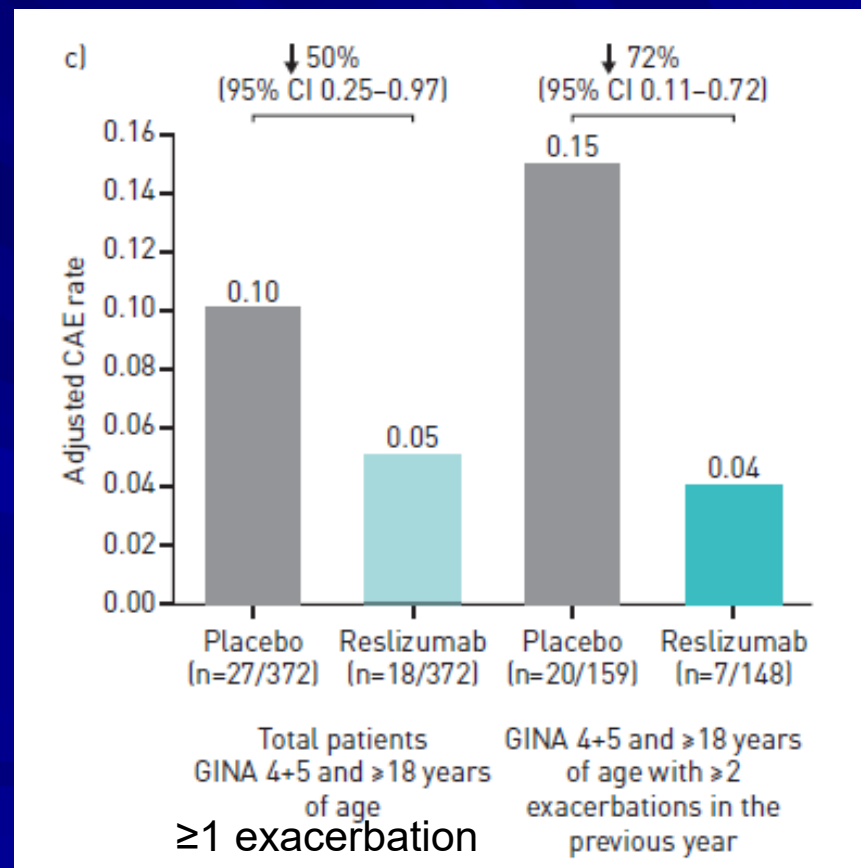
Anti-IL5 receptor monoclonal antibody benralizumab in severe eosinophilic asthma
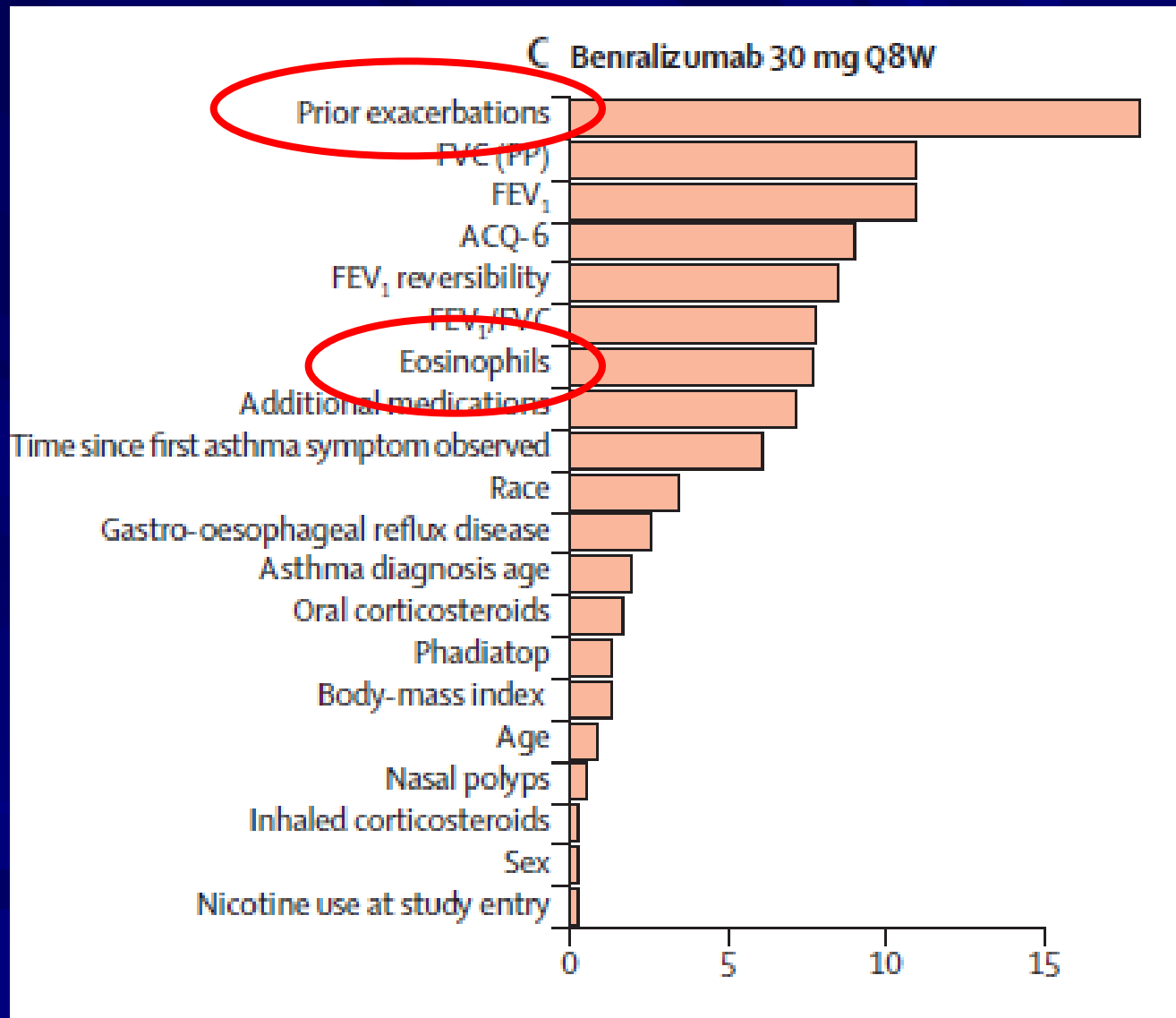
Anti-IL5R monoclonal antibody benralizumab reduces exacerbation rate in severe eosinophilic asthma
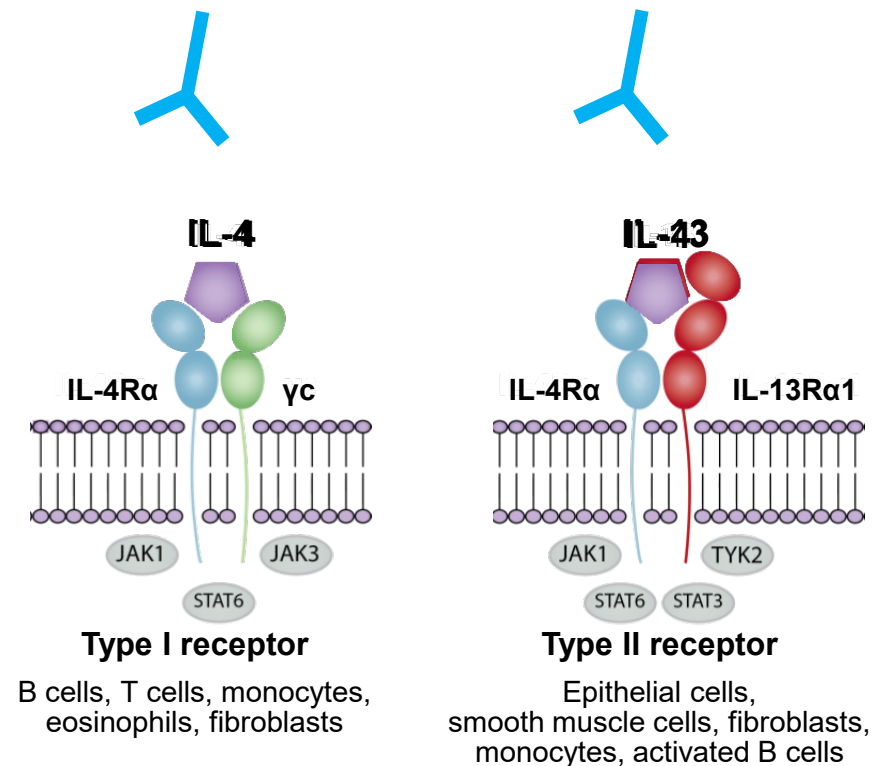

Adolescents and adults on high dose ICS+LABA
with uncontrolled asthma (ACQ ≥ 1.5) and
at least 2 exacerbations in the last year.

SIROCCO study. E. Bleecker et al, Lancet 2016.

Benralizumab: predictors of response
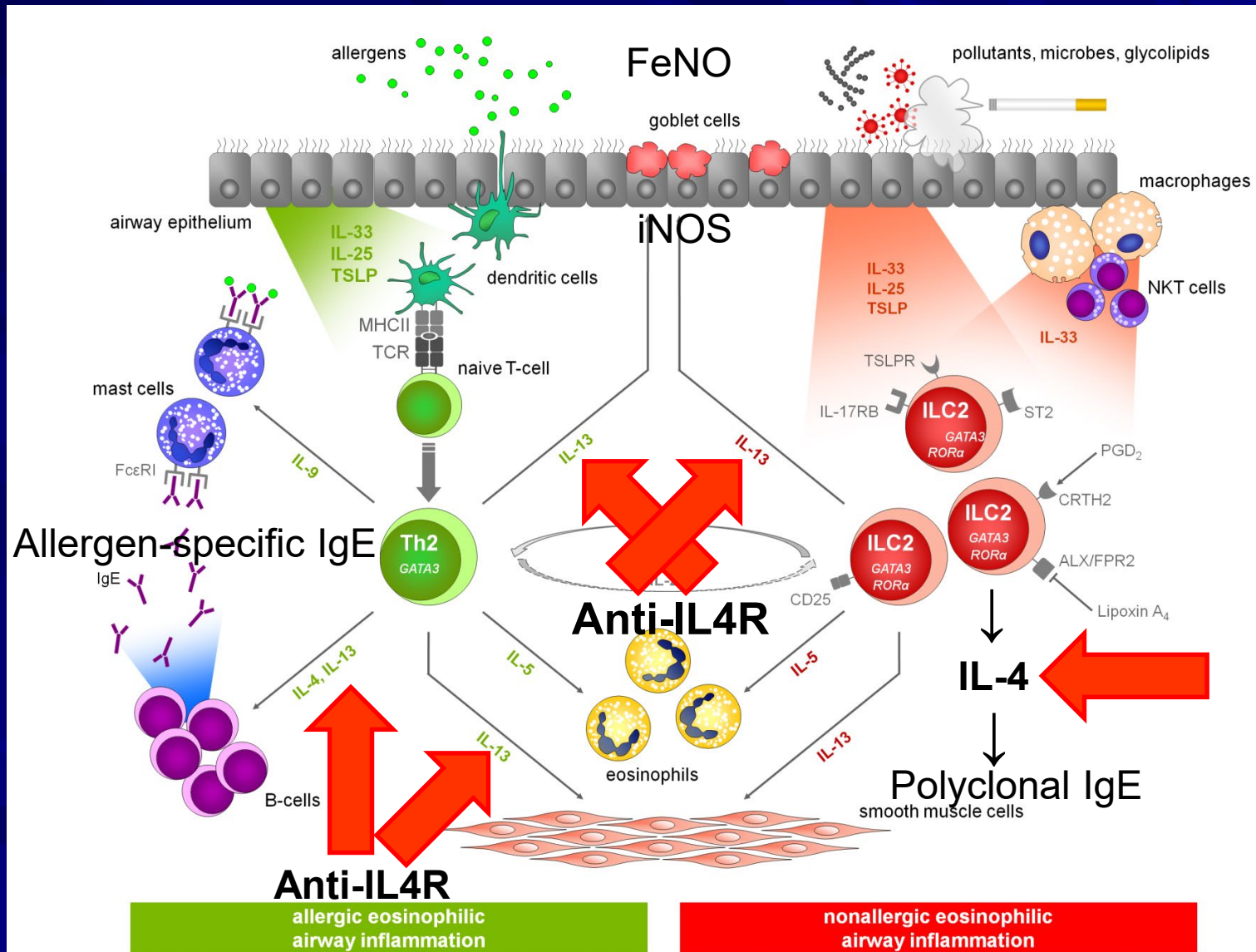

M. FitzGerald et al, Lancet RM 2018.

# Anti-IL4Rα monoclonal antibody dupilumab: mechanism of action

- **Dupilumab** is a fully human IL-4Rα monoclonal antibody inhibiting **IL-4** and **IL-13** signaling pathways, key drivers of Type 2 inflammation.

- **Dupilumab** is approved for the treatment of adults with moderate-to-severe atopic dermatitis; and has also shown efficacy in patients with other Type 2 inflammatory diseases including nasal polyposis with chronic rhinosinusitis.

IL-4

IL-4Rα   γc

JAK1   JAK3

STAT6

Type I receptor

B cells, T cells, monocytes, eosinophils, fibroblasts

IL-43

IL-4Rα   IL-13Rα1

JAK1   TYK2

STAT6   STAT3

Type II receptor

Epithelial cells, smooth muscle cells, fibroblasts, monocytes, activated B cells

Anti-IL4 receptor (IL4R) monoclonal antibody dupilumab

Brusselle G. et al. Nat Med 2013.

Anti-IL4R dupilumab improves lung function in uncontrolled moderate-to-severe asthma
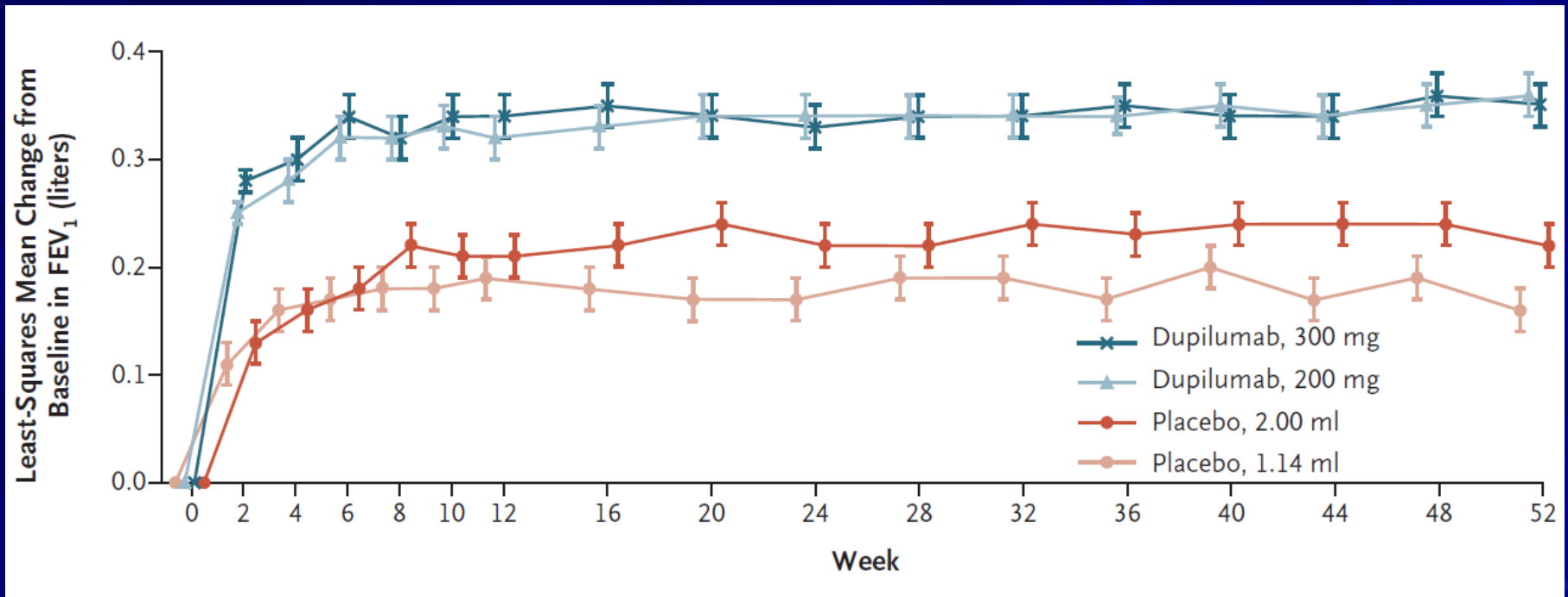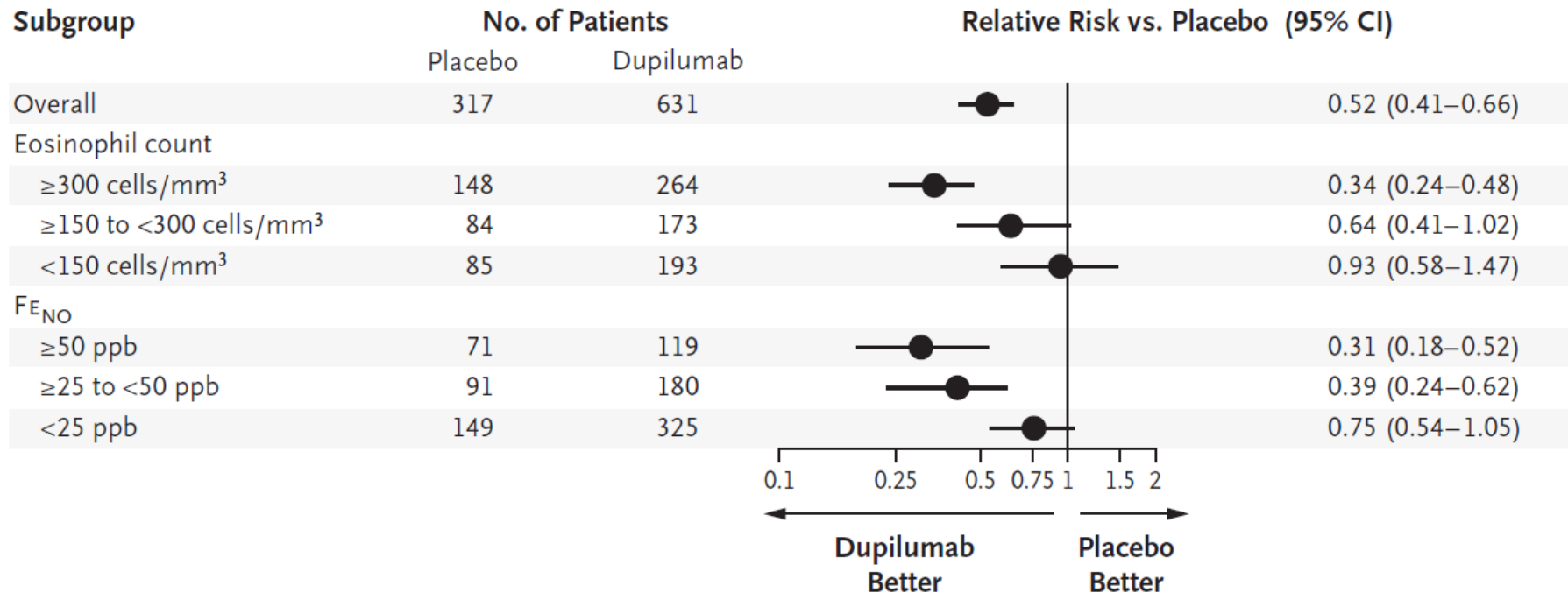

Adolescents and adults with uncontrolled asthma (ACQ-5 > 1.5)
on medium-to-high dose ICS plus up to two additional controllers
and ≥ 1 severe exacerbation in the previous year;
NO minimum requirement for blood eosinophil count or FENO.

LIBERTY ASTHMA QUEST study. Castro M. et al, NEJM 2018.

Dupilumab prevents exacerbations in uncontrolled moderate-to-severe asthma

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/mm^3	148	264	0.34 (0.24–0.48)
≥150 to <300 cells/mm^3	84	173	0.64 (0.41–1.02)
<150 cells/mm^3	85	193	0.93 (0.58–1.47)
$F_{E_{NO}}$			
≥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)

Dupilumab Better ← → Placebo Better

NO minimum requirement for blood eosinophil count or FENO.

LIBERTY ASTHMA QUEST study. Castro M. et al, NEJM 2018.

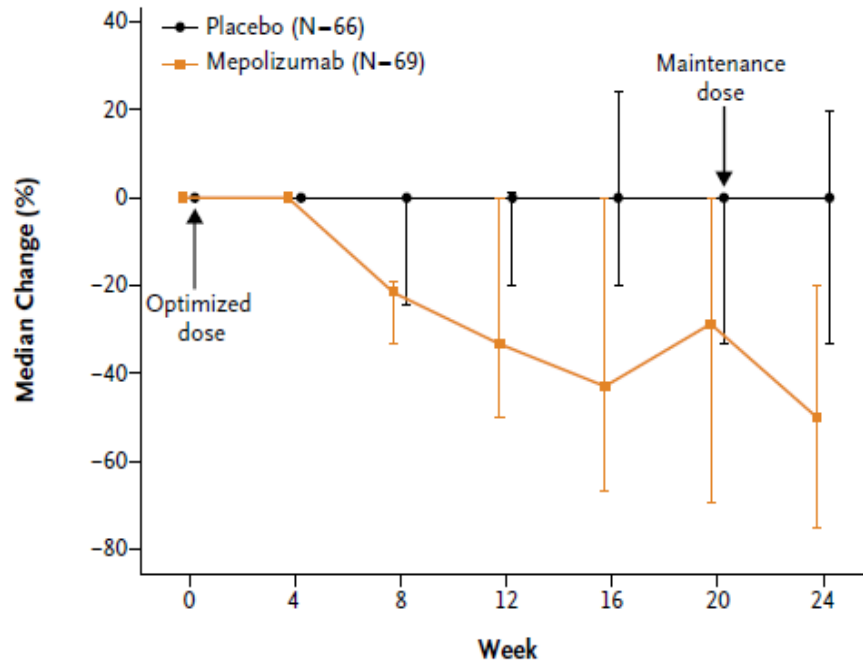# Anti-cytokine (receptor) monoclonal antibodies as add-on therapy in severe asthma

Monoclonal antibody	Therapeutic target	Phenotypic Biomarkers	Route of administration Dosing	Indication
Benralizumab	IL-5 Receptor alpha (IL-5Rα)	Blood eosinophil levels *Sputum eosinophil levels*	SC 30 mg every 4 weeks (first three doses), followed by 30 mg every 8 weeks	Severe eosinophilic asthma
Dupilumab	IL-4 Receptor alpha (IL-4Rα)	Increased FENO and/or blood eosinophil levels	SC 200 mg or 300 mg every 2 weeks	Severe type 2 (eosinophilic) asthma
Mepolizumab	IL-5	Blood eosinophil levels *Sputum eosinophil levels*	SC 100 mg every 4 weeks	Severe eosinophilic asthma
Reslizumab	IL-5	Blood eosinophil levels *Sputum eosinophil levels*	IV 3mg/kg every 4 weeks	Severe eosinophilic asthma

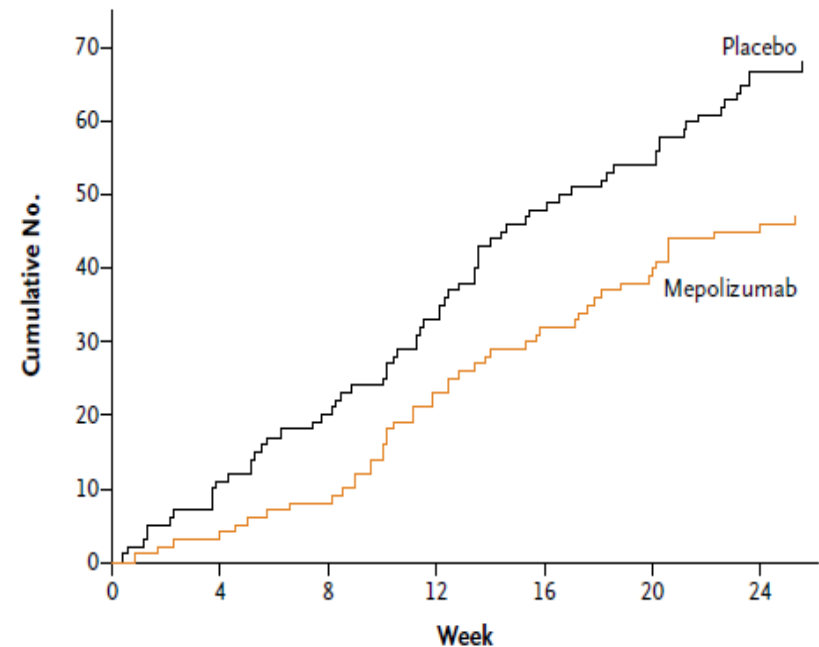# **Severe Asthma Management**

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Oral glucocorticoid-sparing effect of mepolizumab in severe eosinophilic asthma
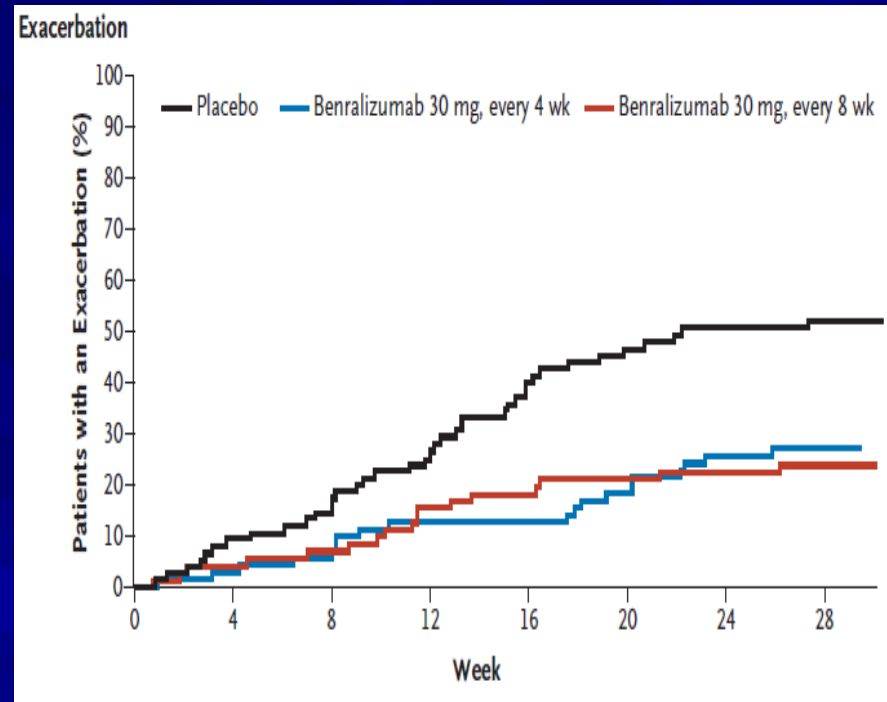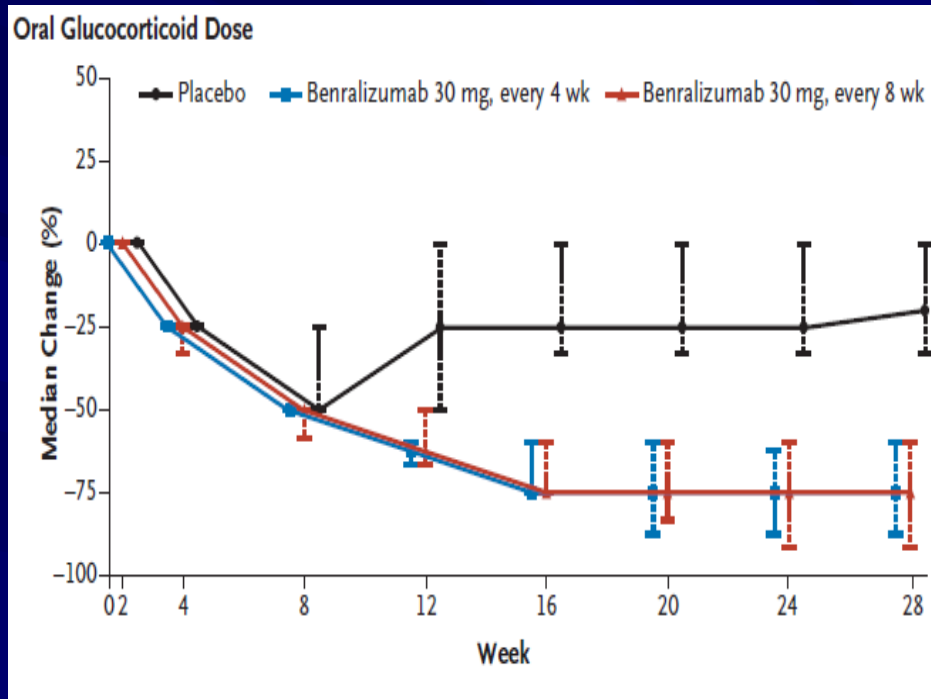

Asthma patients requiring oral steroids for at least 6 months
(plus high dose ICS + second controller);
blood eosinophil count at optimization phase >150/µl or >300/µl in preceding year.
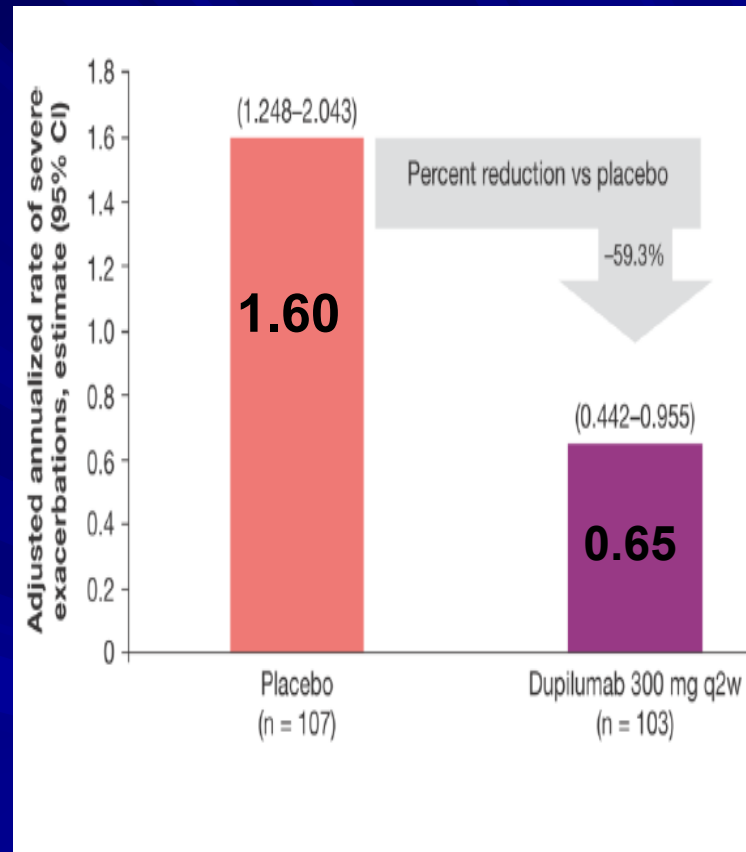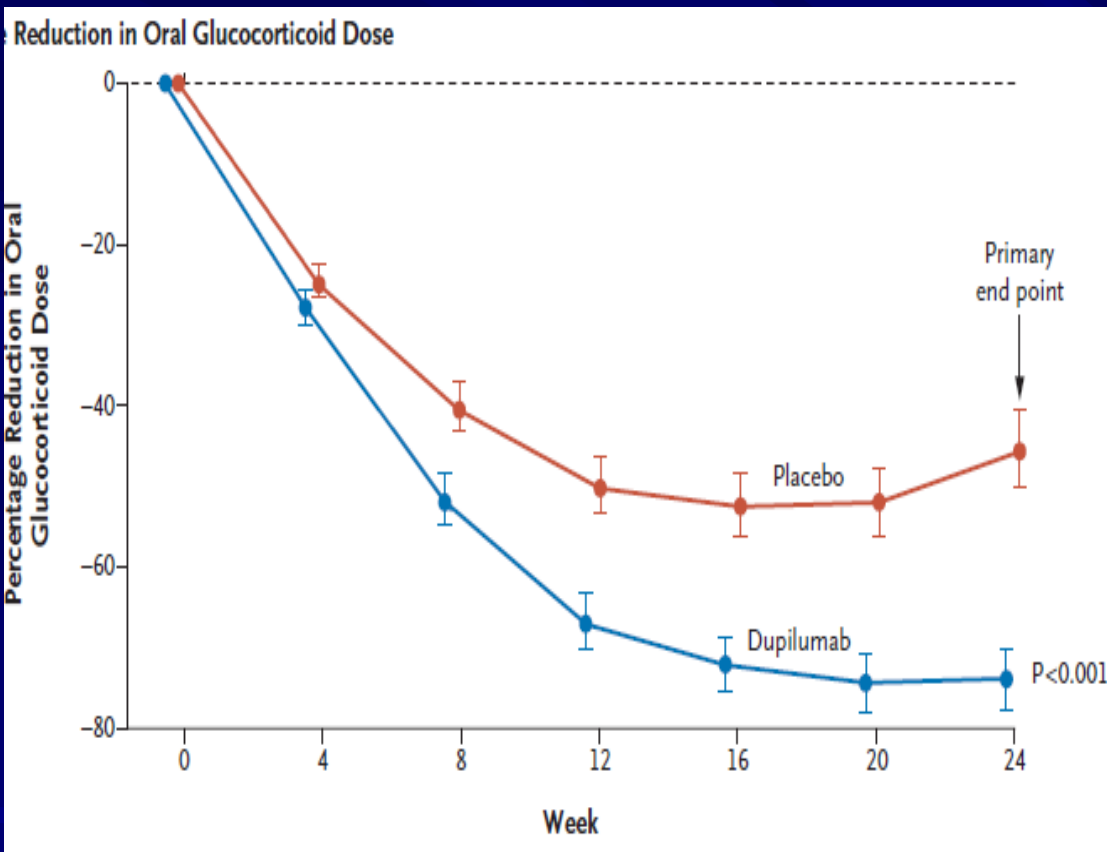
SIRIUS study. Bel E. et al, NEJM 2014.

Oral glucocorticoid-sparing effect of benralizumab in severe eosinophilic asthma

Asthma patients requiring oral steroids for at least 6 months
(plus high dose ICS+LABA);
blood eosinophil count at baseline >150/μl.

ZONDA study. Nair P. et al, NEJM 2017.

Oral glucocorticoid-sparing effect of dupilumab in OCS-dependent severe asthma

Asthma patients requiring oral steroids for at least 6 months
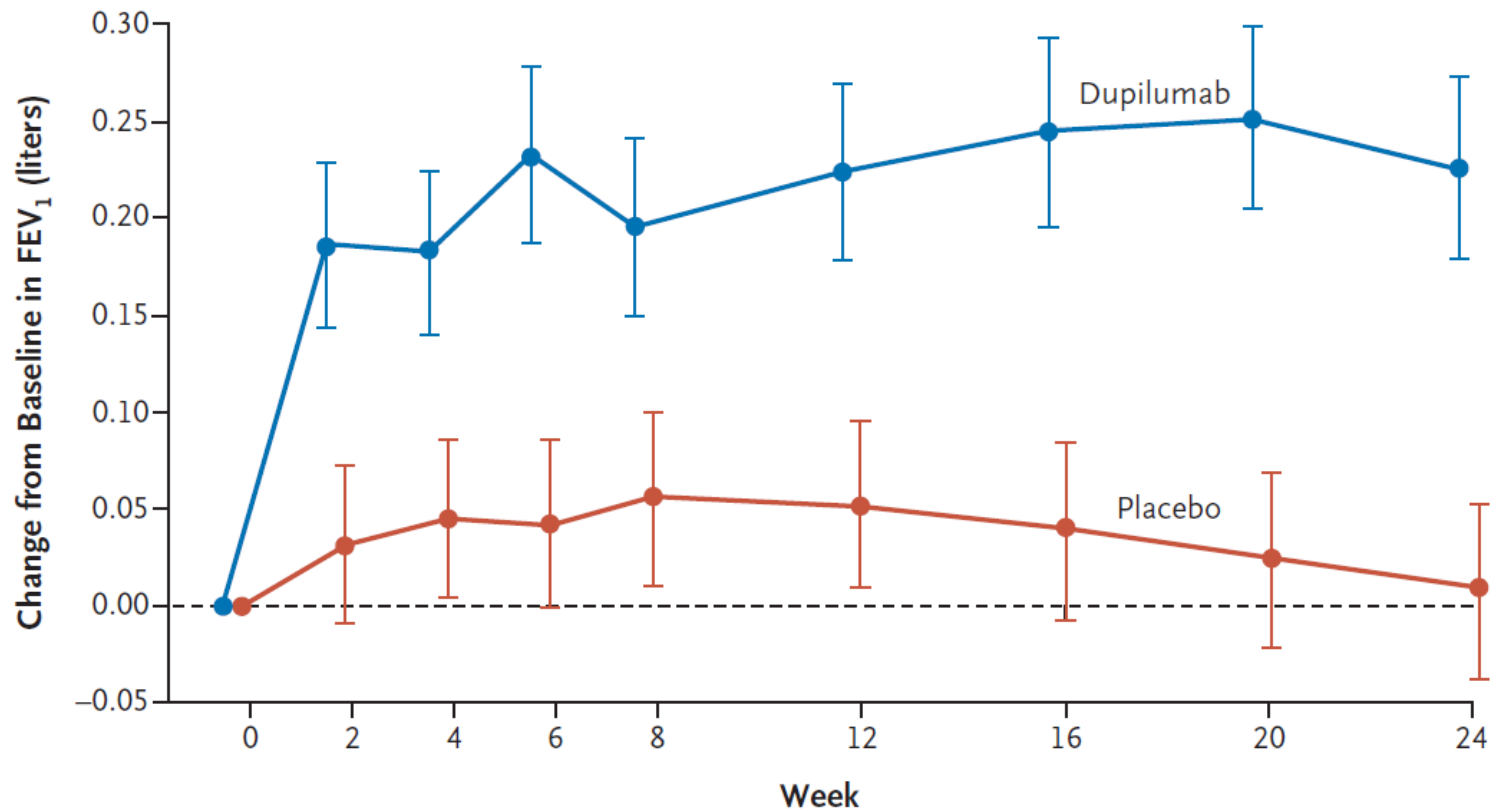(plus high dose ICS + up to 2 controllers);
no minimum requirement of Type 2 biomarkers (blood eosinophil count or FENO).

LIBERTY ASTHMA VENTURE trial. Rabe K. et al, NEJM 2018.
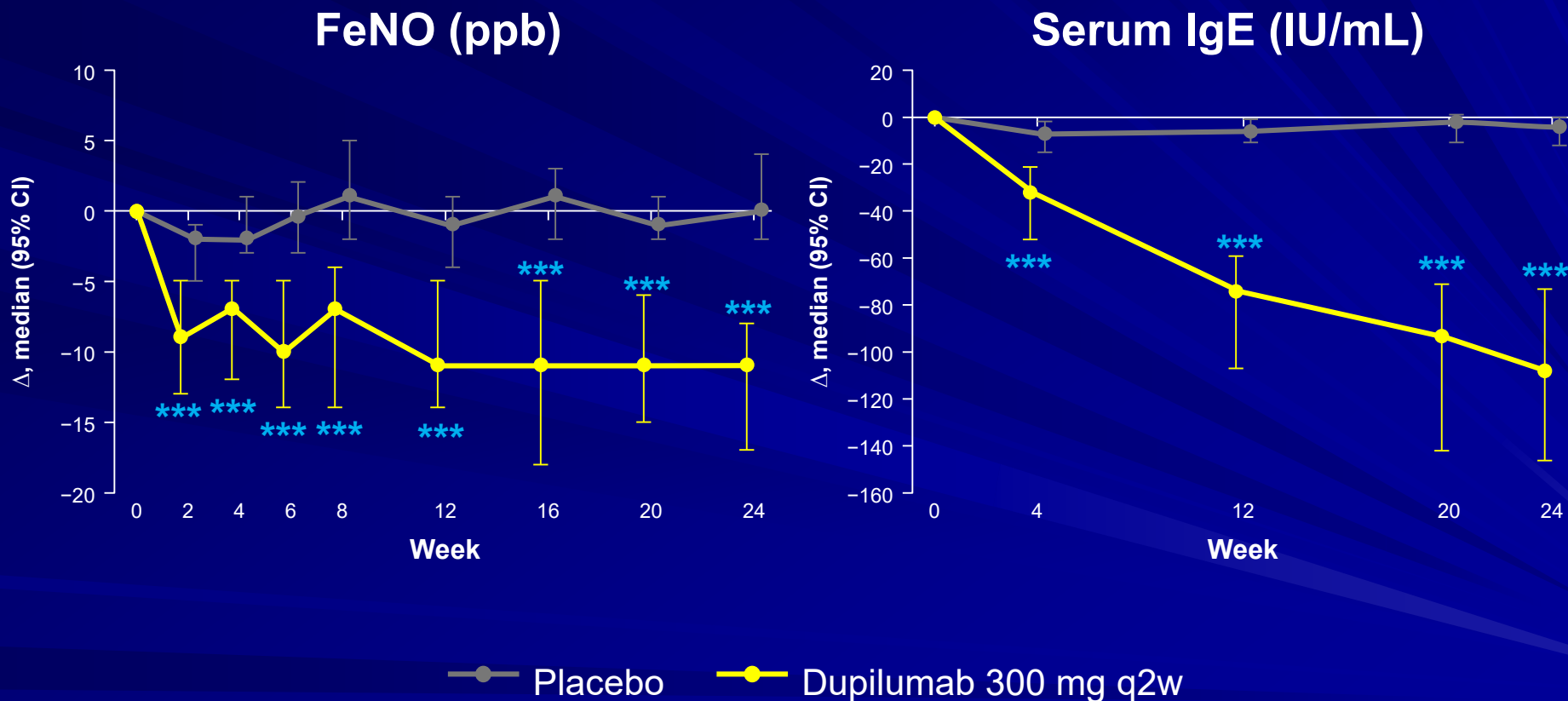
Effect of dupilumab on lung function in OCS-dependent severe asthma

Change from Baseline in FEV$_1$ before Bronchodilator Use

LIBERTY ASTHMA VENTURE trial. Rabe K. et al, NEJM 2018.

Dupilumab Reduced FeNO and Serum Total IgE in OCS-dependent severe asthma

FeNO (ppb)

Serum IgE (IU/mL)

Placebo   Dupilumab 300 mg q2w

Rabe K. et al, ERS Congress Paris 2018.

Dupilumab safety: overview of adverse events

Event	Placebo Group (N = 107)	Dupilumab Group (N = 103)
	number (percent)	
Any adverse event	69 (64)	64 (62)
Any serious adverse event	6 (6)	9 (9)
Any adverse event leading to death	0	0
Any adverse event leading to permanent discontinuation of trial regimen	4 (4)	1 (1)
Adverse event occurring in ≥5% of patients in either group†		
Viral upper respiratory tract infection	19 (18)	9 (9)
Bronchitis	6 (6)	7 (7)
Sinusitis	4 (4)	7 (7)
Influenza	6 (6)	3 (3)
Eosinophilia‡	1 (1)	14 (14)
Injection-site reaction§	4 (4)	9 (9)
≥1 measurement of blood eosinophil count >3000 cells/mm^3	1 (1)	13 (13)

LIBERTY ASTHMA VENTURE trial. Rabe K. et al, NEJM 2018.

Oral glucocorticoid-sparing effect of monoclonal antibodies in severe asthma

Drug	Trial Acronym	Dosing and Route of administration	Median percent reduction in daily OCS dose
mepolizumab	SIRIUS	SC 100 mg every 4 wk	-50% vs baseline; -50% vs placebo
benralizumab	ZONDA	SC 30 mg every 4 or 8 wk *	-75% vs baseline; -50% vs placebo
dupilumab	LIBERTY ASTHMA VENTURE	SC 300 mg every 2 wk	-70% vs baseline; -28% vs placebo

* benralizumab SC 30 mg every 4 wk (first 3 doses), followed by 30 mg every 4 wk or every 8 wk

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- Conclusion

Useful Biomarkers in the Clinic

For a biomarker to be clinically useful in the management of a disease, the biomarker must be either:

- **<u>Diagnostic</u>**:
  - Chronic disease (*BNP* in heart failure)
  - Acute attack / exacerbation (*troponin* in myocardial infarction);

- **<u>Prognostic</u>**: predicting the course of the disease: e.g. increased *blood eosinophilia* predicts future risk of exacerbations in (severe) asthma;

- **<u>Theragnostic</u>**: predicting the response to therapy: e.g. increased *FeNO* predicts response to ICS in asthma.

Type 2 biomarkers in (severe) asthma

Biomarker	Prognostic	Theragnostic	Therapeutic target
Blood eosinophil count	++	++: anti-IL5, anti-IL5R, anti-IL4Rα; +: anti-IgE	YES
FeNO	++	++ : anti-IL4Rα; +: anti-IgE, anti-IL5, anti-IL5R	NO
Serum total IgE	-	±	YES Local allergen-specific IgE

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Management of Severe Asthma in Adults

- GINA Severe Asthma Pocket Guide:
  - From difficult-to-treat towards severe asthma
  - Phenotyping of severe asthma.
- In patients with type 2 _severe asthma_ receiving maintenance treatment with OCS (_GINA step 5b_), add-on therapy with an anti-type 2 biologic (mepolizumab, benralizumab or dupilumab) is corticosteroid-sparing and reduces exacerbations.

Therapy of Uncontrolled Severe Asthma

- In patients with *type 2 severe asthma* and (frequent) exacerbations despite treatment with (medium-to-) high dose ICS+LABA (*GINA step 5a*), add-on therapy with the following biologics has been shown to be efficacious and safe:
  - omalizumab in severe allergic asthma
  - mepolizumab, reslizumab (IV) and benralizumab in severe eosinophilic asthma
  - dupilumab in severe type 2 asthma.
- Head-to-head comparative pragmatic trials in *type 2 severe asthma* are urgently needed.

PREDICTUMAB 01 TRIAL

PREDICTIVE FACTORS OF RESPONSE TO OMALIZUMAB AND MEPOLIZUMAB IN ALLERGIC AND EOSINOPHILIC SEVERE ASTHMA:

A MULTICENTER PRAGMATIC TRIAL IN BELGIUM

Pr Charles Pilette, MD PhD
Cliniques universitaires St-Luc - pneumologie, Brussels
Institut de Recherche Expérimentale & Clinique
Université catholique de Louvain

On behalf of the asthma-allergy working group of the BSP
(Belgian Society of Pneumology)

Guy Brusselle

Back-up slides

Assess and treat severe asthma phenotypes *cont'd*

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities)

6b Consider *add-on biologic Type 2* targeted treatments

- Consider add-on Type 2-targeted biologic for patients with exacerbations and allergic/eosinophilic biomarkers on high dose ICS-LABA, with/without daily OCS ◑
- Consider **local payer eligibility criteria** ◑ and **predictors of response** when choosing between available therapies
- Also consider cost, dosing frequency, route (SC or IV), patient preference

◑ *Check local eligibility criteria for specific biologic therapies as these may vary from those listed*

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Assess and treat severe asthma phenotypes *cont'd*

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities)

6b Consider *add-on biologic Type 2* targeted treatments

- Consider add-on Type 2-targeted biologic for patients with exacerbations and allergic/eosinophilic biomarkers on high dose ICS-LABA, with/without daily OCS 🕐
- Consider local payer eligibility criteria 🕐 and **predictors of response** when choosing between available therapies
- Also consider cost, dosing frequency, route (SC or IV), patient preference

Which biologic is appropriate to start first?

Anti-IgE

*Is the patient eligible for **anti-IgE** (for severe allergic asthma)?*
- Sensitization on skin prick testing or specific IgE 🕐
- Total serum IgE and weight within dosage range 🕐
- Exacerbations in last year 🕐

no

no

Anti-IL5 / Anti-IL5R

*Is the patient eligible for **anti-IL5 / anti-IL5R** (for severe eosinophilic asthma)?*
- Exacerbations in last year 🕐
- Blood eosinophils ≥300/µl 🕐

Eligible for neither?
*Return to section **6a***

🕐 *Check local eligibility criteria for specific biologic therapies as these may vary from those listed*

Assess and treat severe asthma phenotypes *cont'd*

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities)

6b Consider *add-on biologic Type 2* targeted treatments

- Consider add-on Type 2-targeted biologic for patients with exacerbations and allergic/eosinophilic biomarkers on high dose ICS-LABA, with/without daily OCS ⏱
- Consider local payer eligibility criteria ⏱ and **predictors of response** when choosing between available therapies
- Also consider cost, dosing frequency, route (SC or IV), patient preference

Which biologic is appropriate to start first?

Anti-IgE

*Is the patient eligible for **anti-IgE** (for severe allergic asthma)?*

- Sensitization on skin prick testing or specific IgE ⏱
- Total serum IgE and weight within dosage range ⏱
- Exacerbations in last year ⏱

What factors may predict good response to anti-IgE?

- Blood eosinophils ≥260/µl ++
- FeNO ≥20 ppb +
- Allergen-driven symptoms +
- Childhood-onset asthma +

If eligible, trial of omalizumab for ≥4 months ⏱

Good response? yes → **Good response to T2-targeted therapy**

no ↓

STOP add-on

Consider switching to a different Type 2-targeted therapy, if eligible

no →

Anti-IL5 / Anti-IL5R

*Is the patient eligible for **anti-IL5 / anti-IL5R** (for severe eosinophilic asthma)?*

- Exacerbations in last year ⏱
- Blood eosinophils ≥300/µl ⏱

What factors may predict good response to anti-IL5/5R?

- Higher blood eosinophils +++
- More exacerbations in previous year +++
- Adult-onset of asthma ++
- Nasal polyposis ++

If eligible, trial of anti-IL5 or anti-IL5R for ≥4 months ⏱

Good response? yes

no ↓

STOP add-on

Consider switching to a different Type 2-targeted therapy, if eligible

no → **Little/no response to T2-targeted therapy**

Eligible for neither?
Return to section **6a**

⏱ *Check local eligibility criteria for specific biologic therapies as these may vary from those listed*

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Effects of biologics on biomarkers in severe asthma

		Blood eos	Sputum eos	FeNO	Serum IgE
OCS	oral steroids	↓↓	↓↓	↓↓	↓
Anti-IL-5	mepolizumab reslizumab	↓↓	↓↓	↔	↔
Anti-IL-5R	benralizumab	↓↓↓	↓↓	↔	↔
Anti-IL-13	*lebrikizumab* *tralokinumab*	↑	↔	↓↓	↓
Anti-IL-4R	dupilumab	↑	↓	↓↓	↓↓
Anti-IgE	omalizumab	↔	↓	↓↓	↑ (↓)

eos: eosinophils

Courtesy: Ian Pavord