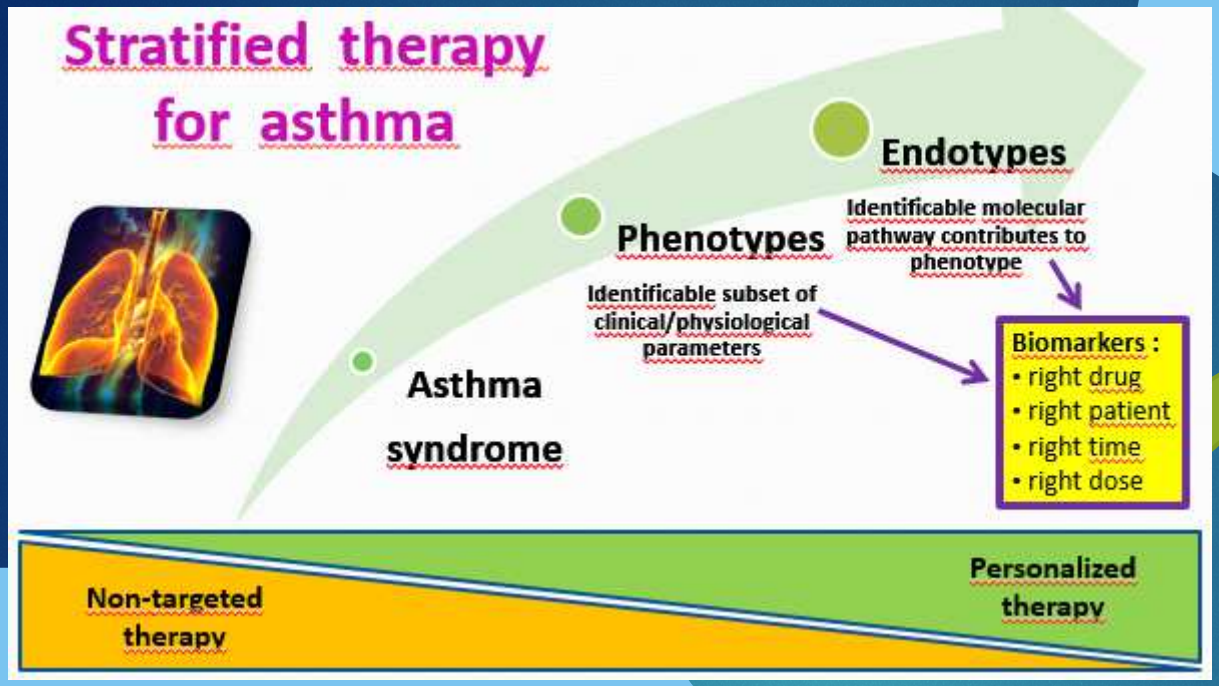
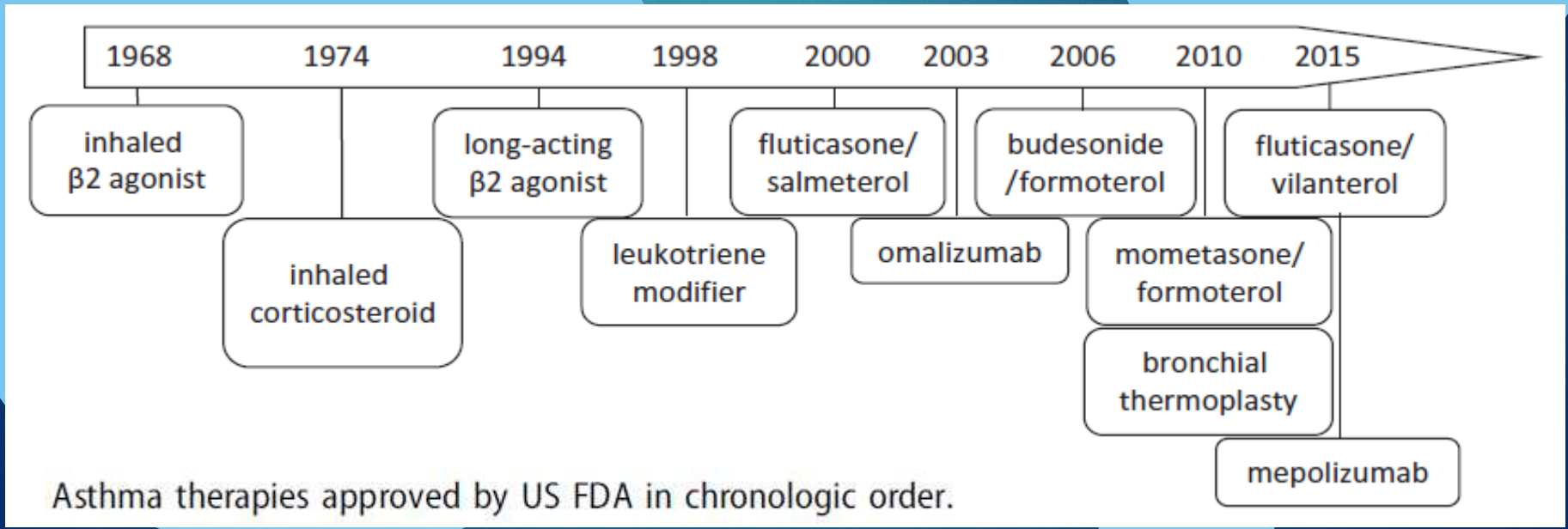
" New MABS on the block for asthma"

Carlo Lombardi

Departmental Unit of Allergology-Immunology & Respiratory Diseases
Istituto Ospedaliero Fondazione Poliambulanza (Brescia, Italy)
National Board of Italian Society of Allergology-Asthma-Clinical Immunologyl (SIAAIC) & Società Italiana di Pneumologia (SIP)
President of Italian Chapter of Interasma

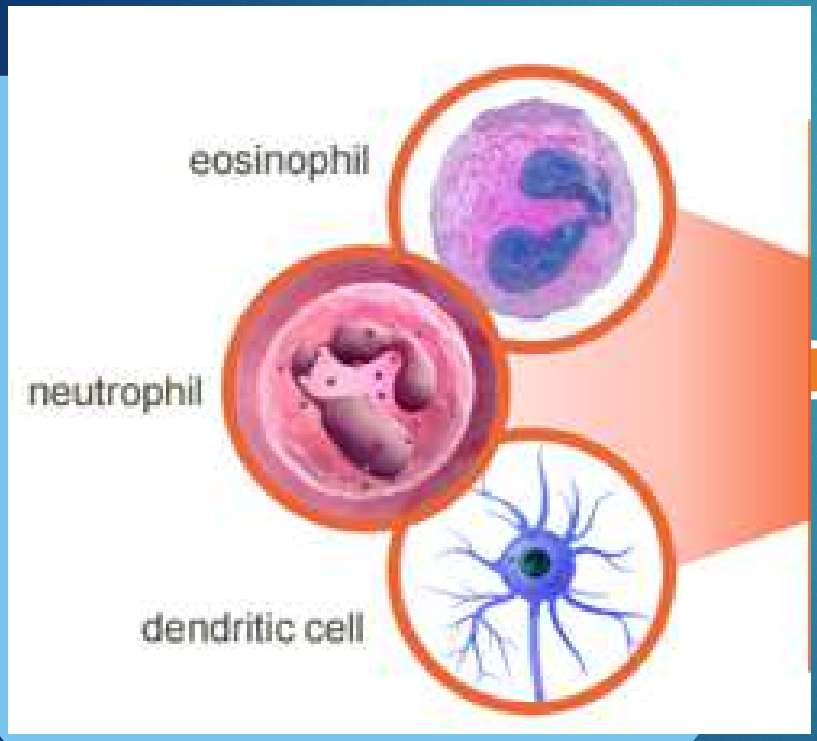


50 years of asthma Pharmaco-therapy



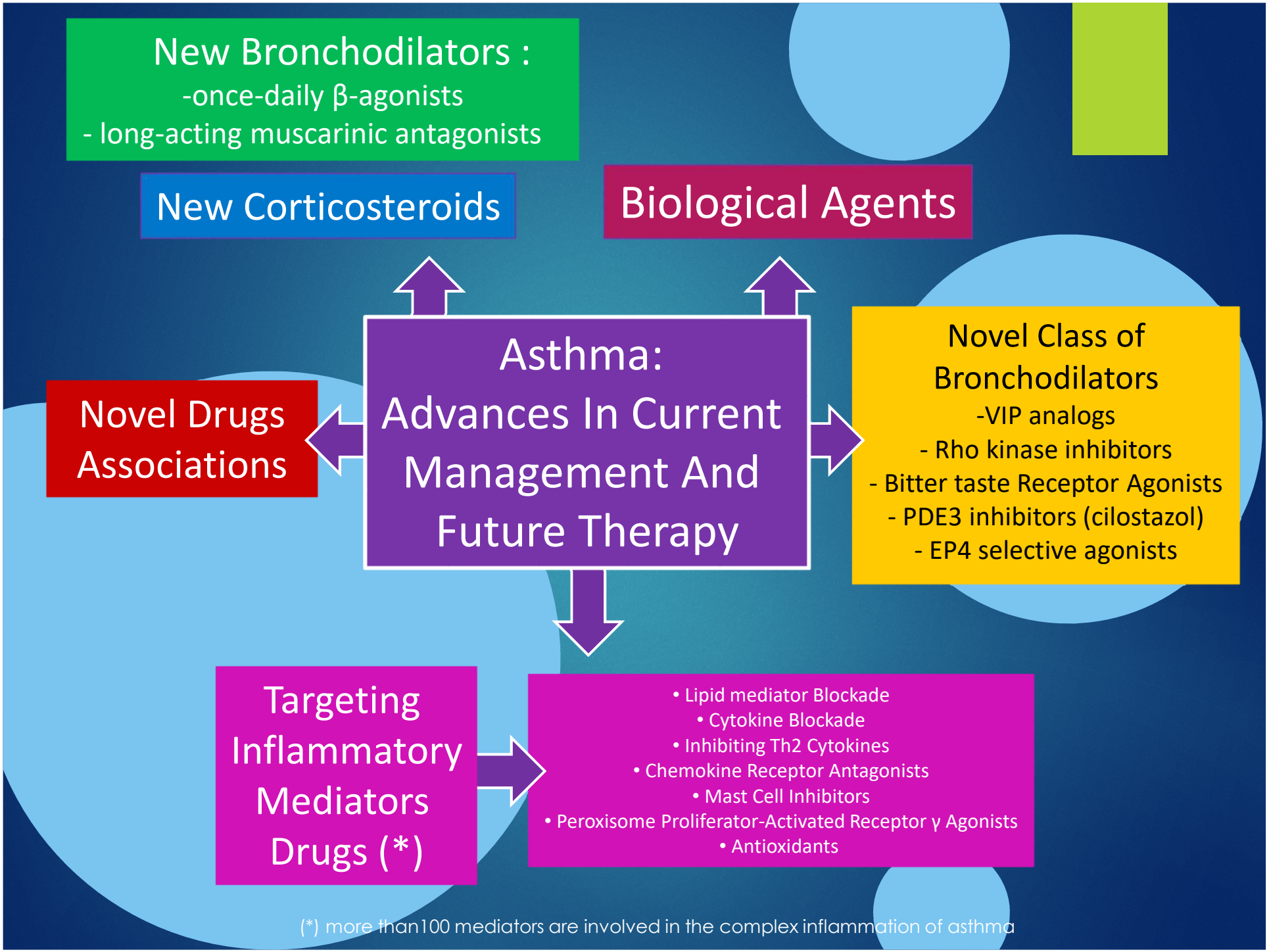
Asthma therapies approved by US FDA in chronologic order.

Asthma therapeutic strategy : from secondary prevention to primary disease modification

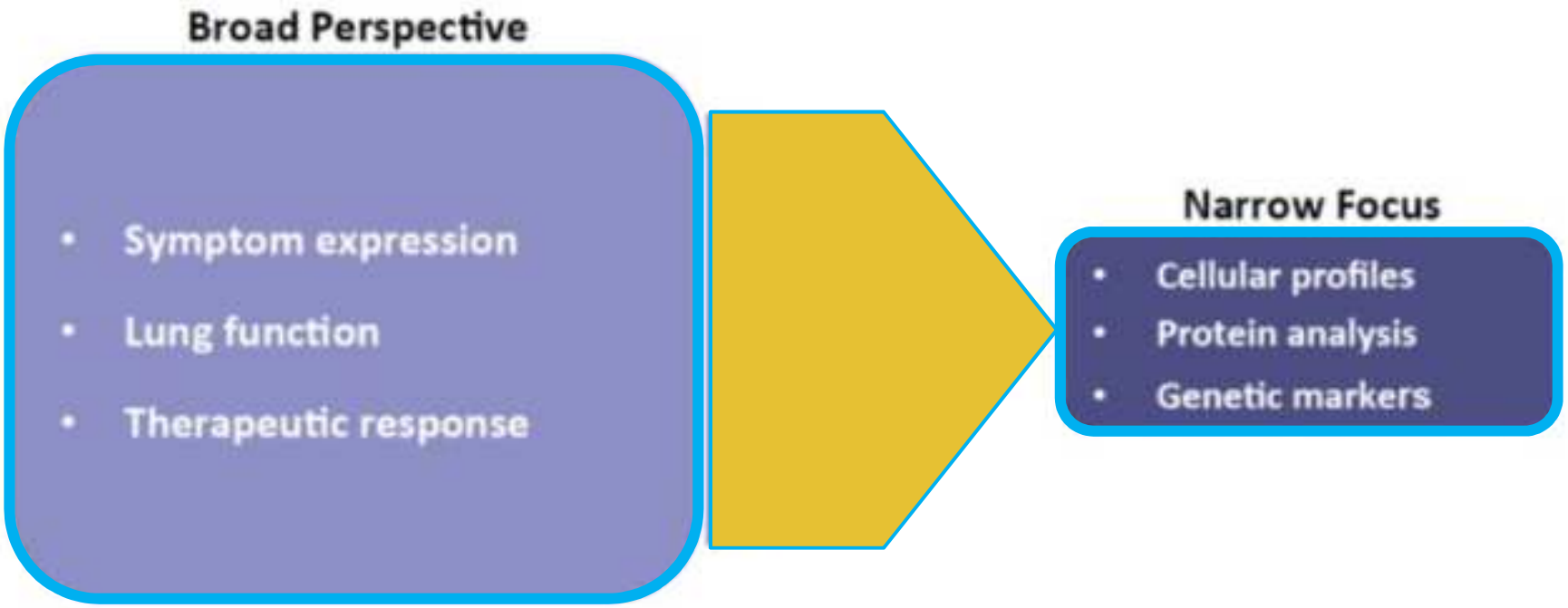


Targeted Biologicals

Once Daily Inhaled

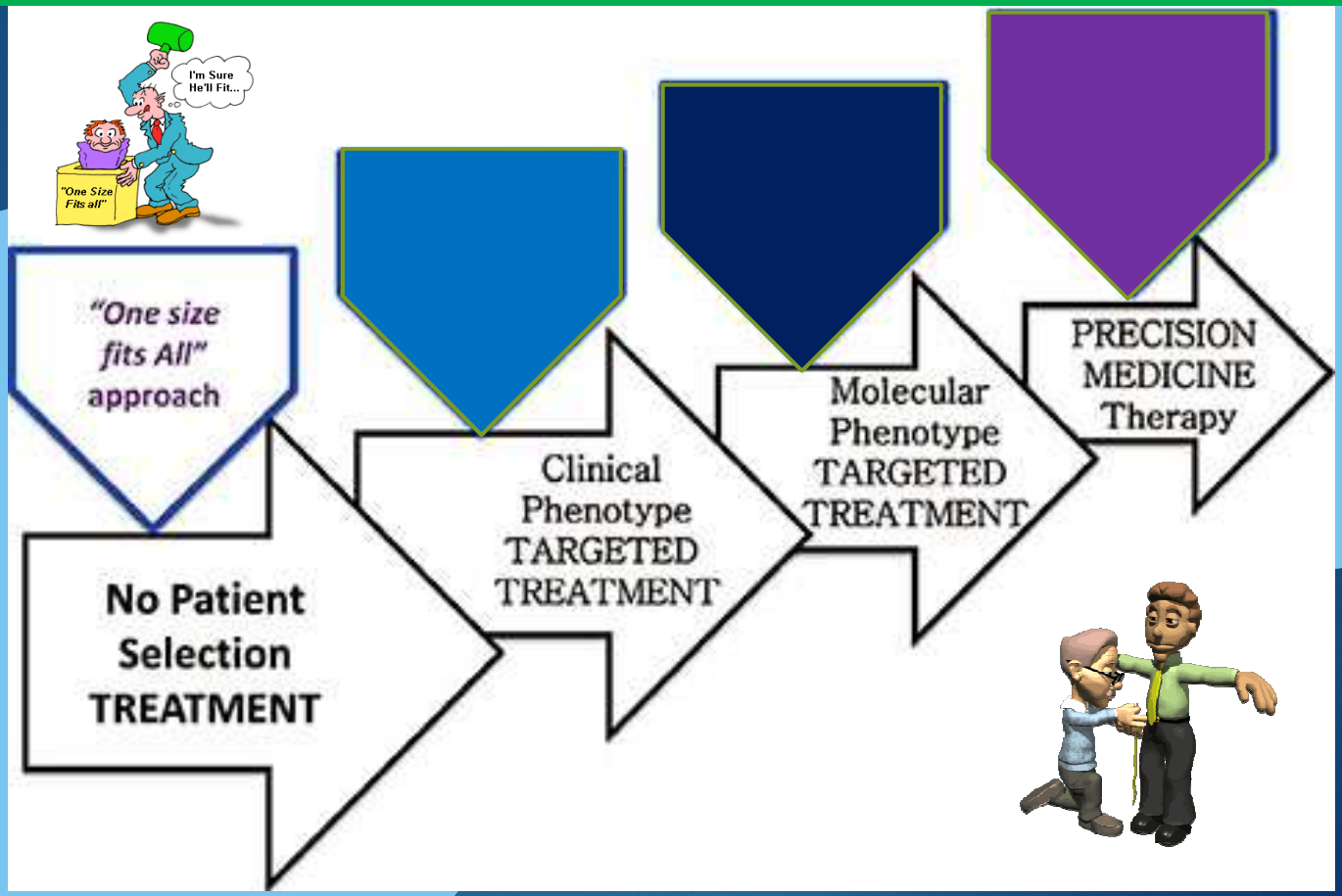

New Bronchodilators :
-once-daily β-agonists
- long-acting muscarinic antagonists
New Corticosteroids
Biological Agents
Asthma:
Advances In Current
Management And
Future Therapy
Novel Drugs
Associations
Novel Class of
Bronchodilators
-VIP analogs
- Rho kinase inhibitors
- Bitter taste Receptor Agonists
- PDE3 inhibitors (cilostazol)
- EP4 selective agonists
Targeting
Inflammatory
Mediators
Drugs (*)
• Lipid mediator Blockade
• Cytokine Blockade
• Inhibiting Th2 Cytokines
• Chemokine Receptor Antagonists
• Mast Cell Inhibitors
• Peroxisome Proliferator-Activated Receptor γ Agonists
• Antioxidants
(*) more than100 mediators are involved in the complex inflammation of asthma

Shifting Focus for Asthma Biomarkers



Vijverberg SJH et al. Biologics: Targets and Therapy. 2013;7:199--210.

Asthma :
Treatment Approach Evolution



Importance of Biomarkers

Barriers to Care in Severe Asthma[1,3,4]

- Inadequate treatment response with standard of care
- Incomplete understanding of inflammatory mechanisms
- Phenotype and endotypes are not well established
- Need for targeted therapies
- Disease heterogeneity

Utility of Biomarkers[2]

- Define populations that will derive most benefit from a drug
- Predict disease course
- Monitor the effects of therapy
- Monitor adverse events
- Identify new biological pathways
- Facilitate identification of new drug targets

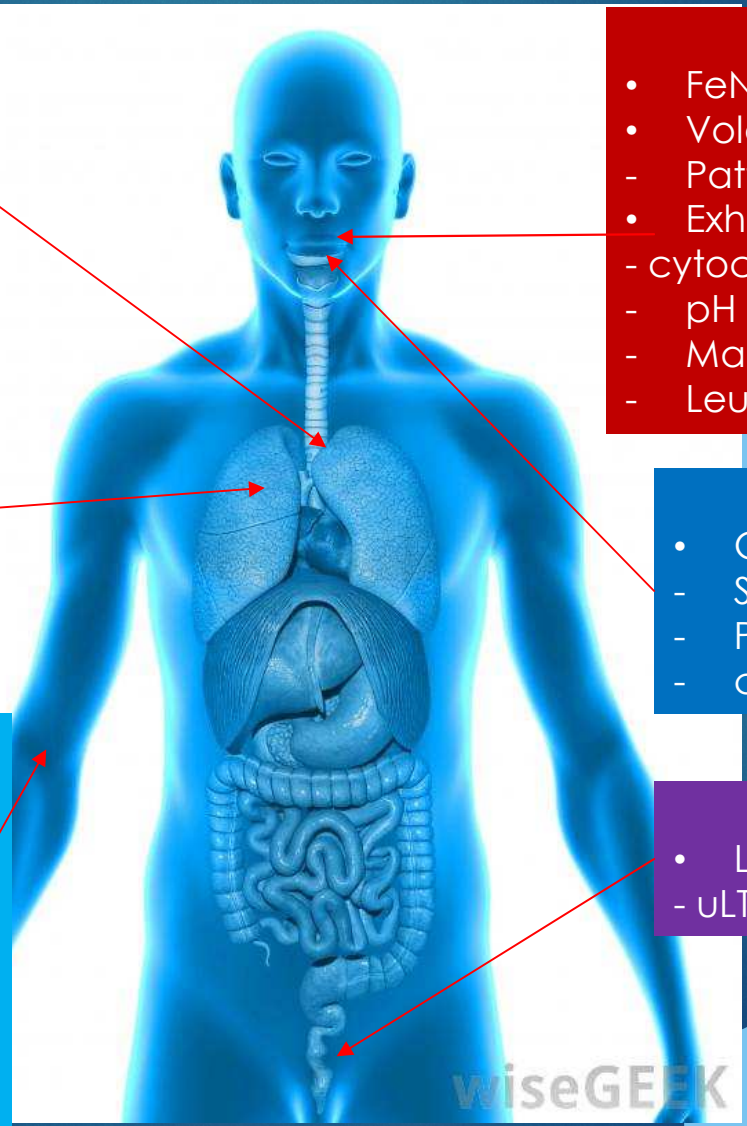
1. Lang DM. Allergy Asthma Proc. 2015;36:418--424. 2. Cazzola M et al. Pulm Pharmacol Ther. 2010;23:493--500. 3. De Groot JC et al. ERJ Open Res. 2015;1:00024–2015; DOI: 10.1183/23120541.00024--2015. 4. Drazen JM et al. J Allergy Clin Immunol. 2012;129:1200--1201.

Emerging Multidisciplinary Biomarker Approaches for Asthma

SPUTUM
- Inflammatory phenotypes
  -eosinophils/neutrophils
- ECP
- Signaling proteins

BAL & biopsy
- Remodeling
- Eosinophils/neutrophils
- Cytokines

PERIPHERAL BLOOD
- Periostin
- Genetics (also see: saliva)
- Granulocyte phenotypes
- Eosinophilia
- IgE
- Cytokines and chemokines
- ECP

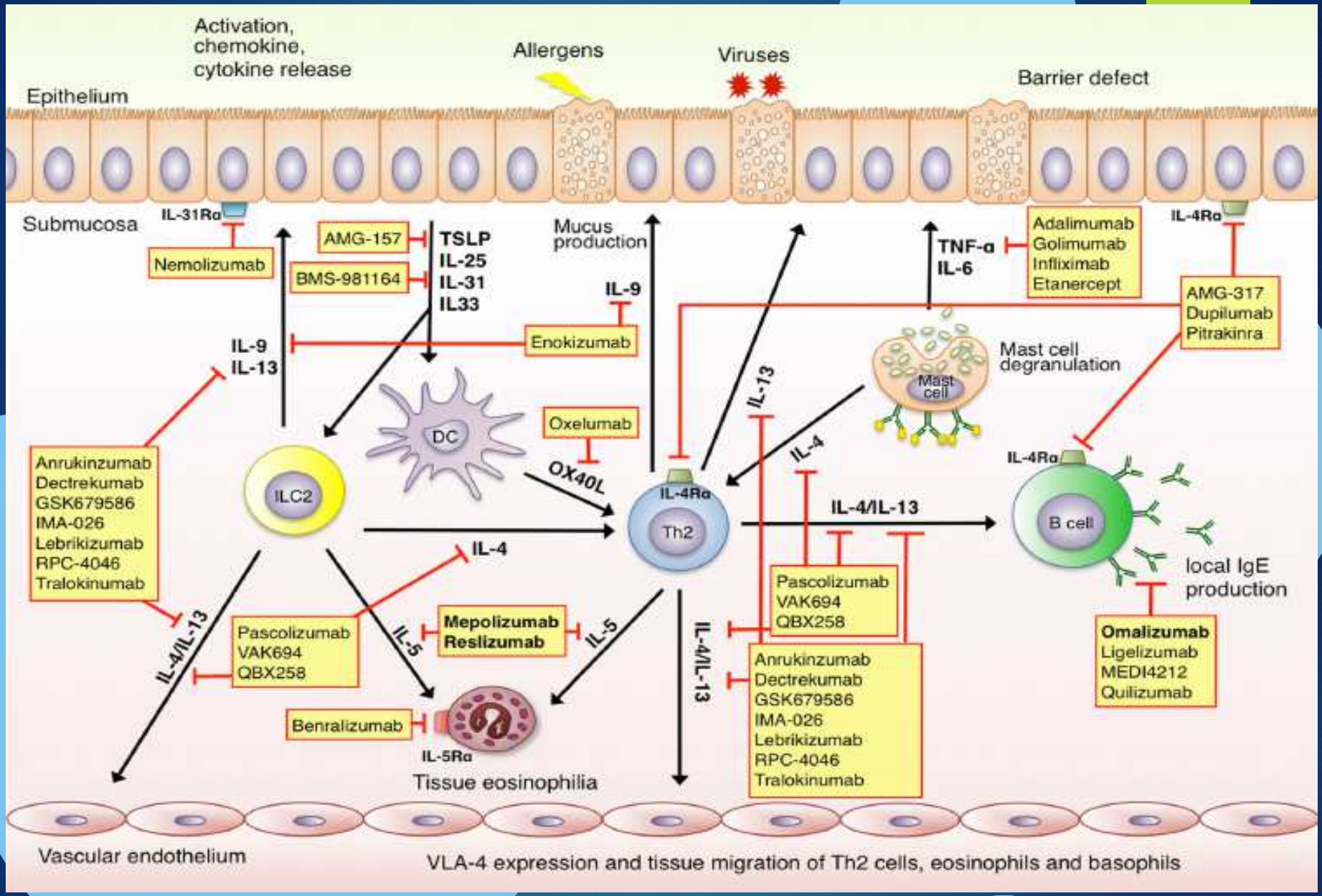


EXHALED AIR
- FeNO
- Volatile organic compounds:
- Patterns
- Exhaled Breath Condensate:
- cytochines & chemokines
- pH
- Markers of oxidative stress
- Leukotrienes

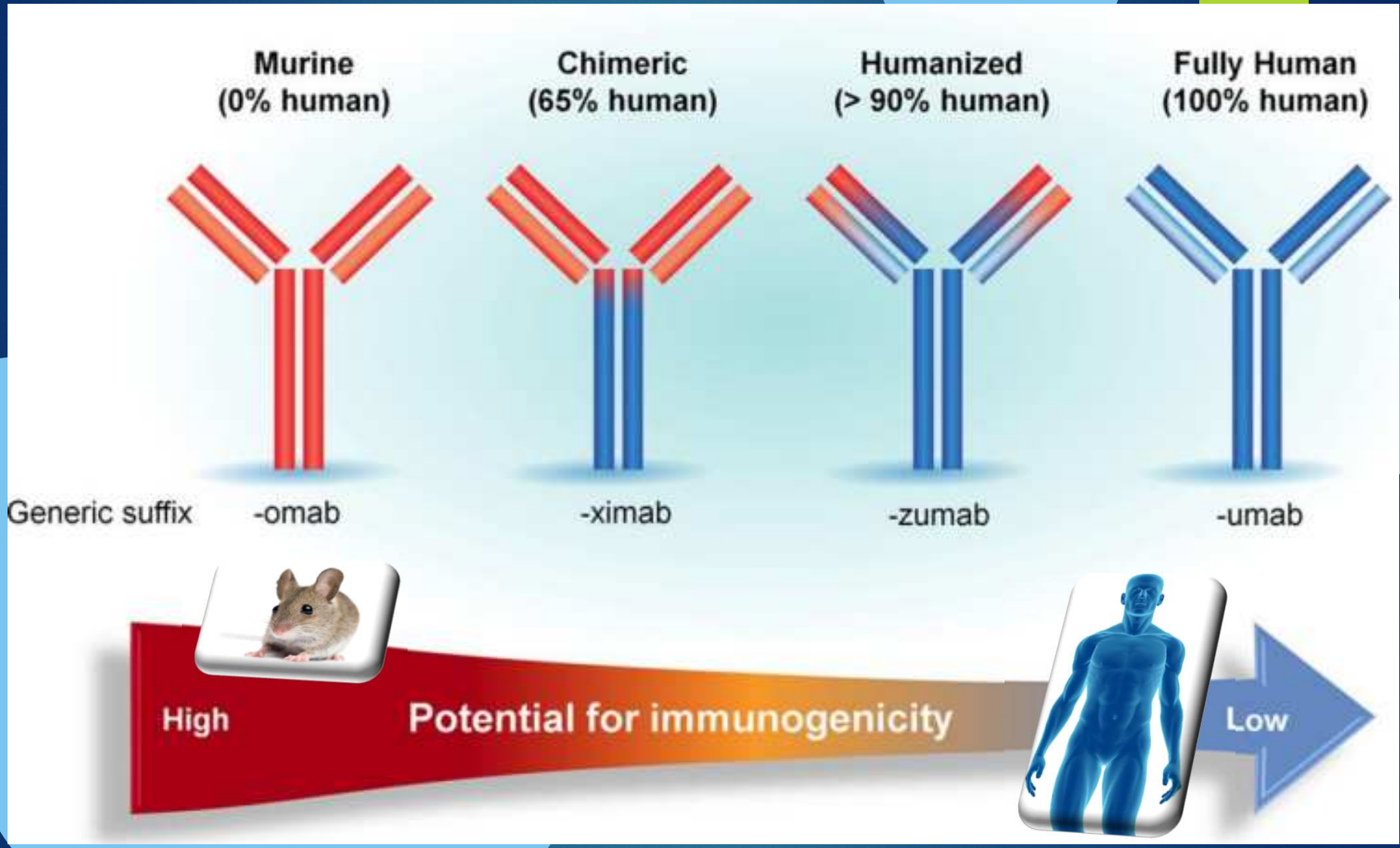
SALIVA
- Genetics:
- Susceptibility genes
- Pharmacogenetic
- cytokines

URINE
- Leukotriene metabolites
- uLTE4


CHANGING PARADIGMS
IN THE TREATMENT OF
SEVERE ASTHMA:
THE ROLE OF
BIOLOGIC THERAPIES



(Tan et al., Curr Allergy Asthma Rep (2016) 16: 70)


Murine
(0% human)
Chimeric
(65% human)
Humanized
(> 90% human)
Fully Human
(100% human)
Generic suffix
-omab
-ximab
-zumab
-umab
High
Potential for immunogenicity
Low

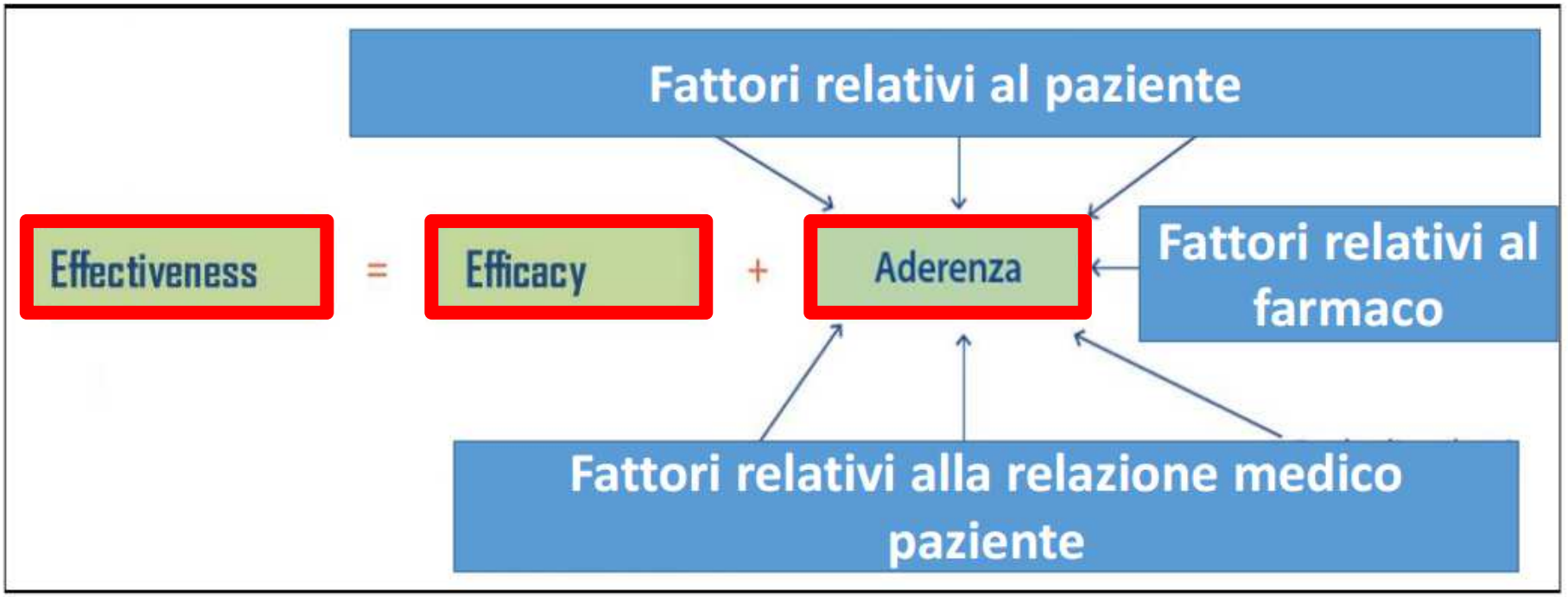
Emerging therapeutic options for the treatment of patients with symptomatic asthma

Therapeutic class	Mode of administration	Mechanism of action	Drug name	Sponsor	Development phase
Anti-interleukin agents	injection	anti-inflammatory	benralizumab	AstraZeneca	3
				Kyowa Hakko Kirin Company	2
				MedImmune	1/2
			reslizumab	Teva	2/3
				GlaxoSmithKline	3
			dupilumab	Sanofi	2/3
			brodalumab	Amgen	2
			lebrikizumab	F. Hoffmann-La Roche	2/3
				Genentech	2
			mepolizumab	GlaxoSmithKline	2/3

Biological Agents

McIvor RA et al., Ann Allergy Asthma Immunol 115 (2015) 265-271

Fattori determinanti dell'efficacia terapeutica nella pratica clinica (effectiveness)



Efficacy

Efficacia del farmaco negli studi clinici

Effectiveness

Efficacia del farmaco nella pratica clinica reale

Eichler HG NATURE REV **DRUG DISCOVERY 2011**

Ribeiro J et al Jornal de Pediatria 2006

Allergy 2009 DOI: 10.1111/j.1398-9995.2009.02161.x

DOI: 10.1111/j.1398-9995.2009.02161.x

Original article

Persistence with asthma treatment is low in Germany especially for controller medication – a population based study of 483 051 patients

Hasford et al.

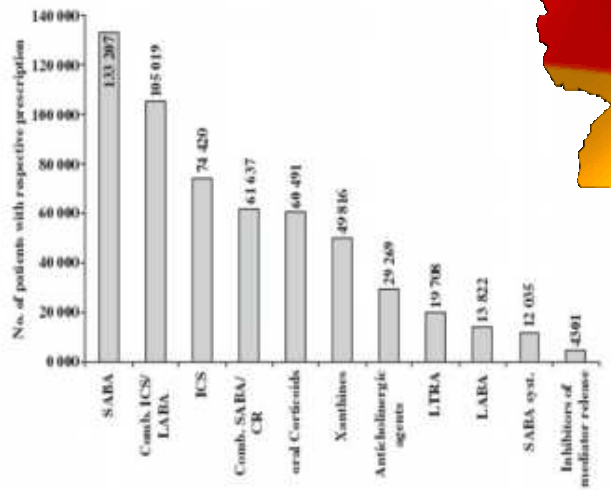
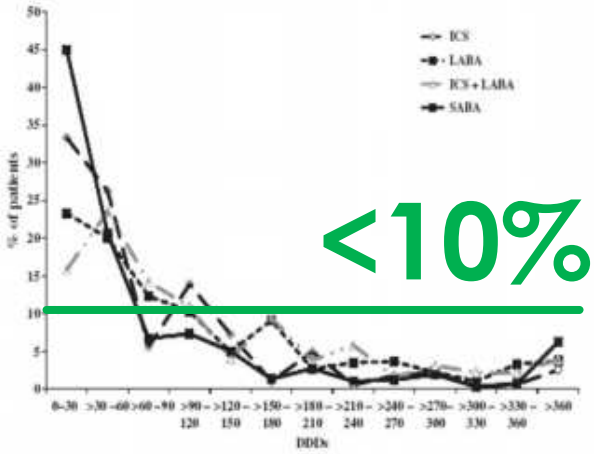


Figure 2. Number of asthma patients with corresponding prescription. SABA, short-acting β_2-agonists; Comb. SABA + CR, SABA + Cromoglycate; SABA sys, systemic SABA; ICS, inhaled corticosteroids; LABA, long acting β_2-agonists; Comb. ICS/LABA, ICS and LABA combined; LTRA, leukotriene receptor antagonists.



<10%

Figure 3. Proportion of patients receiving the indicated number of DDDs over the course of 1 year. ICS, inhaled corticosteroids; LABA, long acting β_2-agonists; SABA, short-acting β_2-agonists.

Aderenza ed asma: i dati italiani

AIFA
Agenzia Italiana del Farmaco

13.6%

Tabella 25. Monitoraggio degli indicatori di appropriatezza d'uso dei medicinali. I dati sono relativi al periodo luglio-giugno 2012-2015

Indicatore	Descrizione dell'indicatore	Lug2014-Giu2015	Lug2013-Giu2014	Lug2012-Giu2013
H-DB 4.4	Percentuale di pazienti in trattamento con farmaci per le sindromi ostruttive delle vie respiratorie aderenti al trattamento	13,6	12,9	12,6

Asthma therapy: Adherence to biological agents

Drop-out rate among patients treated with omalizumab for severe asthma: Literature review and real-life experience

M. Caminati[1*], G. Senna[1], G. Stefanizzi[1], R. Bellamoli[1], S. Longhi[1], F. Chieco-Bianchi[2], G. Guarnieri[3], S. Tognella[4], M. Olivieri[5], C. Micheletto[6], G. Festi[7], E. Bertocco[8], M. Mazza[9], A. Rossi[7], A. Vianello[2] and on behalf of North East Omalizumab Network study group

members of the North East Omalizumab Network Study Group for their contribution to the manuscript: C. Barp (Belluno), L. Bonazza (Bolzano), MA Crivellaro (Padova), A Dama (Verona), G. Donazzan (Bolzano), G. Idotta (Cittadella, PD), C. Lombardi (Brescia), M. Nalin (Rovigo), C. Pomari (Negrar, VR), M. Schiappoli (Verona).

BMC Pulmonary Medicine (2016) 16:128

Drop-out rate among patients treated with omalizumab for severe asthma: Literature review and real-life experience

Patient population ($n = 221$)	Drop-out patients (70, 32 %)
Males, n (%)	25 (35.71)
Females, n (%)	45 (64.29)
Age-years, mean (SD)	46.79 (14.82)
Treatment duration-months, mean (SD)	27.69 (20.94)
Reason for drop-out, n (%)	
Lack of efficacy	18 (26)
Patient's decision discontinuation	34 (49)
Efficacy	4 (6)
Adverse events (local or systemic reactions)	5 (7)
Onset of contraindications	6 (8)
Patient moved to another referral center	3 (4)

68%

BMC Pulmonary Medicine (2016) 16:128

Nonspecific immunosuppression:
- **Corticosteroids**

Corticosteroids are effective across all three diseases, but toxicity precludes widespread and long-term use

Allergens
MHC class II
TCR
Dendritic cell
T_H0 cell

IL-4
IL-4-specific blockers:
- Altrakincept (Immunex)
- Pascolizumab (GSK)

Partial efficacy in asthma; development discontinued

T_H2 cell

Dual IL-4 and IL-13-specific blockers:
- Pitrakinra (Aerovance)
- AMG317 (Amgen)
- **Dupilumab** (Regeneron/Sanofi)

Dupilumab is effective across all three diseases

4

IL-5-specific blockers:
- **Mepolizumab** (GSK)
- **Reslizumab** (Teva)
- **Benralizumab** (AZ)

IL-5

IL-4

IL-13

IL-13-specific blockers:
- **Tralokinumab** (AZ)
- Anrukinzumab (Pfizer)
- **Lebrikizumab** (Roche)

Lebrikizumab is effective in asthma ('T_H2-high' subgroup)

1

3

Mepolizumab is effective in asthma (in subgroup with high eosinophils); effective in CSwNP; not effective in AD

Eosinophil

B cell

IgE

FcεRI

Mast cell

Basophil

Histamine

Antihistamines

2

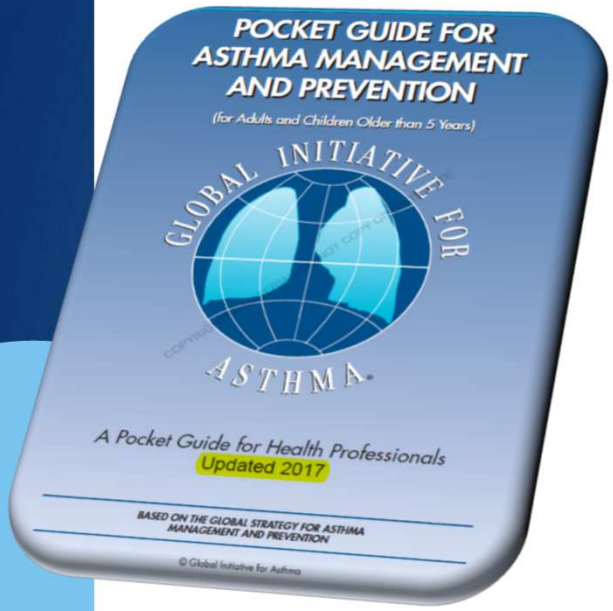
Omalizumab is effective in allergic asthma and asthmatics with co-morbid CSwNP; not effective in AD

IgE-specific mAbs:
- **Omalizumab** (Novartis/Genentech)

Figure 3 | **Targeting key proximal drivers of the type-2 pathway versus end-product mediators.** Different clinical

Gandhi et al. Nature Review Drug Discovery 2016

Stepwise approach to control asthma symptoms and reduce risk

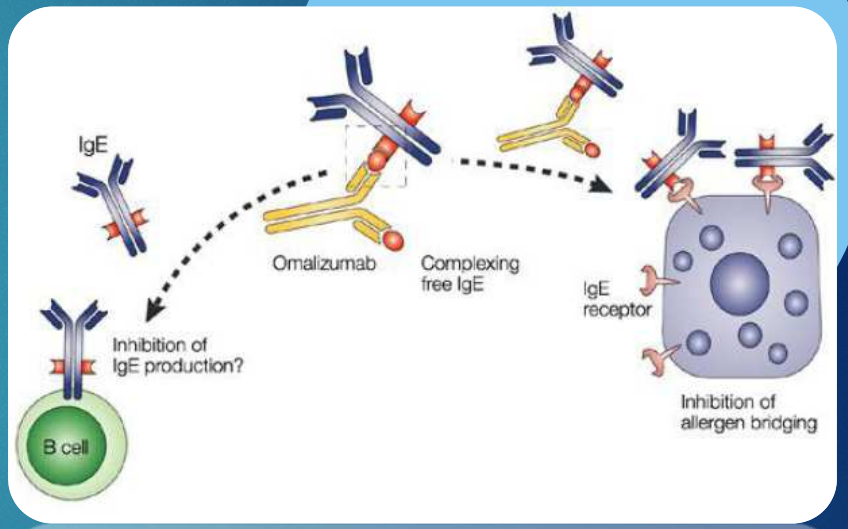


2017

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER CHOICE	Low dose ICS		Low dose ICS/LABA**	Med/high ICS/LABA	Refer for add-on treatment e.g. tiotropium,** anti-IgE, anti-IL5*
Other controller options	*Consider low dose ICS*	*Leukotriene receptor antagonists (LTRA) Low dose theophylline**	*Med/high dose ICS Low dose ICS+LTRA (or + theoph*)*	*Add tiotropium** † High dose ICS + LTRA (or + theoph*)*	*Add low dose OCS*
RELIEVER	As-needed short-acting beta$_2$-agonist (SABA)		As-needed SABA or low dose ICS/formoterol#		

Anti-IgE (Omalizumab)

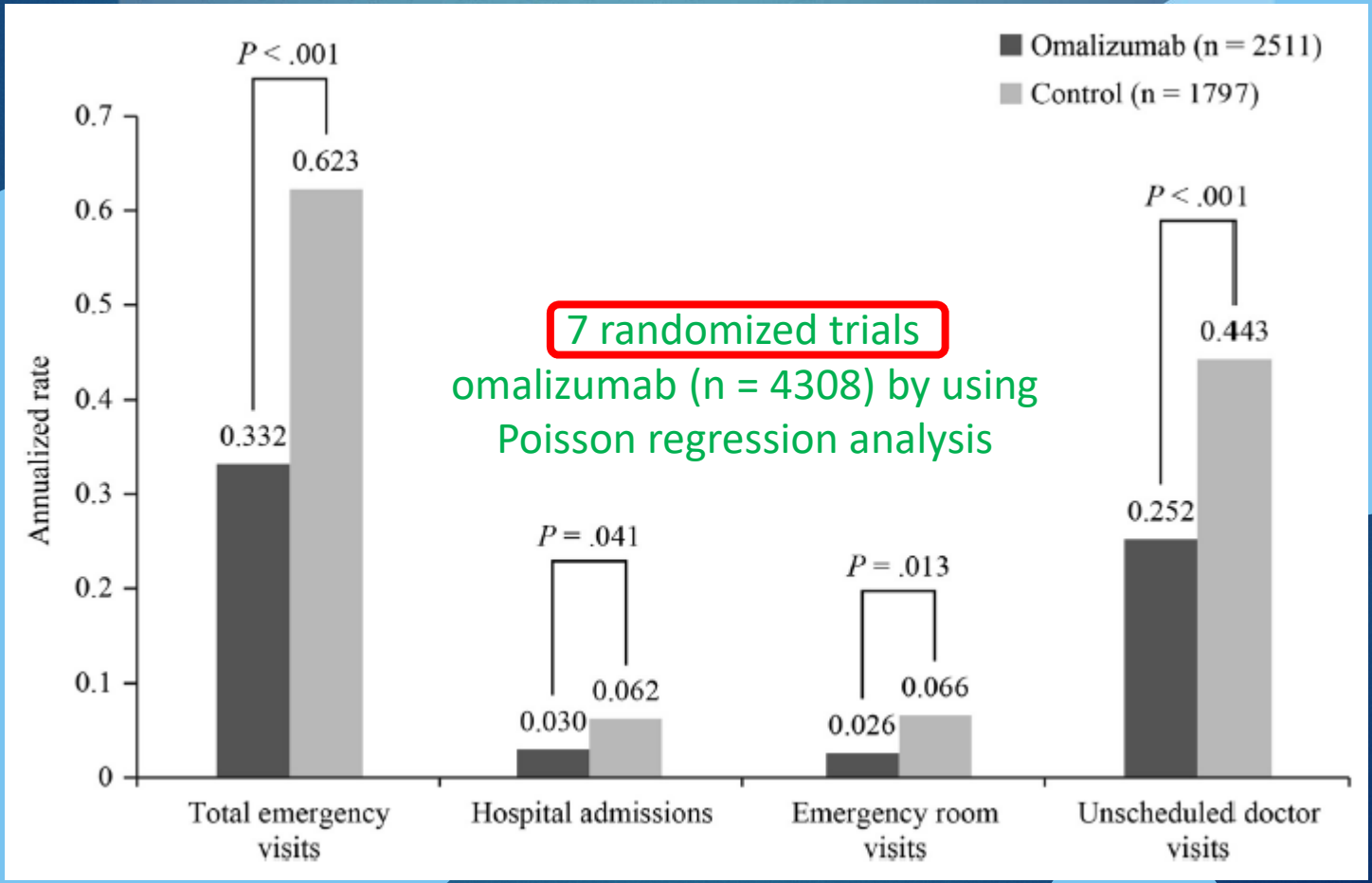
- Inhibits allergen bridging
- Suppress new IgE production
- Down regulates IgE receptor on Mast Cells/Basophils
- Reduce the efficiency of antigen presentation to T lymphocytes



Clinical Commentary Review

Omalizumab in Asthma: An Update on Recent Developments

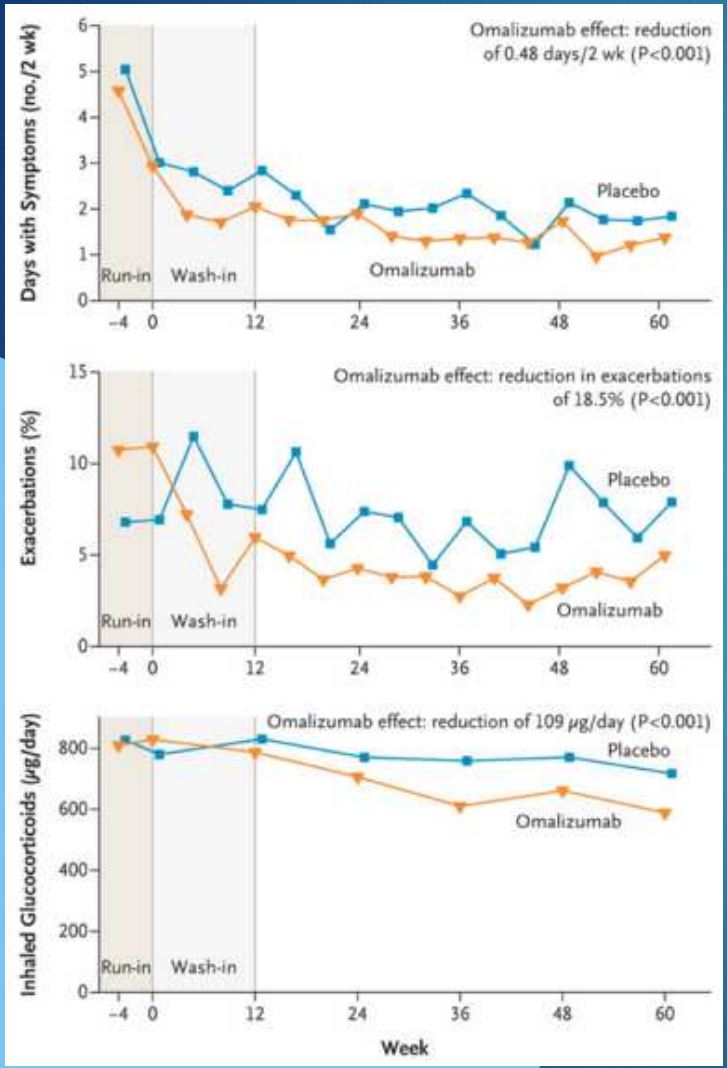
Marc Humbert, MD, PhD[a], William Busse, MD[b], Nicola A. Hanania, MD, MS[c], Philip J. Lowe, PhD[d], Janice Canvin, MD[e], Veit J. Erpenbeck, MD, PhD[f], and Stephen Holgate, MD, FMedSci[g] *Le Kremlin-Bicêtre, France; Madison, Wis; Houston, Texas; Basel, Switzerland; Horsham, UK; and West Sussex, Southhampton, UK*

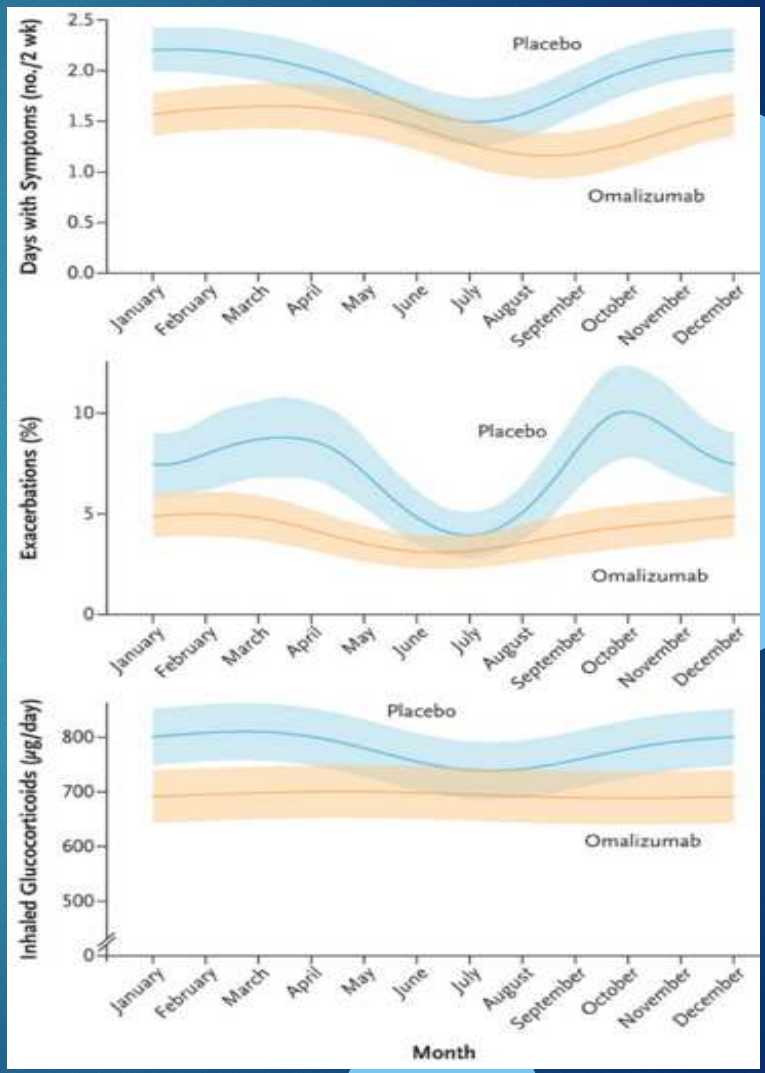


7 randomized trials
omalizumab (n = 4308) by using
Poisson regression analysis

(J Allergy Clin Immunol Pract 2014; 2: 525-36)

« Variation /Seasonal Variation in Days With Symptoms, Frequency of Exacerbations,And Dose of Inhaled Glucocorticoids »





Busse WW, et al. *N Engl J Med*. 2011;364:1005-1015.

Omalizumab nella pratica clinica – REAL LIFE

Respiratory Medicine (2009) 103, 1725–1731

Omalizumab in patients wi
allergic asthma in a real-li

S. Korn [a], A. Thielen [b], S. Seyfried [b], C

[a] Pulmonary Dept., Mainz University Hospital, Langenbeckstr
[b] Novartis Pharma GmbH, Roonstr. 25, 90429 Nuremberg, Ge

Received 31 March 2009; accepted 2 May 2009
Available online 9 June 2009

KEYWORDS
Asthma;
IgE;
Omalizumab;
Allergy;
Therapy

Summary
Omalizumab is a humanized r
ope for the treatment of uncc
optimal therapy with inhalec
Between 2005 and 2007 28
costeroids, median serum IgE
anti-IgE were treated prosp
marketing surveillance trial a
The median follow-up tim
450 mg omalizumab every 4
treatment on daily (−76%) a
uled health care contacts (−8
increase from 2.9 to 4.5). Ov
the majority of physicians (8
adverse events were recorde
This post-marketing surve

Respiratory Medicine (2008) 102, 71–76

Effectiveness of omali
patients treated in rea

Mathieu Molimard[a,*], Frédéric C

[a]INSERM, Unité 657, IFR 99, Université Victor Segal
33076 Bordeaux Cedex, France
[b]Université Louis Pasteur et Département de Pneu
[c]Service de Pneumologie, Hopital Larrey, CHU de T
[d]Novartis Pharma S.A.S., 2–4 Rue Lionel Terray, 92

Received 2 April 2007; accepted 15 August 2007
Available online 24 October 2007

KEYWORDS
Severe asthma;
Omalizumab;
Anti IgE;
Effectiveness;
Treatment;
Real life

Summary
Objective
compassio
Methods:
physician
for omali
demograp
omalizumab trea
obtained at inclus
obtained and reg
undesirable effec
Results: Data we
inappropriate ma
unsatisfactory the
to evaluate effica

Respiratory Medicine (2009) 103, 1633–1642

available at www.sciencedirect.com
ScienceDirect
journal homepage: www.elsevier.com/locate/rmed

"Real-life" effectiveness of omalizumab in
patients with sistent allergic asthma
The PERSIST s

G. Brusselle [a], A. Michils [b], R. Louis [c], L. Dupont [d], B. Van de Maele [e],
A. Delobbe [f], C. Pilette [g], C.S. Lee [h,i,j,*], S. Gurdain [k], S. Vancayzeele [k],
P. Lecomte [k], C. Hermans [k], K. MacDonald [h], M. Song [h,j], I. Abraham [h,i]

[a] Department of Respiratory Medicine, Ghent University Hospital and Ghent University, Ghent, Belgium
[b] Department of Respiratory Medicine, Erasme Hospital and Free University of Brussels, Brussels, Belgium
[c] Department of Respiratory Medicine, Liege University Hospital and Liege University, Liege, Belgium
[d] Department of Respiratory Medicine, Leuven University Hospital and Leuven University, Leuven, Belgium
[e] Department of Respiratory Medicine, AZ. St. Jan Brugge Oostende Campus H. Serruys, Oostende, Belgium
[f] Department of Respiratory Medicine, Citade
[g] Department of Respiratory Medicine, Catho
University of Louvain, Louvain, Belgium
[h] Matrix45, Earlysville, VA, USA
[i] Center for Health Outcomes and Pharmacoe
Tucson, AZ, USA
[j] School of Nursing, University of Pennsylvania
[k] Novartis Pharma, Vilvoorde, Belgium

ARTICLE IN PRESS
+ MODEL
Respiratory Medicine (2010) xx, 1–5

available at www.sciencedirect.com
ScienceDirect
journal homepage: www.elsevier.com/locate/rmed

SHORT COMMUNICATION

izumab reduces oral corticosteroid use in
nts with severe allergic asthma: Real-life data

M. Molimard [a,*], R. Buhl [b], R. Niven [c], V. Le Gros [d], A. Thielen [e], J. Thirlwell [f],
R. Maykut [g], G. Peachey [f]

[a] Département de Pharmacologie, CHU Pellegrin-Carreire, de Bordeaux – Université Victor Segalen-INSERM U657, 33076 Bordeaux cedex, France
[b] Pulmonary Department, Mainz University Hospital, Mainz, Germany
[c] University Hospital of South Manchester and the University of Manchester, Manchester, UK
[d] CR&D, Novartis Pharma SAS, Rueil-Malmaison, France
Novartis Pharma GmbH, Nuremberg, Germany
Novartis Horsham Research Centre, Horsham, West Sussex, UK
Novartis Pharma AG, Basel, Switzerland

eceived 7 May 2010; accepted 4 June 2010

KEYWORDS
Anti-IgE;
Oral corticosteroids;

Summary
Background: Long-term oral corticosteroid (OCS) therapy is associated with significant burden
on patients and healthcare resources; treatments that may help reduce their use are impor-

Respiratory Medicine (2010) xx, 1–7

available at www.sciencedirect.com
ScienceDirect
journal homepage: www.elsevier.com/locate/rmed

Italian real-life experience of omalizumab

M. Cazzola [a,b,*], G. Camiciottoli [c], M. Bonavia [d], C. Gulotta [e], A. Ravazzi [f],
A. Alessandrini [g], M.F. Caiaffa [h], A. Berra [i], P. Schino [j], P.L. Di Napoli [j],
R. Maselli [k], G. Pelaia [k], E. Bucchioni [l], P.L. Paggiaro [m], L. Macchia [n]

International Journal of Clinical Pharmacology and Therapeutics, Vol. 49 – No. 12//2011 (713-721)

Original

©2011 Dustri-Verlag Dr. K. Feistle
ISSN 0946-1965

DOI 10.5414/CP201586
e-pub: November 28, 2011

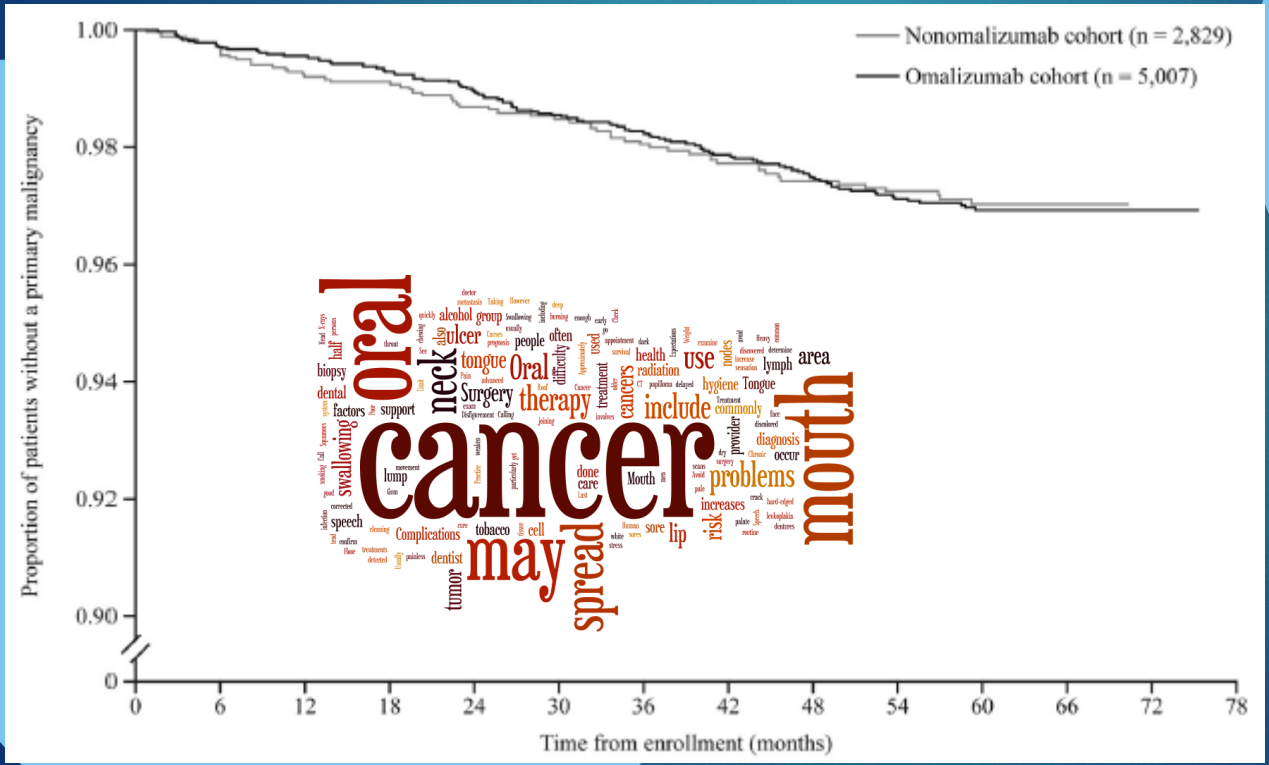
Omalizumab decreases exacerbation frequency, oral intake of corticosteroids and peripheral blood eosinophils in atopic patients with uncontrolled asthma

G. Pelaia[1], L. Gallelli[1], P. Romeo[1], T. Renda[1], M.T. Busceti[1], A. Proietto[2],
R.D. Grembiale[1], S.A. Marsico[3], R. Maselli[1] and A. Vatrella[4]

[1]Department of Experimental and Clinical Medicine, University "Magna Græcia" of Catanzaro, [2]Department of Clinical and Experimental Medicine and Pharmacology, University of Messina, [3]Department of Cardiothoracic and Respiratory Sciences, Second University of Naples, and [4]Department of Clinical and Experimental Medicine, University "Federico II" of Naples, Italy

Incidence of malignancy in patients with moderate-to-severe asthma treated with or without omalizumab

EXCELS was a prospective observational cohort study in patients (>12 years of age) with moderate-to-severe allergic asthma. There were 2 cohorts: omalizumab (taking omalizumab at baseline: 2696 pts) and nonomalizumab (no history of omalizumab treatment : 1689 pts).



Conclusion: Results from EXCELS suggest that omalizumab therapy is not associated with an increased risk of malignancy.

(Long A. et al., J Allergy Clin Immunol 2014;134:560-7)

The Xolair Pregnancy Registry (EXPECT): The safety of omalizumab use during pregnancy

As of November 2012, 188 of 191 pregnant women were exposed to omalizumab during their first trimester.

TABLE IV. Known pregnancy outcomes for registrants*

Outcome	Pregnancies (N = 169)
Live birth, n	156†
Percentage of registrants (95% CI)	92.3 (87.2, 95.8)
Elective termination, n	1
Percentage of registrants (95% CI)	0.6 (0.0, 3.3)
Stillborn/fetal death (≥20 wk), n	1
Percentage of registrants (95% CI)	0.6 (0.0, 3.3)
Spontaneous abortion (<20 wk)	11
Registrants enrolled prior to 20 wks, n	128
Percentage of registrants (95% CI)	8.6 (4.4, 14.9)

*One pregnancy per woman.
†One hundred fifty-two singleton infants and 4 pairs of twins.

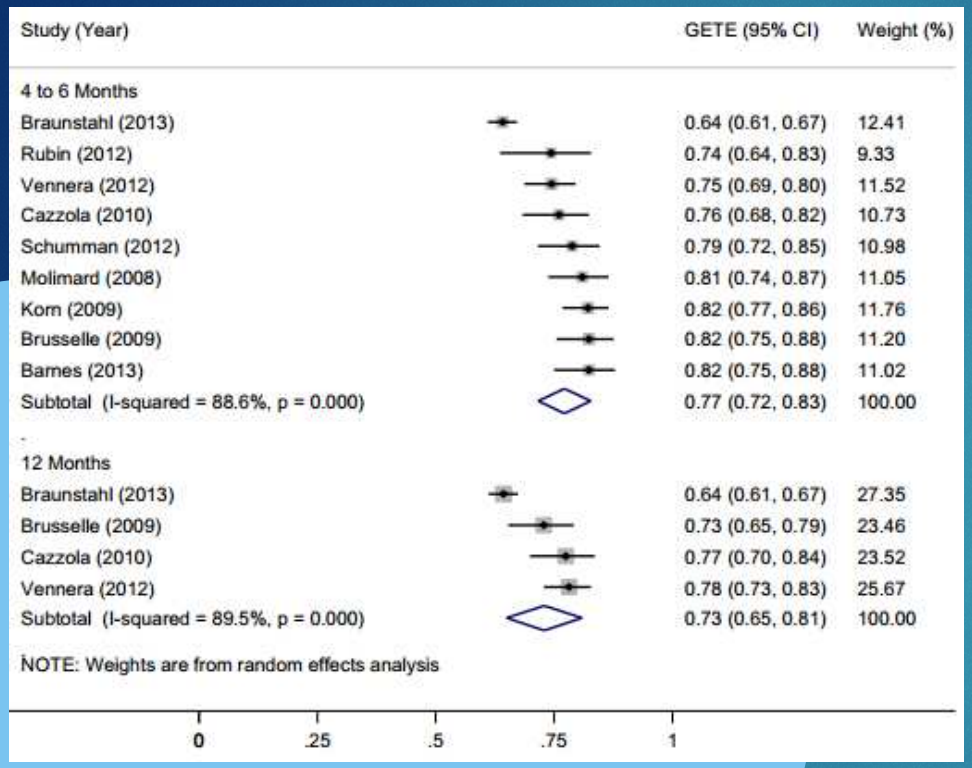
TABLE V. Neonatal outcomes

Outcome	N	% (95% CI)
All infants	160	
Singleton infants	152	
Premature birth (<37 wk)	22	14.5 (9.3, 21.1)
Small for gestational age*	16†	10.9 (6.4, 17.1)
Low birth weight (<2.5 kg)	4‡	3.2 (0.9, 8.0)
Infants with major or conditional defects§		
Major birth defects‖	7	4.4 (1.8, 8.8)
Conditional defects¶	14	8.8 (4.9, 14.2)

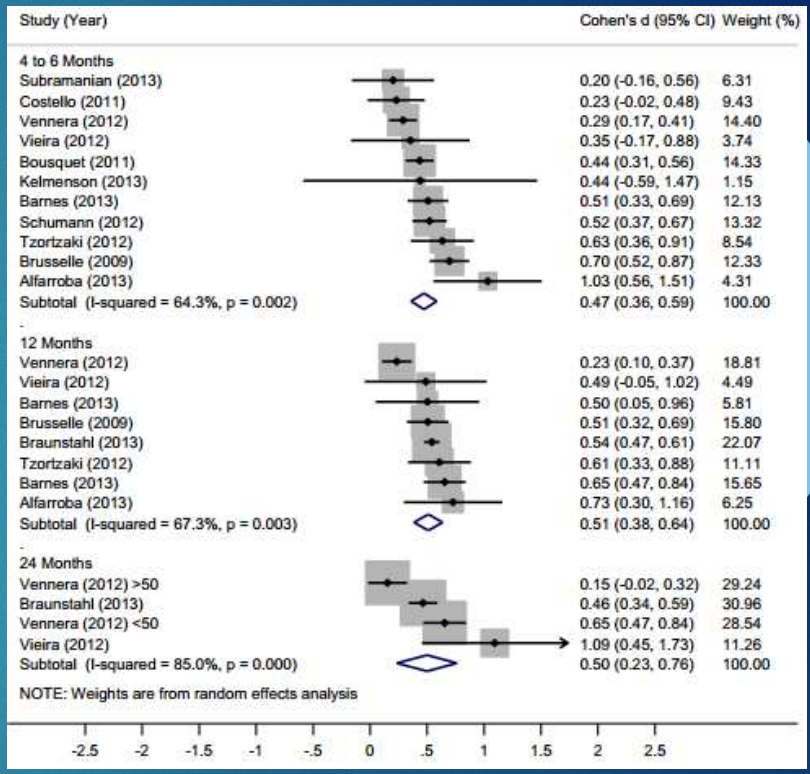
Based on data collected to date, the prevalence of major congenital defects in EXPECT continues to be no higher than those reported in the general population with asthma.

(Namazy J et al, J Allergy Clin Immunol 2015;135:407-12)

"Real-life" Effectiveness Studies of Omalizumab in Adult Patients with Severe Allergic Asthma: Meta-analysis



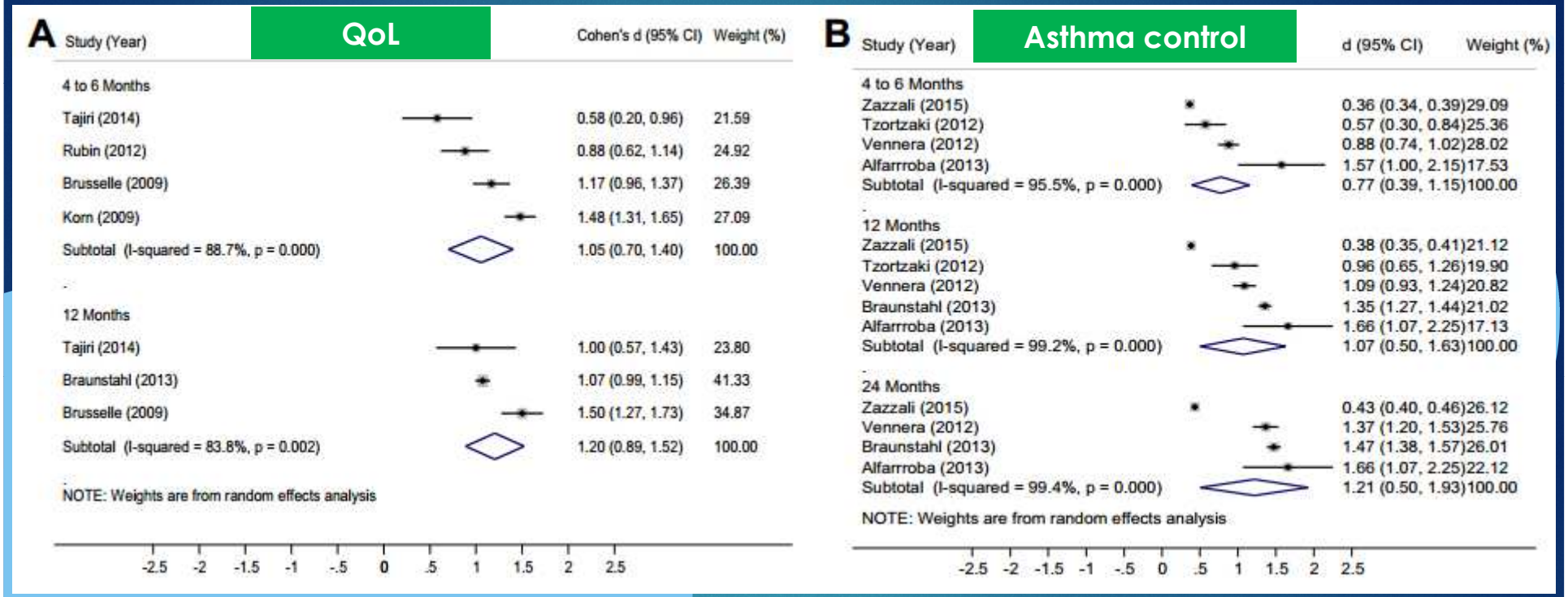
Global Evaluation of Treatment Effectiveness



Improvements in forced expiratory volume (% predicted)

(Alhossan et al., J Allergy Clin Immunol Pract march 2017)

"Real-life" Effectiveness Studies of Omalizumab in Adult Patients with Severe Allergic Asthma: Meta-analysis



CONCLUSIONS:

This meta-analysis of non-controlled studies documents the real-life pharmacotherapeutic effectiveness of omalizumab, as add-on treatment to ICS – long-acting b2-agonists agents, in improving outcomes in patients with severe allergic asthma under conditions of heterogeneity in patients, clinicians, sites, and treatment patterns.

The results mirror, complement, and extend the efficacy data from randomized controlled trials

(Alhossan et al., J Allergy Clin Immunol Pract march 2017)

Follow-up of asthma control and quality of life after discontinuation of omalizumab in severe asthmatic patients

This is a prospective, observational study. Omalizumab therapy was stopped in 16 severe allergic asthmatic patients who previously treated with omalizumab over a 3 years period. Asthma Control Test (ACT), Asthma Quality of Life Questionnaire (AQLQ), pulmonary function test and severe exacerbations were recorded for one year at three month intervals after discontinuation of omalizumab.

The mean age was 53.5±9.5 and duration of asthma was 21.2±11.2 years. Serum total IgE level was 380.3±196 IU/mL. Mean duration of omalizumab treatment was 54.6±15 months. Loss of asthma control was documented in 10/16 patients (62.5%). The mean time to the first moderate to severe asthma exacerbation after discontinuation was 2.68±2.2 months. No correlation was

The number of exacerbation within the last 12 months increased from 1.3±0.9 to 3.4±3.2 (p=0.006),

Conclusions

The discontinuation of omalizumab after the successful long term therapy was associated of early loss of asthma control, moderate to severe exacerbation of the disease, and impaired quality of life.

Nayci et al. World Allergy Organization Journal 2015, 8(Suppl 1):A75

Targeting patients with asthma for omalizumab therapy: choosing the right patient to get the best value for money

Results of cost-effectiveness of omalizumab from the seven studies of trials of omalizumab as add-on therapy for patients with severe asthma.

Source	Country	ICER
Brown[102]	Canada	€821,000/QALY
Campbell[103]	USA	$287,200/QALY
Dewilde[104]	Sweden	€56,091/QALY
Dal Negro[105]	Italy	€26,000/QALY
Nooten[106]	Netherlands	€38,371/QALY
Oba[107]	USA	€378 /0.5-point AQLQ increase
Wu[108]	USA	$821,000/QALY

AQLQ, Asthma Quality of Life Questionnaire; ICER, Incremental cost-effectiveness ratio; QALY, quality adjusted life year

omalizumab as an add-on therapy for asthma, has largely not been shown to be cost effective

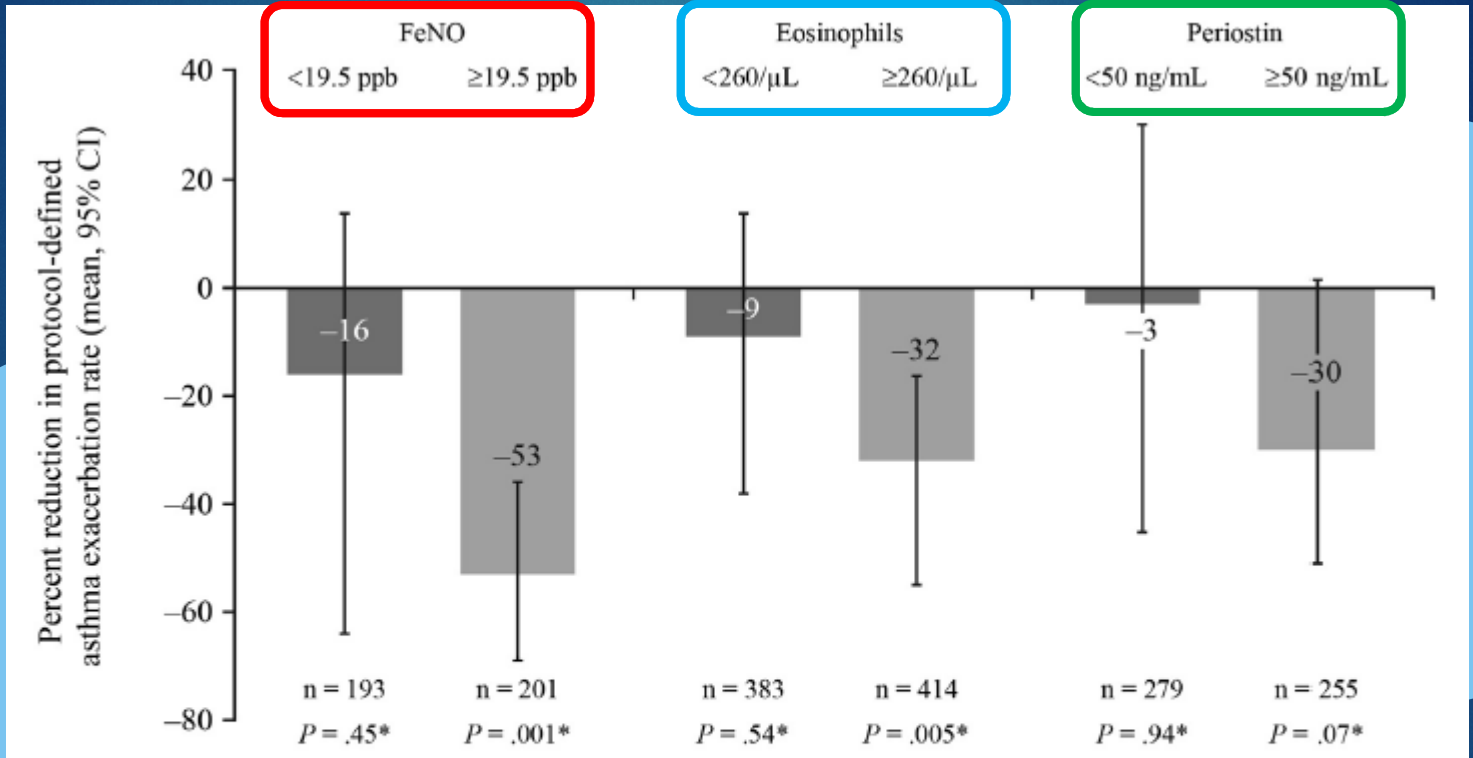
Bias :

- Clinical outcomes not assessed in the current cost-effectiveness models.
- When to stop therapy; another aspect of cost-effectiveness.

(Al Said et al., Ther Adv Chronic Dis 2017, Vol. 8(2-3) 31–45)

Although the patient selection for omalizumab has been based on IgE levels and the presence of antigen sensitization, these criteria have not been a reliable predictor of the treatment response !!!

EXTRA study:
asthma exacerbation rates in the **low- and high-biomarker subgroups**
(exacerbation reduction P values; omalizumab vs placebo in each biomarker subgroup)



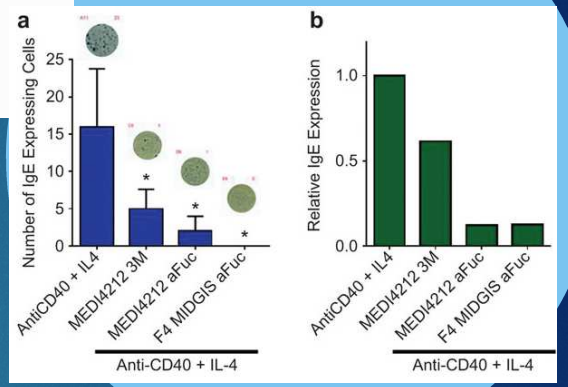
Exacerbation rates						
	Low FeNO at baseline	High FeNO at baseline	Low eosinophils at baseline	High eosinophils at baseline	Low periostin at baseline	High periostin at baseline
Omalizumab	0.60	0.50	0.65	0.70	0.73	0.66
Placebo	0.71	1.07	0.72	1.03	0.72	0.93

(J Allergy Clin Immunol Pract 2014;2:525-36)

New MABS on the block for asthma : New Anti-IgEs

Pharmacokinetics, Pharmacodynamics, and Safety of MEDI4212, an Anti-IgE Monoclonal Antibody, in Subjects with Atopy: A Phase I Study

Sheldon, E., Schwickart, M., Li, J. et al.
Adv Ther (2016) 33: 225.



- **QGE 031 (LIGELIZUMAB)**
- **QUILIZUMAB**

New MABS on the block for asthma : New Anti-IgEs

Efficacy and safety of multiple doses of QGE031 (ligelizumab) versus omalizumab and placebo in inhibiting allergen-induced early asthmatic responses

QGE031 is an investigational anti-IgE antibody that binds IgE with higher affinity than omalizumab.

Thirty-seven patients with mild allergic asthma were randomized to subcutaneous omalizumab, placebo, or QGE031 at 24, 72, or 240 mg every 2 weeks for 10 weeks in a double-blind, parallel-group multicenter study. Inhaled allergen challenges and skin tests were conducted before dosing and at weeks 6, 12, and 18, and blood was collected until 24 weeks after the first dose.

Results

QGE031 elicited a concentration- and time-dependent change in the provocative concentration of allergen causing a 15% decrease in FEV_1 (allergen PC_{15}) that was maximal and approximately 3-fold greater than that of omalizumab ($P = .10$) and 16-fold greater than that of placebo ($P = .0001$) at week 12 in the 240-mg cohort. Skin responses reached 85% suppression at week 12 in the 240-mg cohort and were maximal at week 18. The top doses of QGE031 consistently suppressed skin test responses among subjects but had a variable effect on allergen PC_{15} (2-fold to 500-fold change). QGE031 was well tolerated.

Conclusion

QGE031 has greater efficacy than omalizumab on inhaled and skin allergen responses in patients with mild allergic asthma. These data support the clinical development of QGE031 as a treatment of asthma.

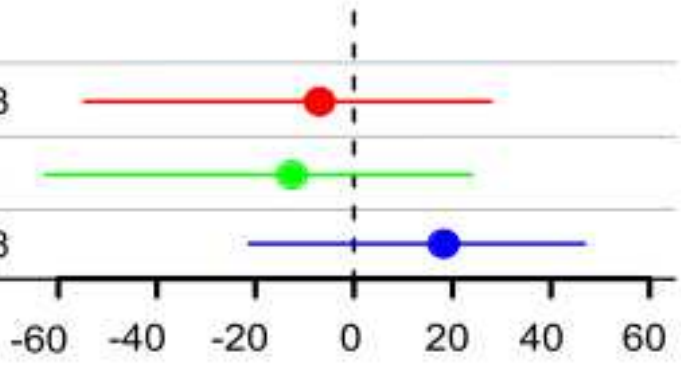
(Gauvreau GM et al., JACI, 2016 october Vol. 138, Issue 4, Pages 1051-1059)

A randomized trial of the efficacy and safety of quilizumab in adults with inadequately controlled allergic asthma

Quilizumab, a humanized IgG1 monoclonal antibody, targets the M1-prime segment of membrane expressed IgE, leading to depletion of IgE-switched and memory B cells.

578 patients were randomized to monthly or quarterly dosing regimens of S.C. quilizumab or placebo for 36 weeks, with a 48-week safety follow-up.

Treatment	n	Number of Exacerbations	Exacerbation Rate	Rate Reduction (%)	90% CI
	145	60	0.62		
150 mg Q	145	63	0.66	-5.7	-54.7 to 27.8
450 mg Q	145	63	0.69	-11.2	-62.7 to 24
300 mg M	143	47	0.5	19.6	-21.3 to 46.8

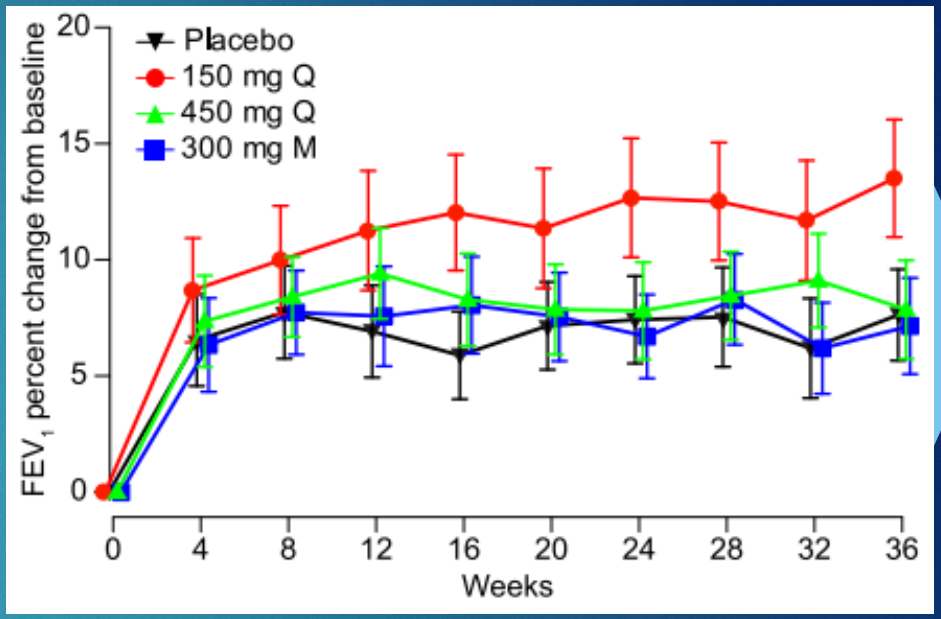


(Harris et al., Respiratory Research (2016) 17: 29)

	Population	Treatment	n	Number of Exac.	Exac. Rate	Rate Reduction (%)
A	Periostin High	Placebo	79	34	0.62	
		150 mg Q	84	34	0.58	6.3
		450mg Q	84	29	0.53	15.7
		300 mg M	78	24	0.48	22.9
	Periostin Low	Placebo	66	26	0.61	
		150 mg Q	61	29	0.75	-22
		450 mg Q	61	34	0.91	-49.3
		300 mg M	65	23	0.52	15.3
B	Eosinophil High	Placebo	53	36	1.02	
		150 mg Q	46	24	0.76	25.5
		450 mg Q	51	22	0.64	36.9
		300 mg M	50	22	0.68	33.4
	Eosinophil Low	Placebo	92	24	0.39	
		150 mg Q	98	39	0.6	-53
		450 mg Q	94	41	0.71	-81.1
		300 mg M	93	25	0.41	-4
C	FeNO High	Placebo	79	42	0.8	
		150 mg Q	84	49	0.86	-7.7
		450 mg Q	87	40	0.71	11
		300 mg M	86	32	0.55	31.2
	FeNO Low	Placebo	66	18	0.4	
		150 mg Q	60	14	0.36	12
		450 mg Q	58	23	0.64	-57.9
		300 mg M	56	15	0.43	-5.2
D	IgE High	Placebo	83	34	0.65	
		150 mg Q	80	33	0.6	7
		450 mg Q	78	35	0.72	-10.8
		300 mg M	68	25	0.55	14.3
	IgE Low	Placebo	62	26	0.59	
		150 mg Q	65	30	0.71	-20.3
		450 mg Q	67	28	0.65	-9
		300 mg M	75	22	0.45	24.5

Rate Reduction with 90% CI: Placebo better / Quilizumab better

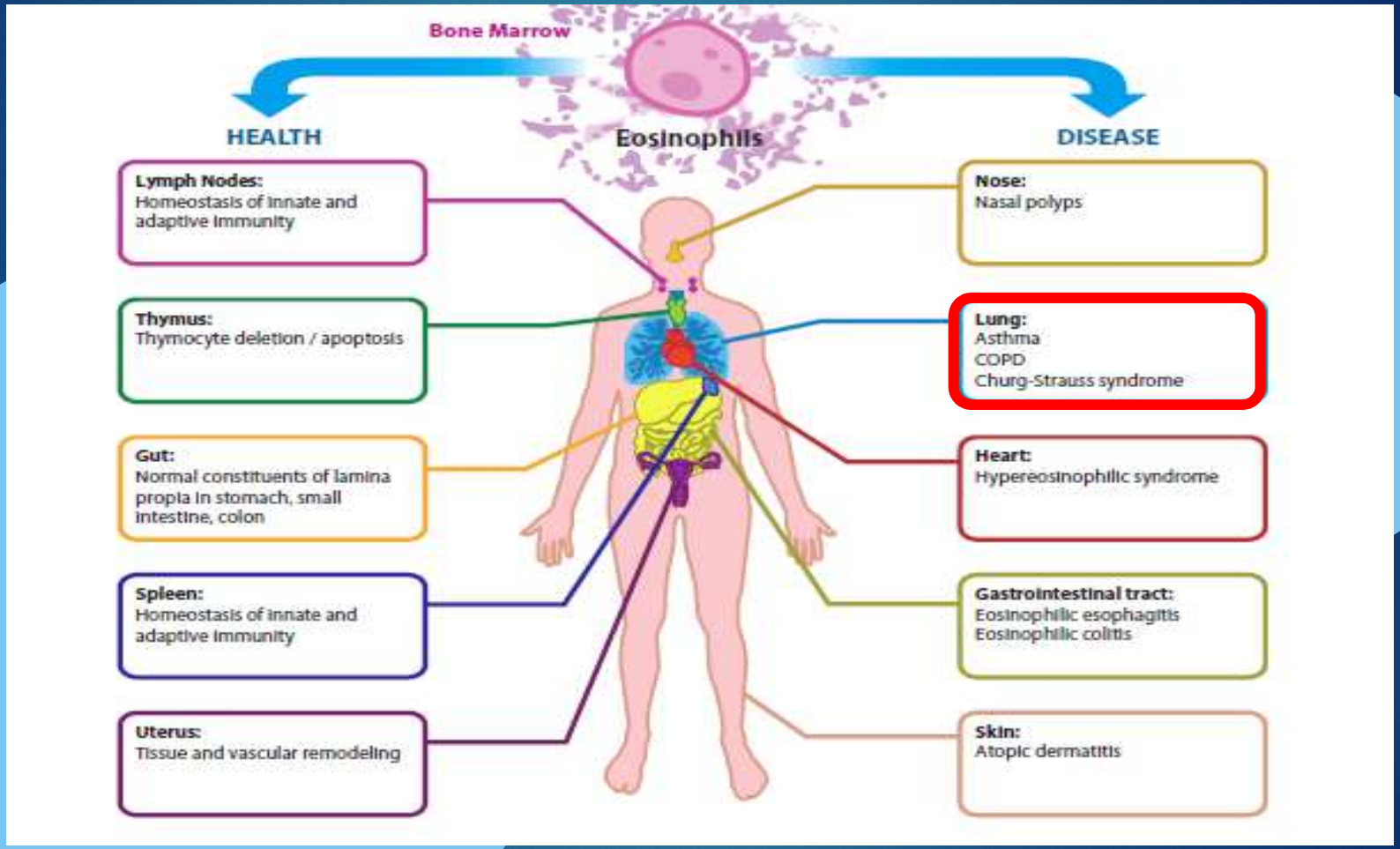
-100 -50 0 50 100



Conclusions: Quilizumab had an acceptable safety profile and reduced serum IgE. However, targeting the IgE pathway via depletion of IgE-switched and memory B cells was not sufficient for a clinically meaningful benefit for adults with allergic asthma uncontrolled by standard therapy.

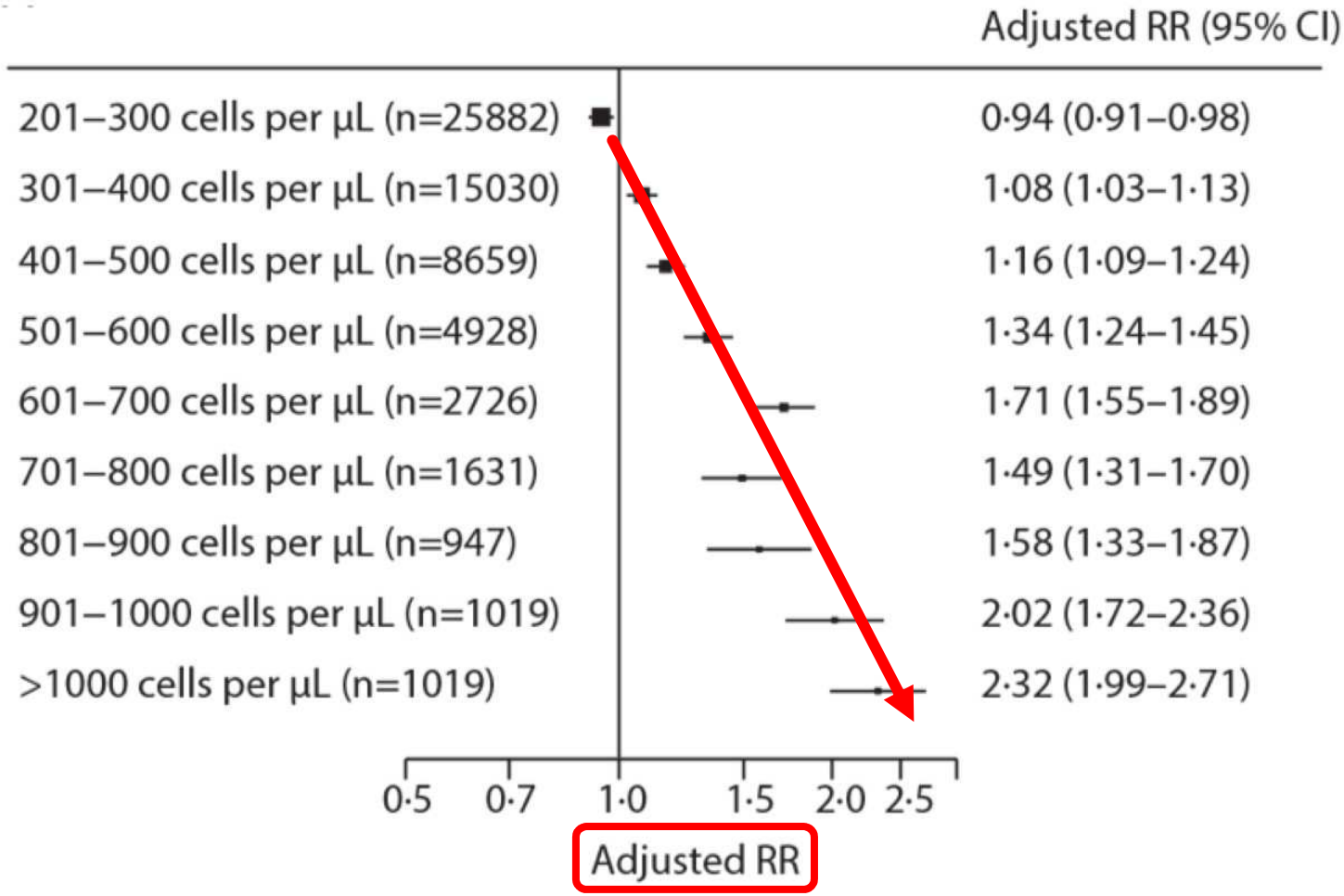
Harris et al. Respiratory Research (2016) 17:29

Role of eosinophils in health and disease



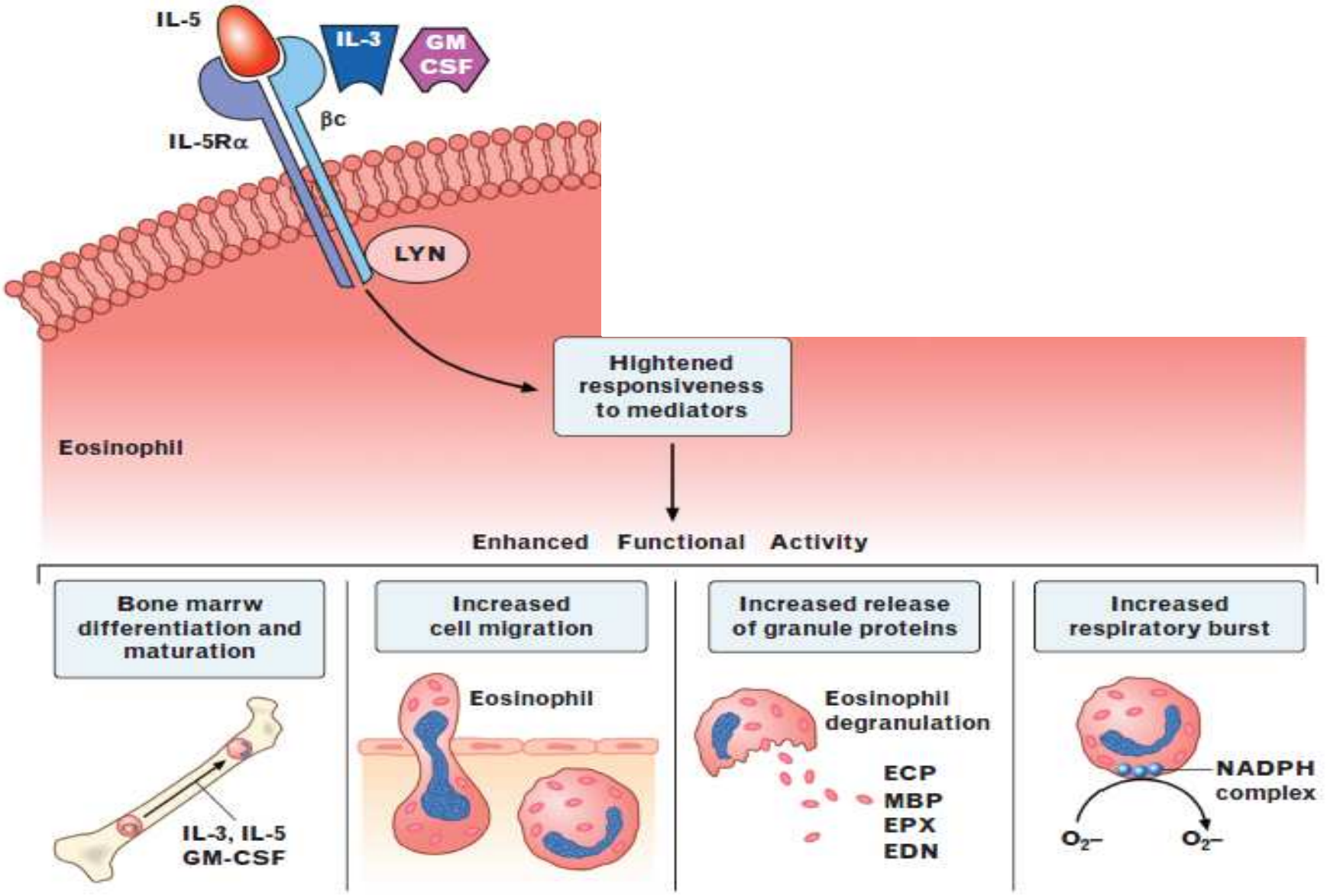
 Clinical & Experimental Allergy, 42 : 712–737

Blood Eosinophils Levels* and Severe Asthma Exacerbations



*Biomarker of Th2-driven inflammation.

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



(Varricchi G et al, Curr. Opin. April 2016)

Clinical trials of mepolizumab in asthma (anti-interleukin-5, IgG_1)

First author/ref/year	Disease severity	No. of patients treated	Dosage/delivery	Outcome summary
Flood-Page *et al.* [58], 2003	Mild asthma	11	750 mg i.v. every 4 weeks for 3 months	↓Blood Eos; ↓Airway Eos only by 50% = PEF, FEV_1, bronchial hyperresponsiveness
Haldar *et al.* [53], 2009	Eosinophilic asthma	61	750 mg i.v. every 4 weeks for 1 year	↓Blood + Sputum Eos; ↓Severe exacerbations; ↑QoL = FEV|, bronchial hyperreactivity
Nair *et al.* [55], 2009	Prednisone-dependent asthma	9	750 mg i.v. every 4 weeks for 5 months	↓Blood + Sputum Eos; ↓Exacerbations; Prednisone sparing effect
Pavord *et al.* [57], 2012	Severe eosinophilic asthma	462	75–250–750 mg i.v. every 4 weeks for 13 infusions	↓Blood + Sputum Eos; ↓Exacerbations = FEV_1, AQLQ, and ACQ scores
Bel *et al.* [51▪▪], 2014	Severe eosinophilic asthma	135	100 mg s.c. every week for 20 weeks	Glucocorticoid sparing effect; ↓Exacerbations; Improvement ACQ-5 score
Ortega *et al.* [56▪▪], 2014	Severe eosinophilic asthma	385	75 mg i.v. or 100 mg s.c. every 4 weeks for 32 weeks	↓Blood + Sputum Eos; ↓Exacerbations; ↑FEV_1; ↑ACQ-5 score
Basu *et al.* [60], 2015	Severe eosinophilic asthma			Healthcare resources and costs of mepolizumab versus placebo in a clinical trial (MENSA Study)

OPEN ACCESS Freely available online

PLOS | ONE

Efficacy of Anti-Interleukin-5 Therapy with Mepolizumab in Patients with Asthma: A Meta-Analysis of Randomized Placebo-Controlled Trials

Yao Liu, Song Zhang, Dao-wei Li, Shu-juan Jiang*

Department of Respiratory Medicine, Provincial Hospital Affiliated to Shandong University, Jinan, Shandong, China

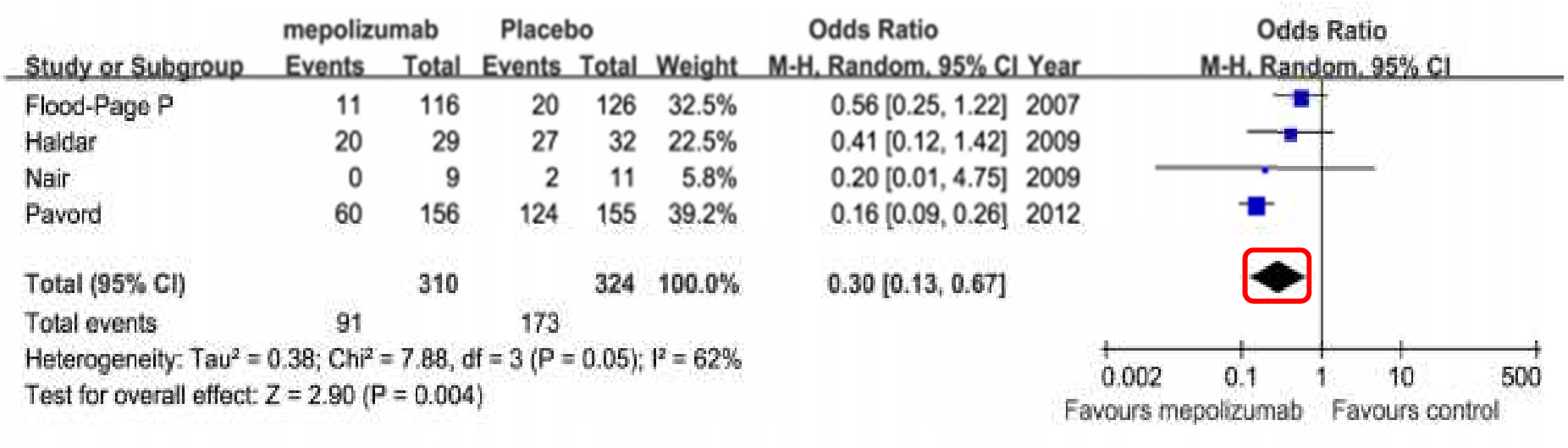
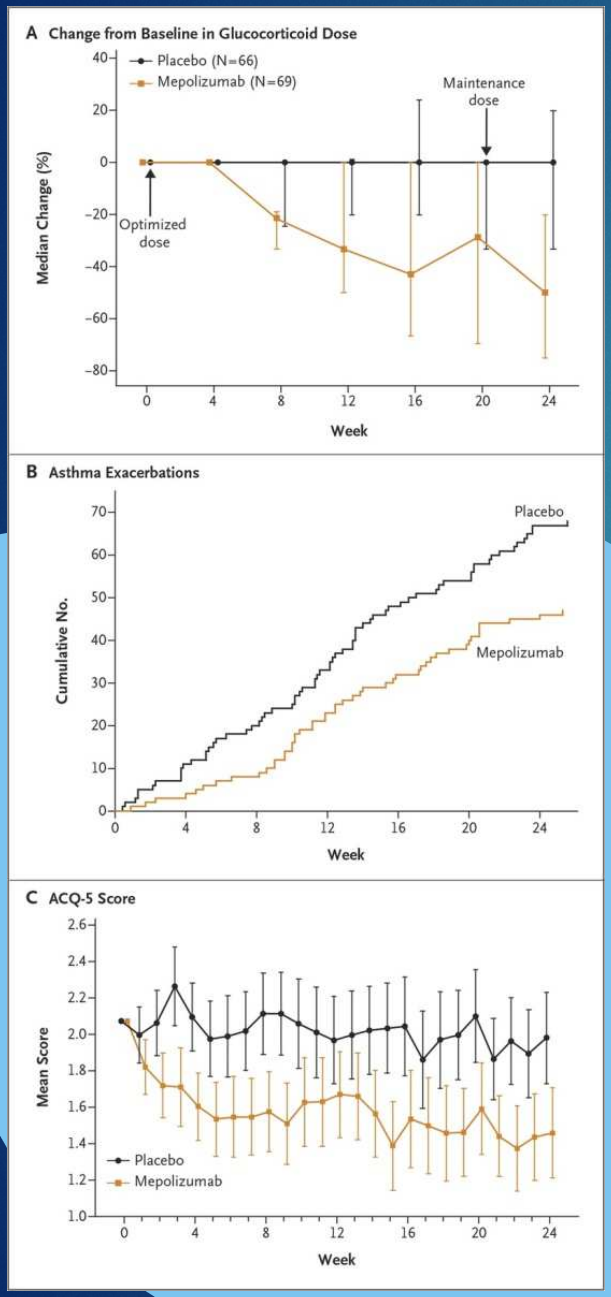


Figure 8. The effects of mepolizumab on exacerbation rates.

Conclusions: Mepolizumab reduces the risk of exacerbations and improves quality of life in patients with eosinophilic asthma, but no significant improvement in lung function outcomes was observed. Further research is required to establish the possible role of anti-IL-5 as a therapy for asthma.

Liu et al , PLoSone 2013

Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma



Mepolizumab : 100 mg SC every 4 weeks

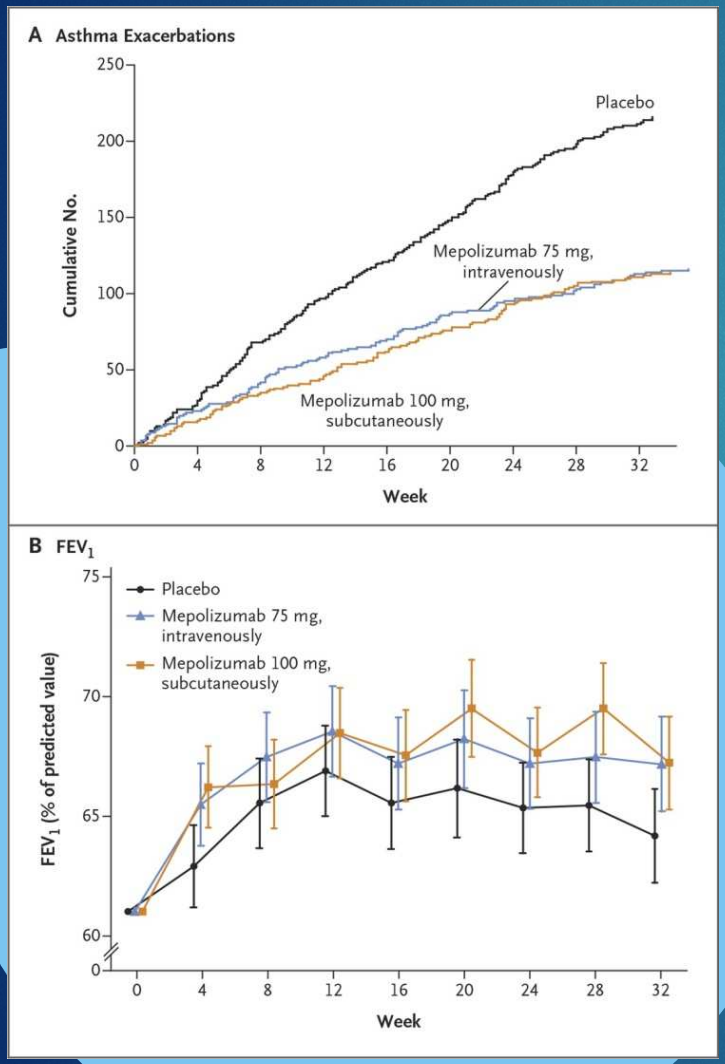
Table 3. Summary of Adverse Events.

Event	Placebo (N=66)	Mepolizumab (N=69)
	no. of patients (%)	
Adverse event		
Any	61 (92)	57 (83)
Nonasthma	60 (91)	57 (83)
Worsening of asthma	8 (12)	2 (3)
Related to study drug*	12 (18)	21 (30)
Leading to discontinuation of study drug or withdrawal from the study	3 (5)	3 (4)
Serious adverse event		
During treatment	12 (18)	1 (1)
Fatal	1 (2)	0

* This determination was made by investigators who were unaware of study-group assignments. Additional details regarding adverse events are provided in Table S6 in the Supplementary Appendix.

Bel EH et al., N Engl J Med Volume 371(13):1189-1197 September 25, 2014

Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma



Mepolizumab: 75 mcg EV / 100 mcg SC

Table 3. Summary of Adverse Events.*

Variable	Placebo (N=191)	Mepolizumab	
		Intravenous (N=191)	Subcutaneous (N=194)
	number of patients (percent)		
All adverse events	158 (83)	161 (84)	152 (78)
Nonasthma event	157 (82)	161 (84)	152 (78)
Worsening of asthma	29 (15)	18 (9)	13 (7)
Drug-related event, per investigator assessment†	30 (16)	33 (17)	39 (20)
Leading to study withdrawal	4 (2)	0	1 (1)
Serious adverse events			
During treatment	27 (14)	14 (7)	16 (8)
Drug-related event, per investigator assessment†	1 (1)	0	1 (1)
Fatal	1 (1)	0	0
Most common adverse events‡			
Nasopharyngitis	46 (24)	45 (24)	33 (17)
Headache	33 (17)	46 (24)	39 (20)
Upper respiratory tract infection	27 (14)	22 (12)	24 (12)
Sinusitis	18 (9)	11 (6)	18 (9)
Bronchitis	18 (9)	14 (7)	9 (5)
Oropharyngeal pain	15 (8)	12 (6)	7 (4)
Injection-site reaction	6 (3)	5 (3)	17 (9)

* A more detailed listing of adverse events is provided in Table S4 in the Supplementary Appendix.
† The status was assigned by investigators while they were unaware of the study-group assignments.
‡ The most common adverse events were those that were reported in at least 5% of the patients in any study group.

Ortega HG et al., N Engl J Med ,Volume 371(13):1198-1207 September 25, 2014

Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies

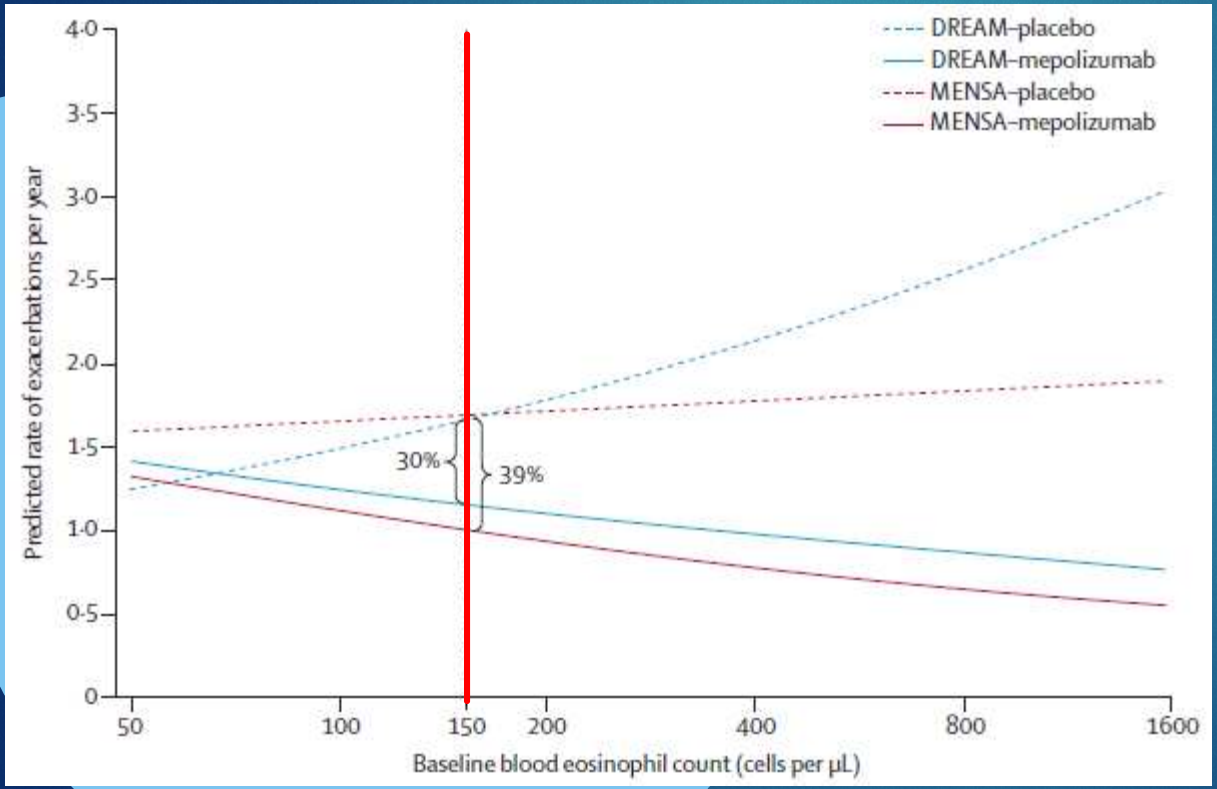
Hector G Ortega, Steven W Yancey, Bhabita Mayer, Necdet B Gunsoy, Oliver N Keene, Eugene R Bleecker, Christopher E Brightling, Ian D Pavord

Lancet Respir Med **2016**
Published **Online**
May 10, 2016

close relationship between baseline blood eosinophil count and clinical efficacy of mepolizumab in patients with severe eosinophilic asthma and a history of exacerbations.

Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies

Hector G Ortega, Steven W Yancey, Bhabita Mayer, Necdet B Gunsoy, Oliver N Keene, Eugene R Bleecker, Christopher E Brightling, Ian D Pavord



Predicted rate of clinically significant exacerbations per year against baseline blood eosinophil counts

Percentage differences in exacerbation rates (mean per person per year) between placebo and mepolizumab at the baseline blood eosinophil count of **150 cells per µL.**

***Lancet Respir Med* 2016** Published **Online** May 10, 2016

Safety

Oral CSs reduction failure

How long?

Exacerbations Reboud after stopping

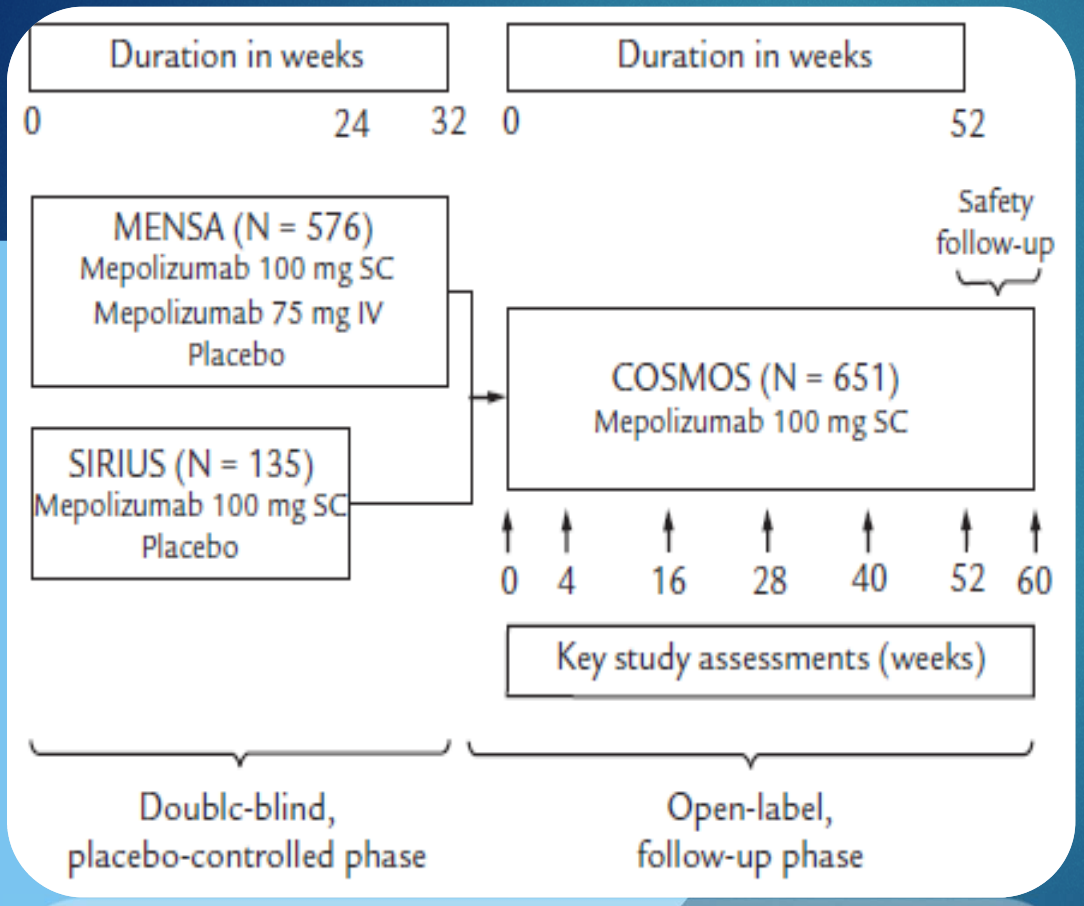
Safety information is available for 1018 patients who took mepolizumab 100 mg subcutaneously. Common adverse events were headache and nasopharyngitis. Injecting an antibody can cause hypersensitivity reactions which may have a delayed onset. Approximately 6% of patients developed antibodies against mepolizumab. Injection site reactions affected 8% versus 3% of the placebo group. As eosinophils have a role in the immune response, mepolizumab may alter the response to parasitic infections. Although there were only a few cases of herpes zoster, two of them were serious. There is currently no information about the drug's safety in pregnancy, lactation or in children younger than 12 years.

The optimum use of mepolizumab is yet to be determined. Not all patients benefit, for example 36% were unable to reduce their dose of oral corticosteroid, withdrew from treatment or had a lack of asthma control.[4] Some of the patients suitable for treatment with mepolizumab may also qualify for treatment with omalizumab so the treatments should be compared. If a patient with severe refractory eosinophilic asthma is prescribed mepolizumab, how long should they take it for? A follow-up of some of the patients in the trials found that after stopping treatment there was a rise in eosinophil count and an increase in asthma symptoms and exacerbations.[5]

Australian Prescriber
AN INDEPENDENT REVIEW

VOLUME 40 : NUMBER 1 : FEBRUARY 2017

Long-term Efficacy and Safety of Mepolizumab in Patients With Severe Eosinophilic Asthma: A Multi-center, Open-label, Phase IIIb Study



COSMOS STUDY

COSMOS was a 52-week, open-label extension study in patients who received mepolizumab or placebo in MENSA or SIRIUS.

558 pts MENSA (mepolizumab: 358; placebo: 200) and 94 pts SIRIUS (mepolizumab: 58, placebo: 36)

(Lugogo et al., Clinical Therapeutics/Volume 38, Number 9, 2016)

Long-term Efficacy and Safety of Mepolizumab in Patients With Severe Eosinophilic Asthma: A Multi-center, Open-label, Phase IIIb Study

No fatal AEs were reported.

Totals of 13 (2%) and 29 (4%) patients experienced systemic and local site reactions, respectively.

No reports of mepolizumab-related anaphylaxis.

Positive ADA(*) samples were infrequent (9% active treatment - 3% placebo), and the levels were generally low and transient.

(*) ADA = AntiDrug Antibody

Implications: These data demonstrate a favorable safety profile of mepolizumab and indicate a durable and stable effect over time, supporting long-term treatment in patients with severe eosinophilic asthma.

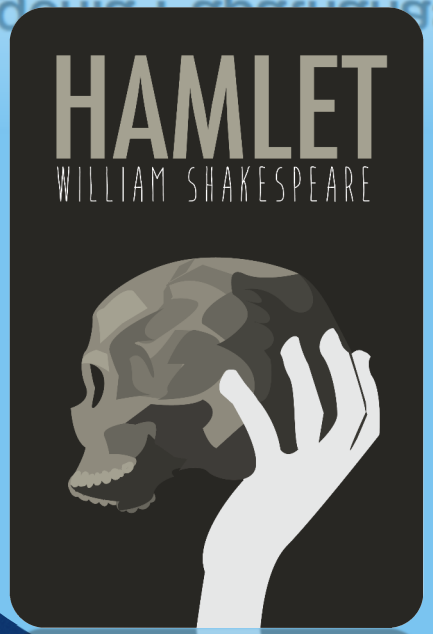
(Lugogo et al., Clinical Therapeutics/Volume 38, Number 9, 2016)

EUROPEAN
CLINICAL RESPIRATORY
JOURNAL

REVIEW ARTICLE

Severe asthma: anti-IgE or anti-IL-5?

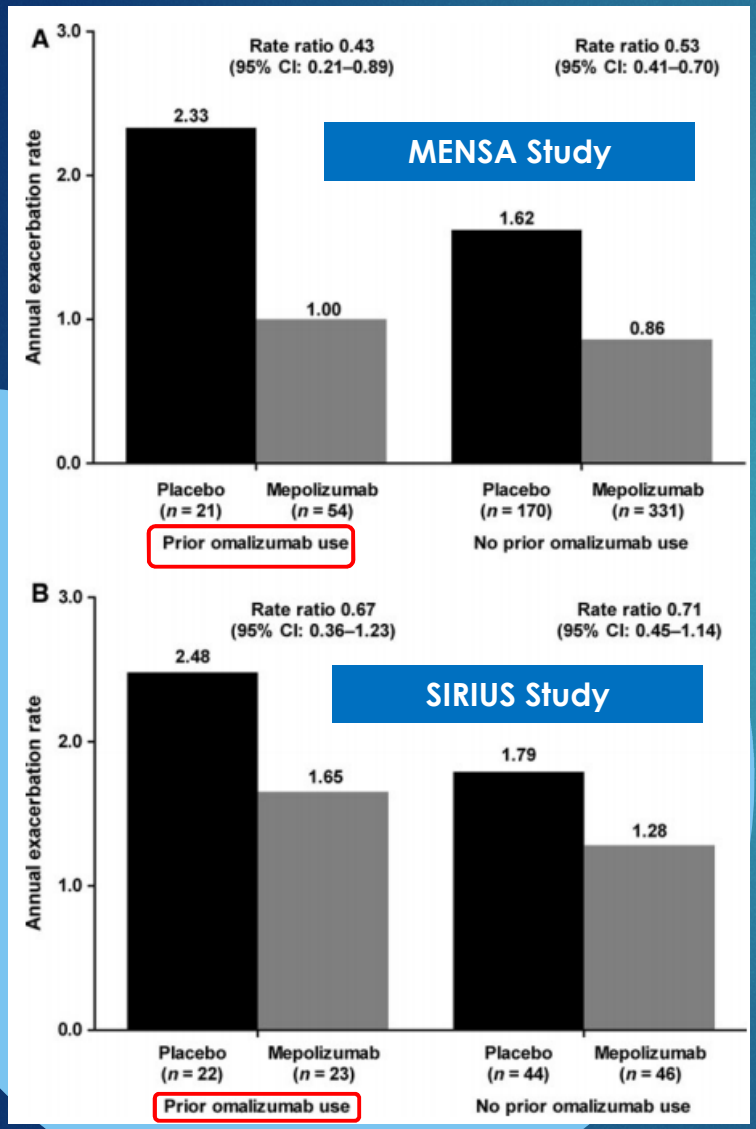
Evgenia Papathanassiou[1], Stelios Loukides[1] and Petros Bakakos[2*]



…" to date, markers indicative of the patient population responding to each treatment are unavailable ".

Eur Clin Respir J. 2016 Nov 7;3

Mepolizumab in Severe Eosinophilic Asthma Patients with History of Omalizumab Treatment

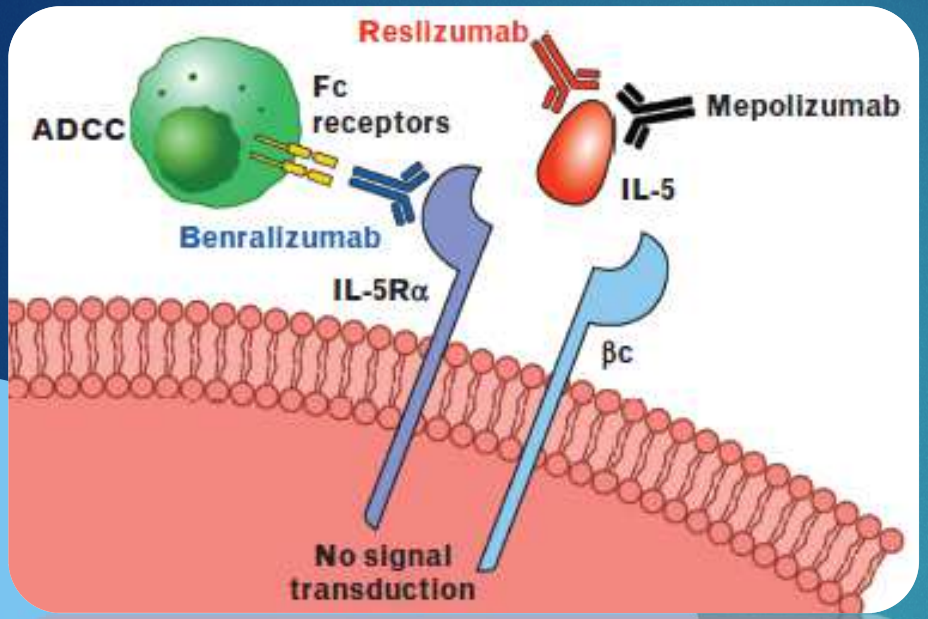


Treatment response with mepolizumab in severe eosinophilic asthma patients with previous omalizumab treatment

These post hoc analyses indicate that patients with severe eosinophilic asthma respond positively to mepolizumab regardless of prior use of omalizumab.

(Magnan A, Bourdin A, Prazma CM, Albers FC, Price RG, Yancey S, Ortega H. Allergy 2016; 71: 1335–1344)

New MABS on the block for asthma : New Anti-IL-5

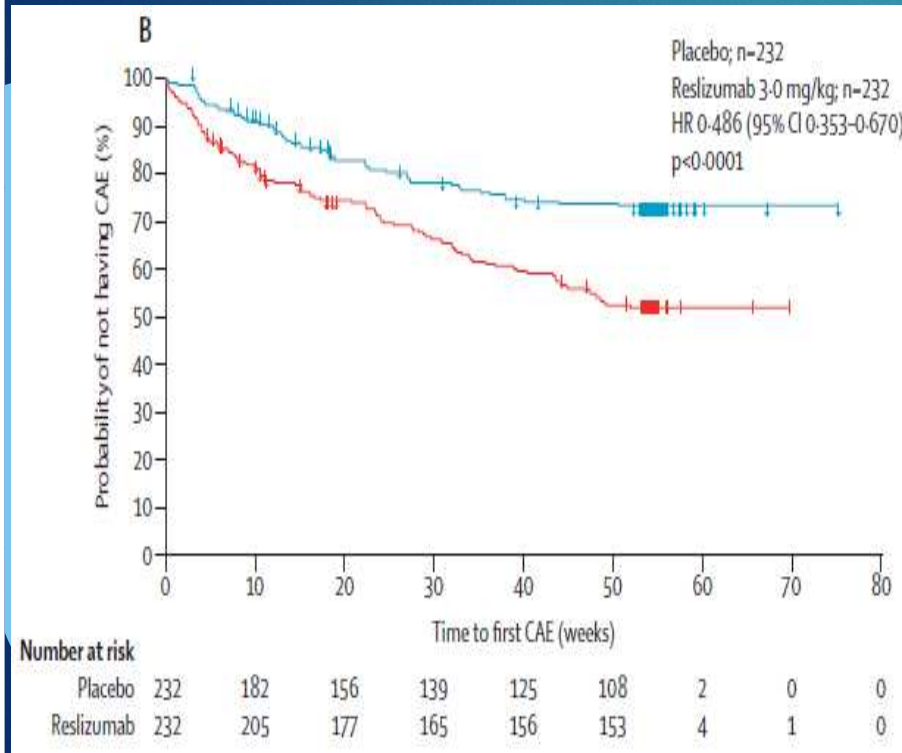


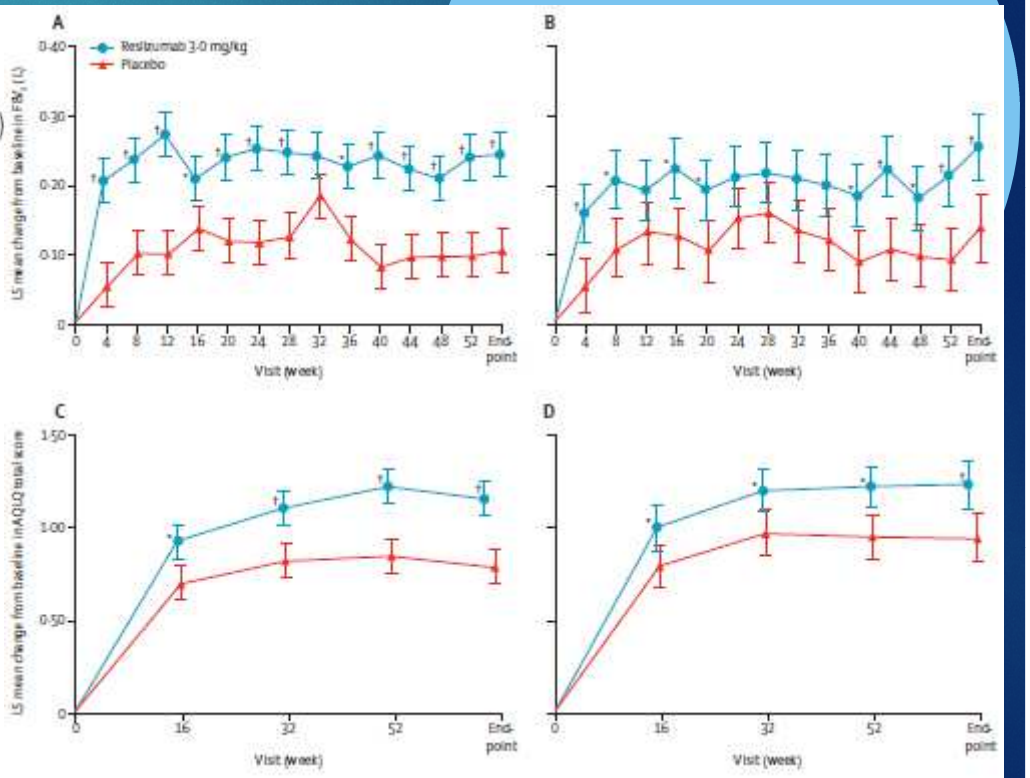
Clinical trials of reslizumab in asthma (SCH55700 – anti-interleukin-5, IgG_4)

First author/ref/year	Disease severity	No. of patients treated	Dosage/delivery	Outcome summary
Kips *et al.* [54], 2003	Severe asthmatics	18	0.03–1 mg/kg i.v. single dose	Safe; ↓Blood Eos
Castro *et al.* [52], 2011	Severe eosinophilic asthma	953	3 mg/kg i.v. every 4 weeks for 12 weeks	↓Blood Eos; ↑FEV_1; ↑ACQ-5 score; Particularly in patients with nasal polyps ±30% patients had nasal polyps

Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials

953 patients were randomly assigned to receive either reslizumab (n=477 [245 in study 1 and 232 in study 2]) or placebo (n=476). IV reslizumab 3 mg/kg or of matching placebo every 4 weeks (13 doses; last dose in week 48).





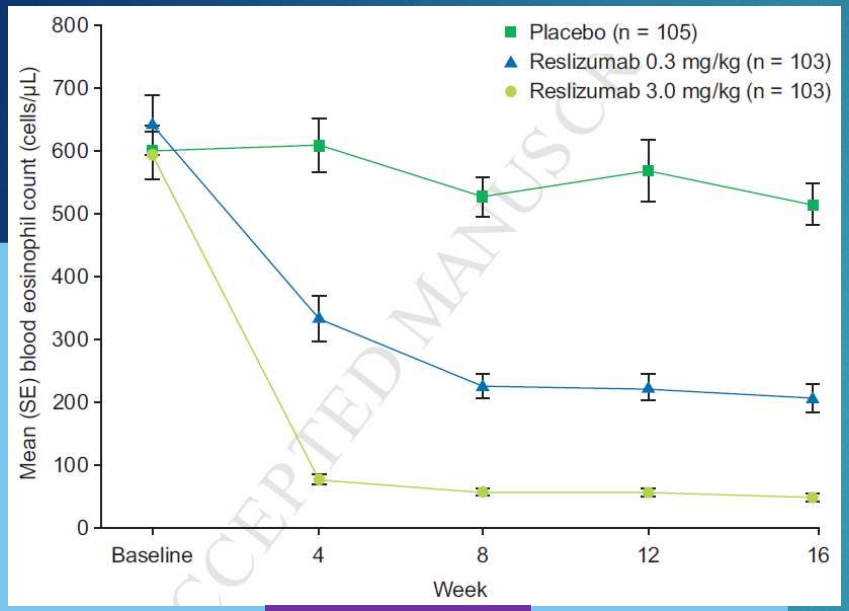
(CAE=clinical asthma exacerbation)

Changes in FEV1 and AQLQ over 52 weeks for studies 1 and 2

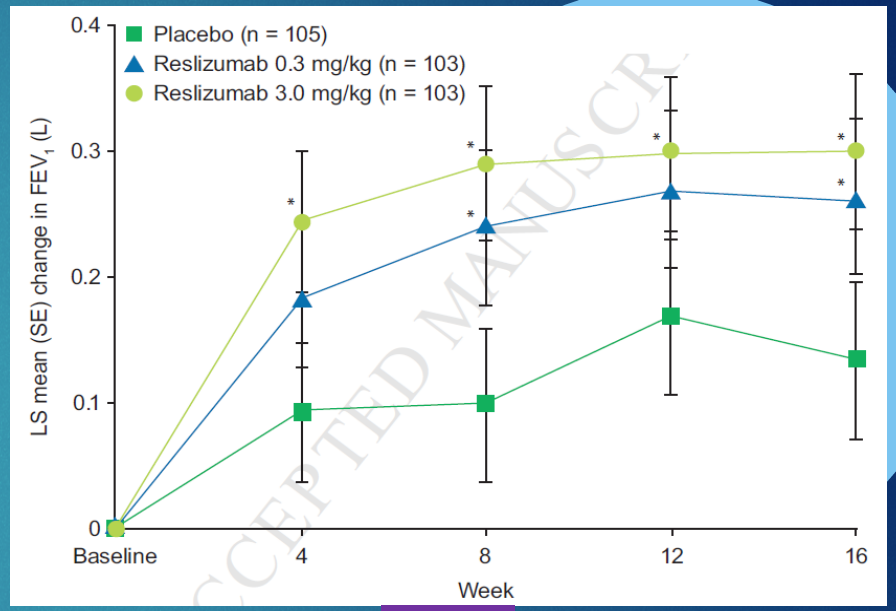
Castro M. et al., Lancet Respir Med 2015; 3: 355–66

Bjermer L, et al. :
" Reslizumab for Inadequately Controlled Asthma with Elevated Blood Eosinophil Levels: a Randomized Phase 3 Study "
CHEST (4 April 2016)

PTS AGE RANGE : 12-75 YRS; N. PTS: 275



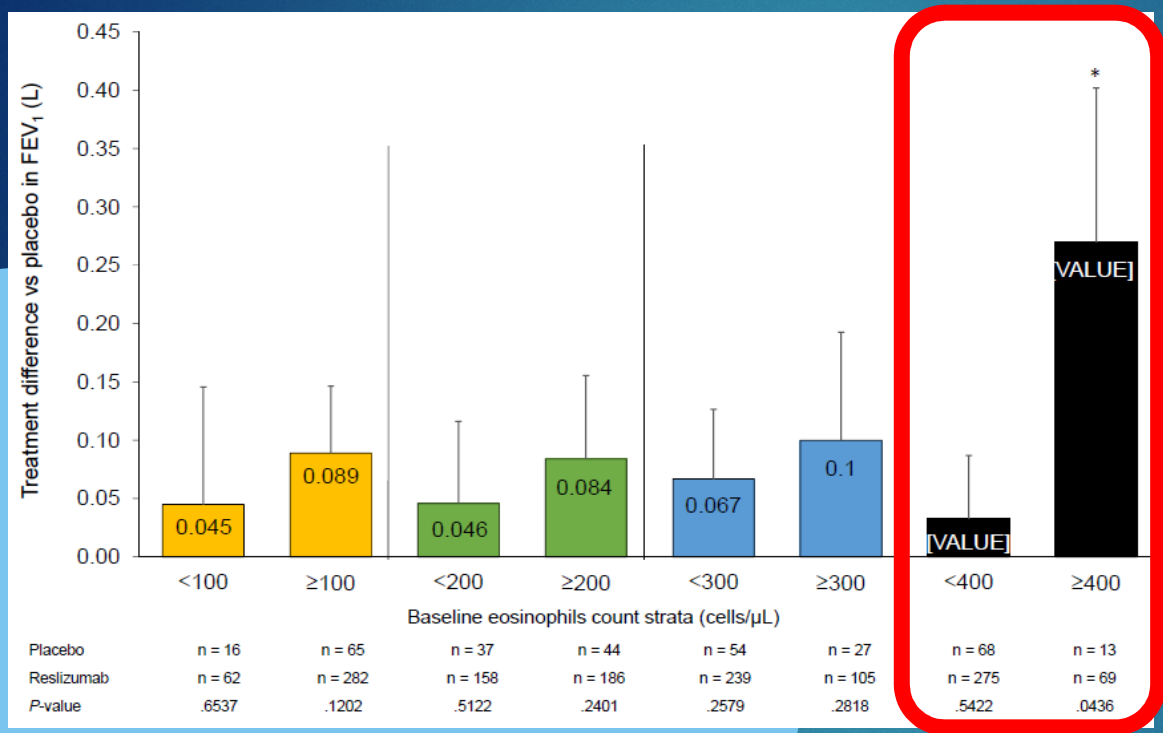
BLOOD EOS



FEV1

CONCLUSIONS: Reslizumab improved lung function, asthma control and symptoms, and quality of life, and was well tolerated in patients with inadequately controlled asthma (despite standard therapy), and elevated blood eosinophils. Overall, the 3.0mg/kg dose of reslizumab provided greater improvements in asthma outcomes (vs 0.3mg/kg), with comparable safety.

Corren J, et al.:
« Phase 3 Study of Reslizumab in Patients with Poorly Controlled Asthma: Effects Across a Broad Range of Eosinophil Counts «
CHEST (24 march 2016)



492 patients received ≥1 dose of placebo (n=97) or reslizumab (n=395).

DBPC

AGE RANGE: 18-75 YRS

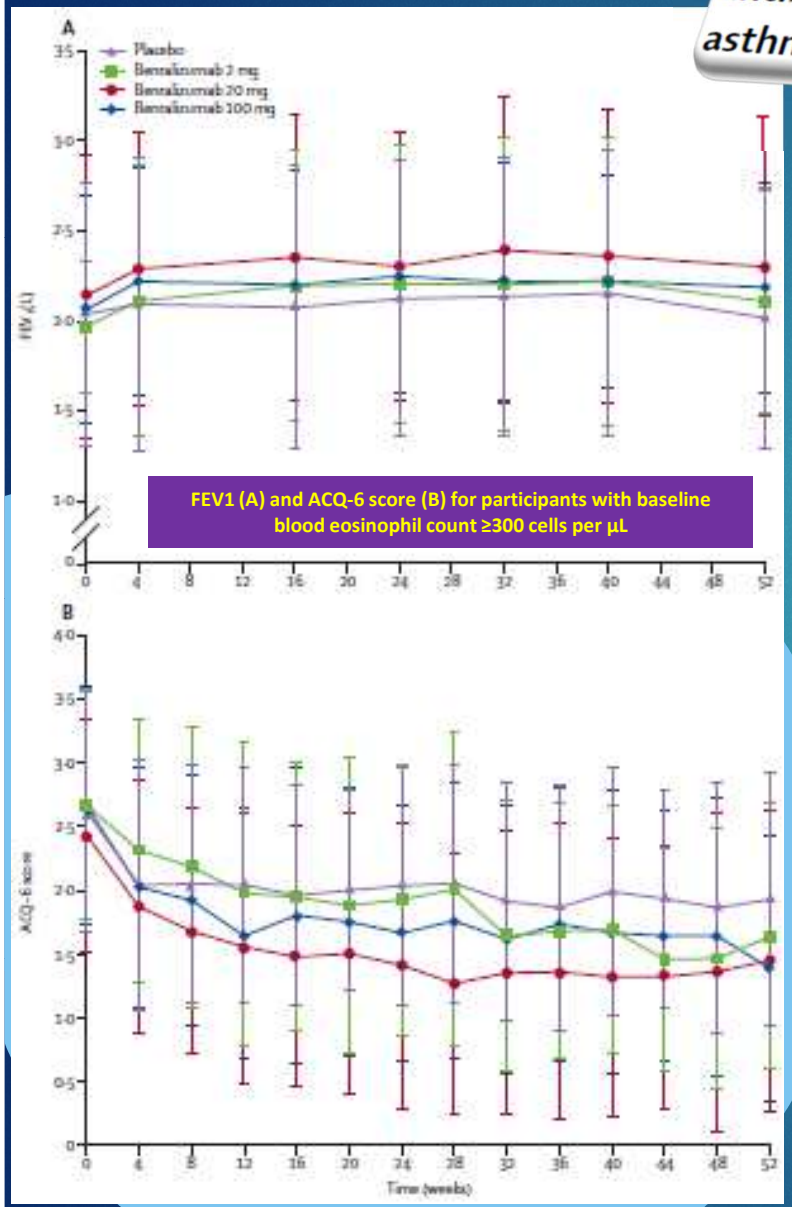
In conclusion, reslizumab 3.0 mg/kg was well tolerated in patients with asthma inadequately controlled on a medium-to high-dose ICS-based regimen. Reslizumab did not meaningfully improve asthma outcomes, including both lung function and measures of symptom control, in patients with blood eosinophil counts <400 cells/µL. These findings support an acceptable benefit–risk profile for reslizumab in asthma patients with a blood eosinophil threshold of ≥400 cells/µL.

New MABS on the block for asthma : New Anti-IL-5

First author/ref/year	Disease severity	No. of patients treated	Dosage/delivery	Outcome summary
Busse *et al.* [63], 2010	Mild atopic asthma	44	0.0003–3 mg/kg i.v. single dose	↓Blood Eos at dose 0.03–3 mg; Eosinopenia lasted 8–12 weeks Transient, mild decrease in WBC CRP increased ±5.5-fold Interleukin-6 increased CPK of peripheral muscular origin increased
Laviolette *et al.* [65], 2013	Eosinophilic asthma	26	1 mg/kg i.v.; 100 mg s.c. every month for 3 doses; 200 mg s.c. every month for 3 doses	↓Eos in blood, sputum and bronchial mucosa; ↓Basophils; Nasopharingitis 25%; Headache 25%; Nausea 22%
Castro *et al.* [64▪▪], 2014	Eosinophilic asthma	384	2–20–200 mg 2 s.c. every 4 weeks for the first 3 doses, then every 8 weeks for 1 year	20 mg and 100 mg↓ asthma; Exacerbation = FEV_1?
Nowak *et al.* [66], 2015	Asthma after acute attack	72	Single dose 0.3 mg/kg i.v. 1 mg/kg i.v. Evaluated up to 6 months	↓Blood Eos; ↓Exacerbations

Clinical trials of benralizumab in asthma (MEDI-563, Anti-interleukin-5a, IgG_1)

Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study



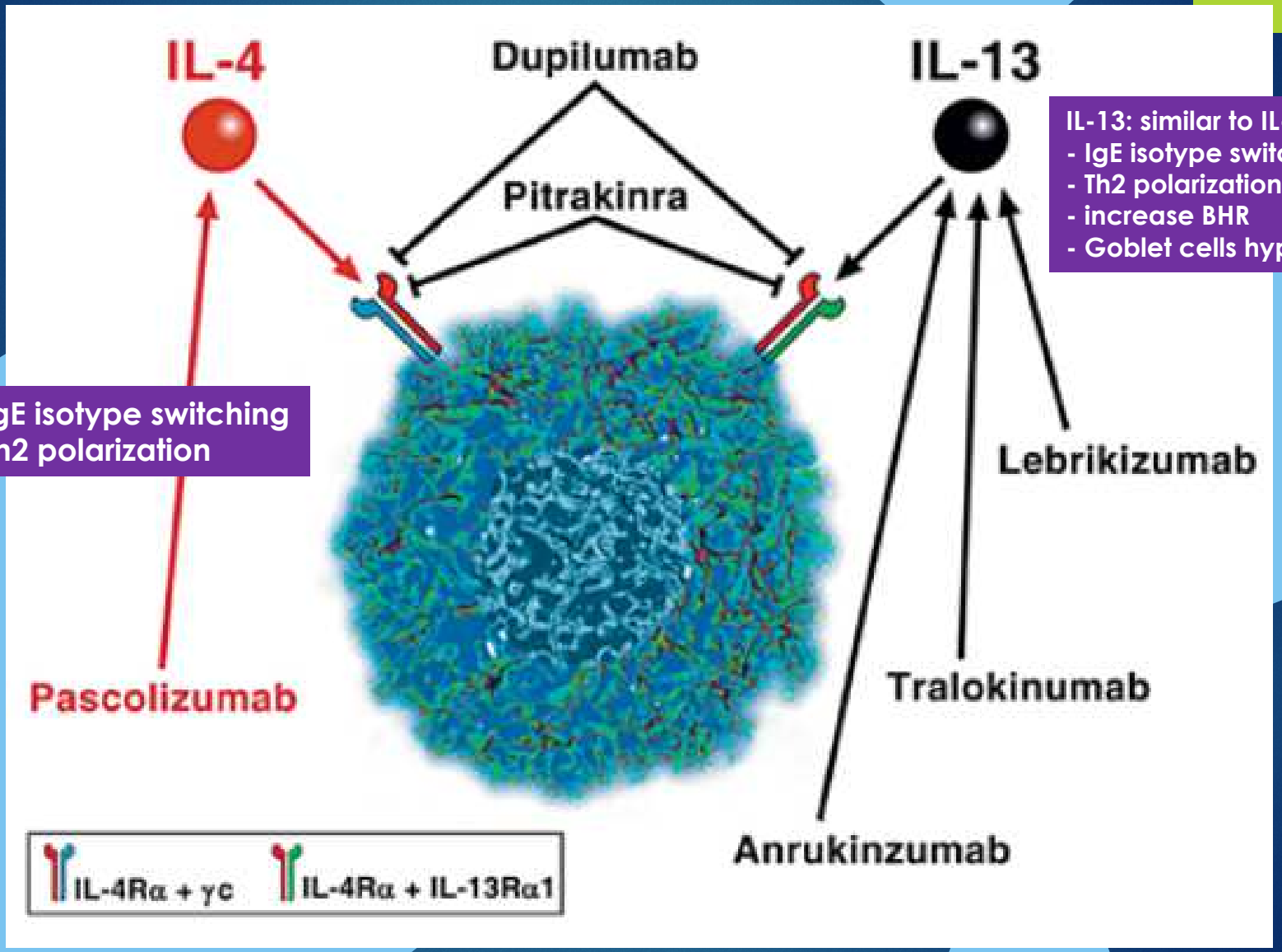
FEV1 (A) and ACQ-6 score (B) for participants with baseline blood eosinophil count ≥300 cells per µL

	Placebo (n=221)	Benralizumab 2 mg (n=81)	Benralizumab 20 mg (n=81)	Benralizumab 100 mg (n=223)	Benralizumab combined (n=385)
Any treatment-emergent adverse event	143 (65%)	56 (69%)	58 (72%)	163 (73%)	277 (72%)
Any serious treatment-emergent adverse event	23 (10%)	10 (12%)	6 (7%)	24 (11%)	40 (10%)
Discontinuation of study drug due to an adverse event	3 (1%)	4 (5%)	2 (2%)	6 (3%)	12 (3%)
Treatment-emergent adverse events by system organ class that occurred in ≥3% of participants in combined benralizumab group					
Infections and infestations	81 (37%)	38 (47%)	33 (41%)	99 (44%)	170 (44%)
Respiratory, thoracic, and mediastinal disorders	87 (39%)	34 (42%)	34 (42%)	89 (40%)	157 (41%)
General disorders and administrative-site conditions	20 (9%)	18 (22%)	18 (22%)	51 (23%)	87 (23%)
Nervous system disorders	28 (13%)	19 (23%)	9 (11%)	38 (17%)	66 (17%)
Musculoskeletal and connective tissue disorders	18 (8%)	13 (16%)	16 (20%)	28 (13%)	57 (15%)
Gastrointestinal disorders	24 (11%)	13 (16%)	15 (19%)	28 (13%)	56 (15%)
Skin and subcutaneous tissue disorders	16 (7%)	5 (6%)	10 (12%)	21 (9%)	36 (9%)
Vascular disorders	8 (4%)	3 (4%)	3 (4%)	20 (9%)	26 (7%)
Injury, poisoning, and procedural complications	13 (6%)	6 (7%)	4 (5%)	14 (6%)	24 (6%)
Investigations	13 (6%)	4 (5%)	1 (1%)	15 (7%)	20 (5%)
Cardiac disorders	6 (3%)	1 (1%)	6 (7%)	8 (4%)	15 (4%)
Metabolism and nutrition disorders	4 (2%)	3 (4%)	2 (2%)	10 (4%)	15 (4%)
Psychiatric disorders	6 (3%)	5 (6%)	2 (2%)	6 (3%)	13 (3%)

Benralizumab at 20 mg and 100 mg doses seemed to reduce asthma exacerbations in adults with uncontrolled eosinophilic asthma and baseline blood eosinophils of at least **300 cells** per µL.

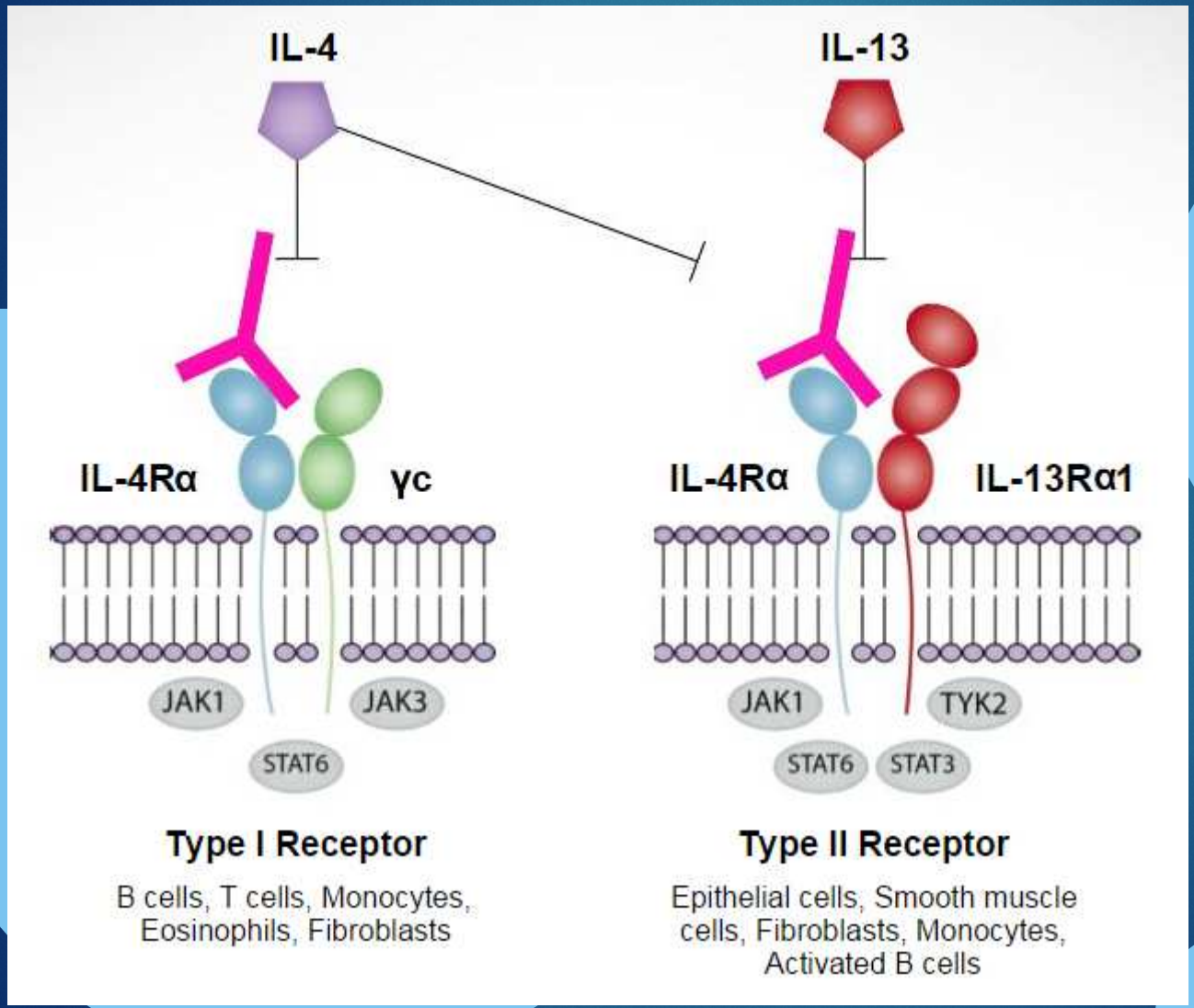
Castro M. et al., Lancet Respir Med 2014; 2: 878–90

New MABS on the block for asthma : IL-13 and IL-4 inhibitors



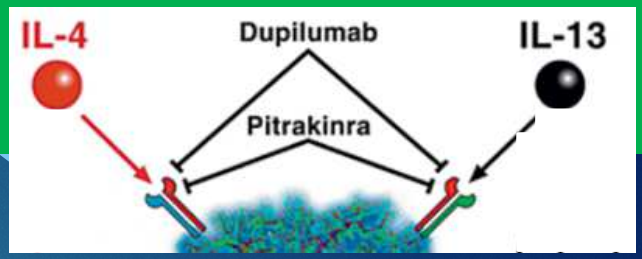
(Bagnasco et al., Int Arch Allergy Immunol 2016;170:122–131)

Dupilumab (anti-IL-4Rα) blocks the IL-4/IL-13 receptor/ligand system



fully human monoclonal antibody to the alpha subunit of the interleukin-4 receptor

Principal clinical studies with biological drugs anti IL-4 and IL-13 in asthma



Drug	First author [ref.] year	Asthma severity	Patients, n	Dosage	Summary of outcomes
Dupilumab	Wenzel [86] 2013	moderate-to-severe; blood eosinophil count of at least 300 cells/μl	52 on dupilumab 52 on placebo	300 mg weekly placebo	↓ asthma exacerbation (3 in dupilumab group, 23 in placebo group) ↑ FEV_1 change of ACQ5 score ↓ inhalation of albuterol or levalbuterol change in evening asthma score
Pitrakinra	Wenzel [84] 2007	atopic	group 1: 12 on pitrakinra 12 on placebo group 2: 16 on pitrakinra 16 on placebo	 25 mg daily s.c. placebo 60 mg 2× daily nebulization placebo	 ↓ FEV_1 17.1 vs. 23.1% (pitrakinra vs. placebo) ↓ FEV_1 4.4 vs. 15.9% (pitrakinra vs. placebo)
	Slager [83] 2012	moderate-to-severe	407 non-Hispanic subjects	10 mg 3 mg 1 mg placebo	↓ asthma exacerbation and night waking activity limitation in pitrakinra arm and homozygous for the rs8832 common G allele ↓ (dose-response linked) asthma exacerbation also in subjects homozygous for the common allele in rs1029489 ($p = 0.005$) and rs8832 ($p = 0.009$) and the intronic SNPs rs3024585, rs3024622 and rs4787956 ($p = 0.03$)

Conflicting results

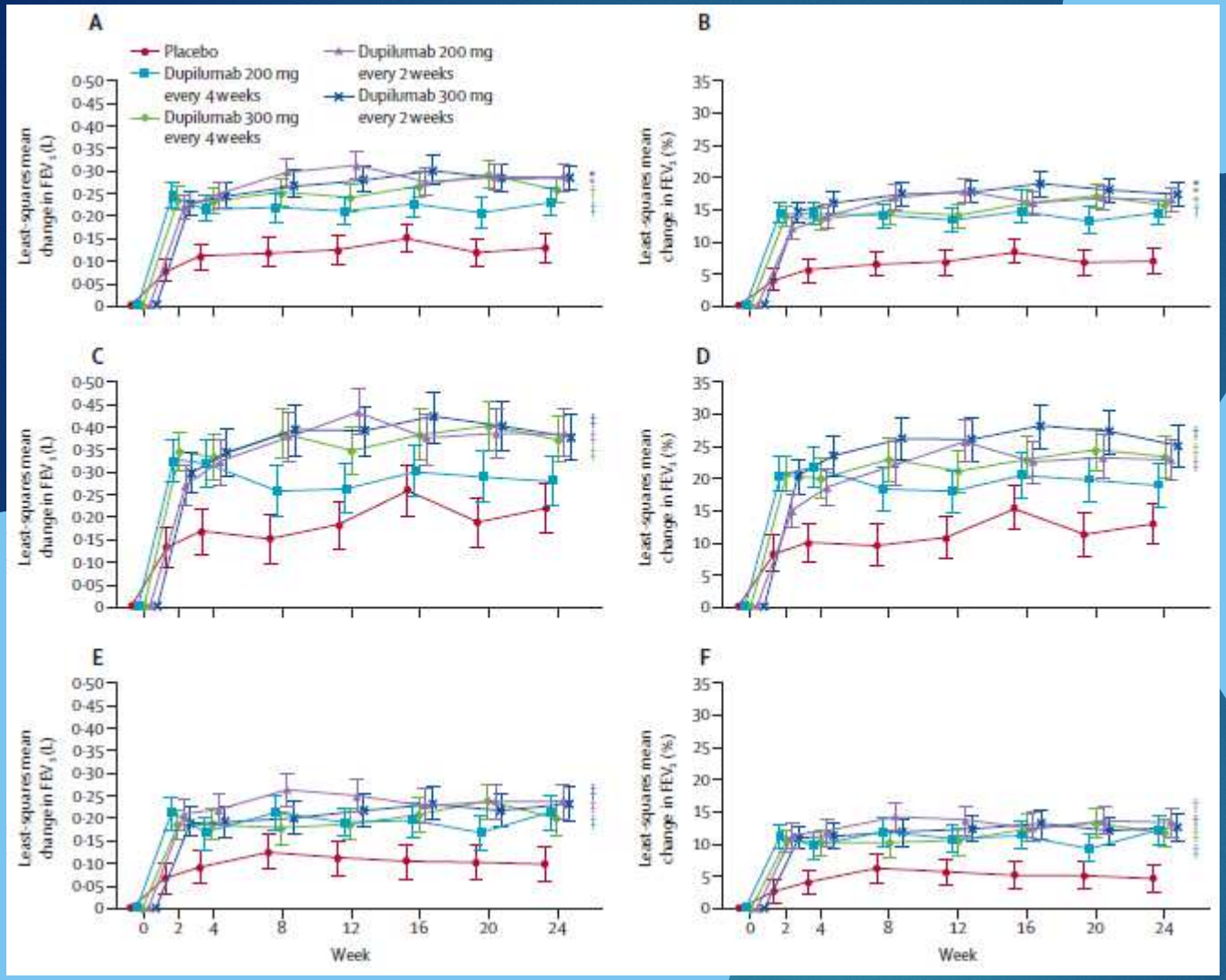
(Bagnasco et al., Int Arch Allergy Immunol 2016;170:122–131)

Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial

Sally Wenzel, Mario Castro, Jonathan Corren, Jorge Maspero, Lin Wang, Bingzhi Zhang, Gianluca Pirozzi, E Rand Sutherland, Robert R Evans, Vijay N Joish, Laurent Eckert, Neil M H Graham, Neil Stahl, George D Yancopoulos, Mariana Louis-Tisserand, Ariel Teper

treatment options as add-on therapy. We aimed to assess the efficacy and safety of dupilumab as add-on therapy in patients with uncontrolled persistent asthma on medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist, irrespective of baseline eosinophil count.

www.thelancet.com **Published online April 26, 2016**



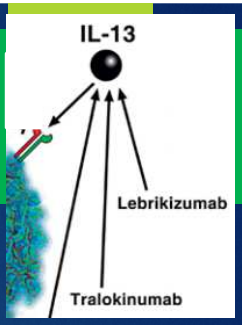
Improvement in FEV1 in liters (A,C, E) and % (B, D, F)

A-B : overall population
C-D: eos > 300 uL
E-F: < 300 uL

Patients with lower levels of blood eosinophils may also respond.

Interpretation Dupilumab increased lung function and reduced severe exacerbations in patients with uncontrolled persistent asthma irrespective of baseline eosinophil count and had a favourable safety profile, and hence in addition to inhaled corticosteroids plus long-acting β_2-agonist therapy could improve the lives of patients with uncontrolled persistent asthma compared with standard therapy alone.

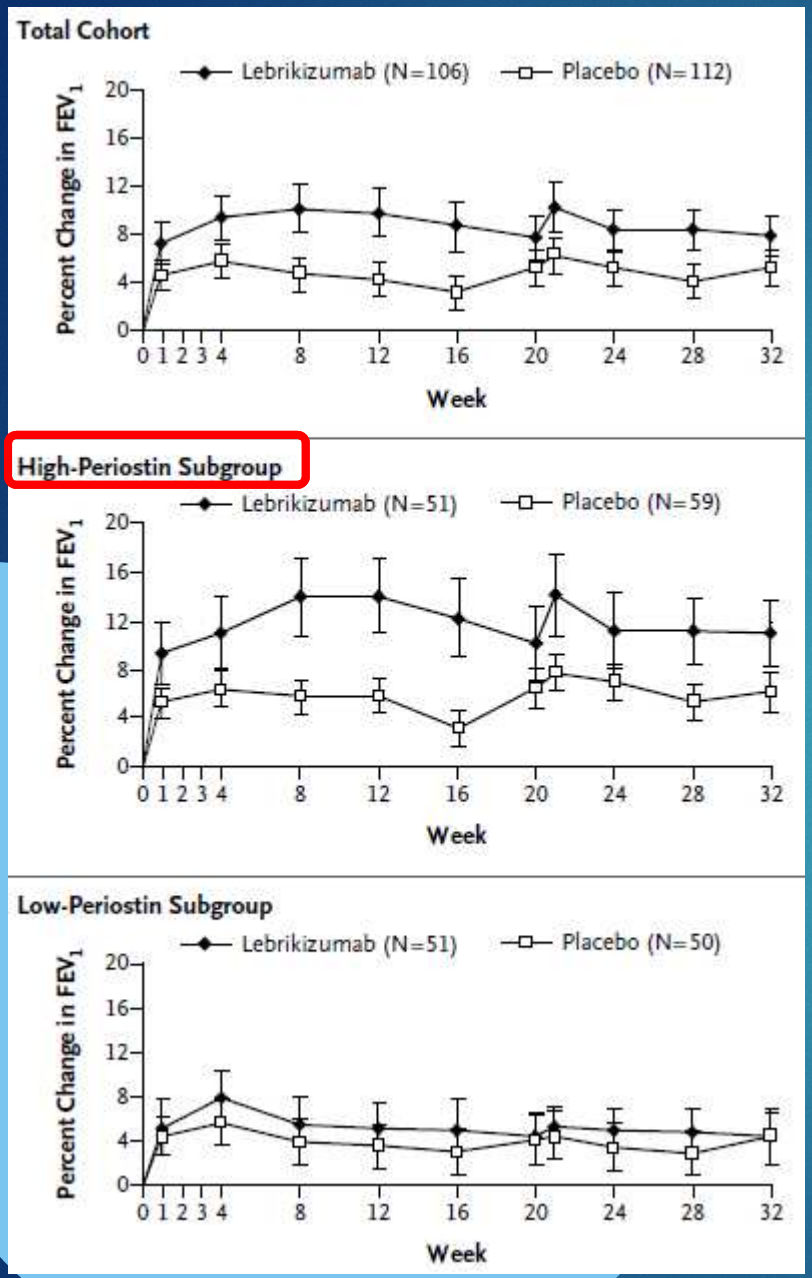
Principal clinical studies with biological drugs anti IL-13 in asthma



Drug	First author [ref.] year	Asthma severity	Patients, n	Dosage	Summary of outcomes
Tralokinumab	Piper [69] 2013	moderate-to-severe; uncontrolled	194	150 mg 300 mg 600 mg placebo	modified from baseline in mean ACQ score (−0.76± 1.04)
	Brightling [70] 2015	severe uncontrolled	452	(1) tralokinumab every 2 weeks (2) tralokinumab every 4 weeks (3) placebo every 2 weeks (4) placebo every 4 weeks	↓ asthma exacerbation vs. placebo in high-periostin and high-DPP-4 groups FEV_1 in high-periostin and high-DPP-4 groups
Lebrikizumab	Hanania [67] 2015	moderate-to-severe	463	37.5 mg 125 mg 250 mg placebo s.c. every 4 weeks	↓ asthma exacerbation in high-periostin group no dose response ↑ FEV_1 in high-periostin group
	Scheerens [66] 2014	mild	29	13 lebrikizumab 16 placebo s.c. every 4 weeks	greater response in high-IgE, high-eosinophil and high-periostin patients
	Noonan [68] 2013	not controlled despite ICS therapy	212	125 mg 250 mg 500 mg placebo s.c. monthly	changes in FEV_1 were higher in patients receiving lebrikizumab but not clinically significant
	Corren [6] 2011	steroid-dependent	219	250 mg placebo	↑ FEV_1 in high-periostin group

(Bagnasco et al., Int Arch Allergy Immunol 2016;170:122–131)

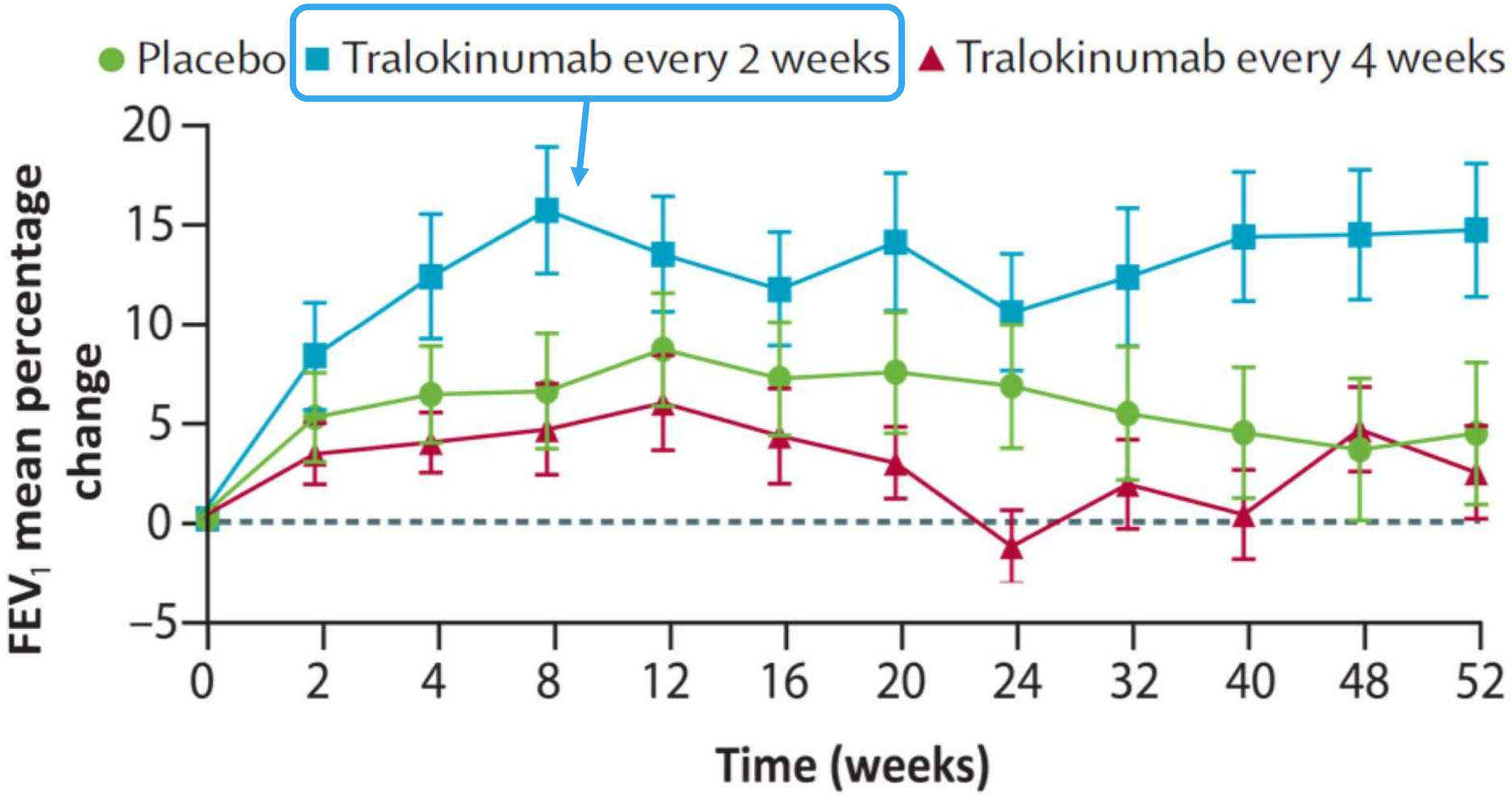
Lebrikizumab Treatment in Adults with Asthma



Lebrikizumab treatment was associated with improved lung function. Patients with **high pretreatment levels of serum periostin had greater improvement** in lung function with lebrikizumab than did patients with low periostin levels.

(Corren et al., N Engl J Med 2011;365:1088-98)

Tralokinumab : Anti-IL-13 in patients with high DPP-4



DPP-4: Dipeptidyl Peptidase-4

Brightling CE, et al. *Lancet Respir Med.* 2015;3:692-701.

Single Biomarkers cut-offs of T-Helper-2 Cell (TH2) inflammation

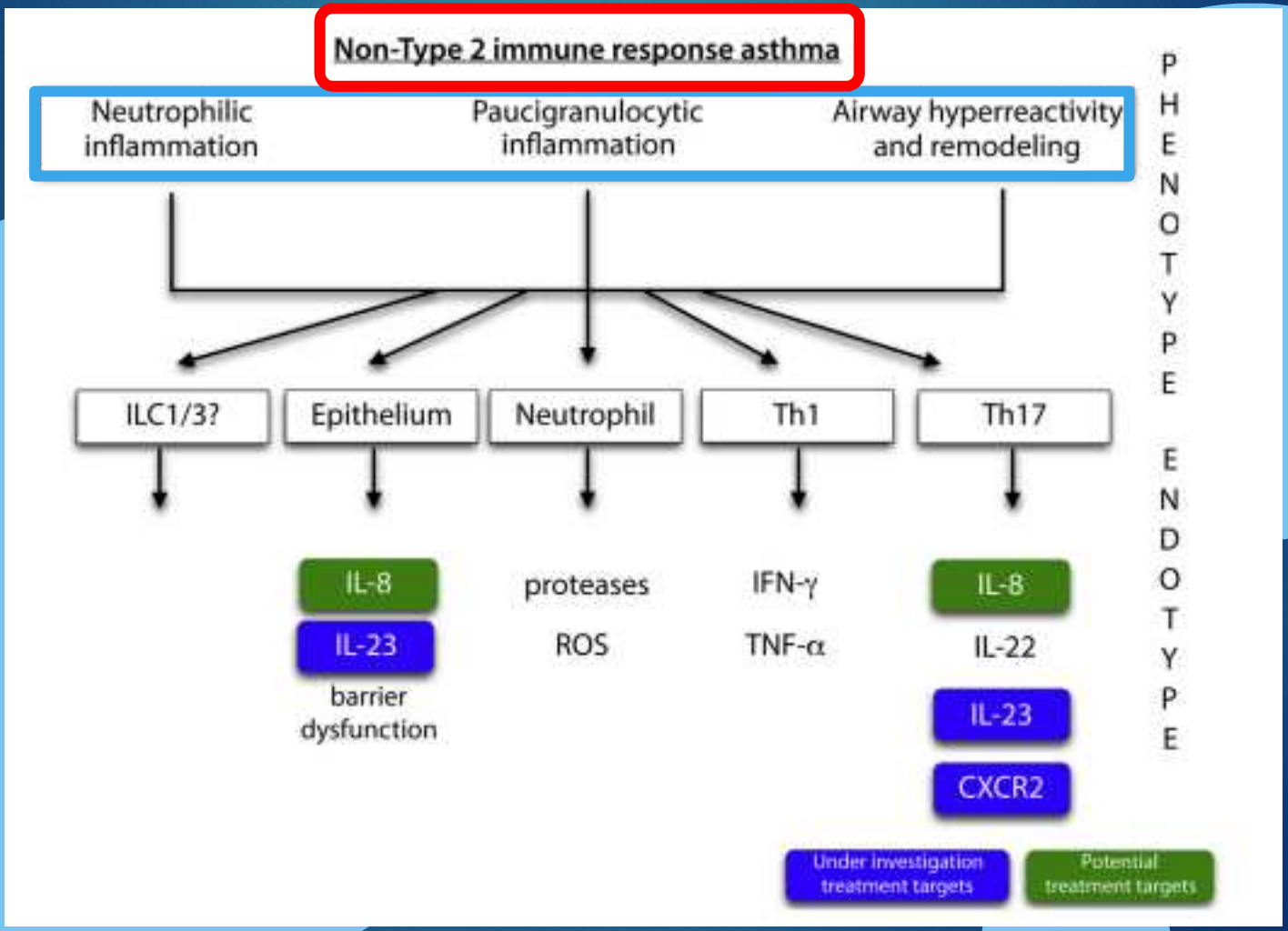
Biomarker	Targeted therapy	Outcomes studied	Selection criteria/biomarker cut-offs	Value[a]
Single biomarkers				
Sputum eosinophils	Mepolizumab [47]	Exacerbations	Sputum eosinophil >3%	+++
	Mepolizumab [9]	Exacerbations and reduction in prednisolone dose	Sputum eosinophil >3%	++
Blood eosinophils	Mepolizumab [8]	Exacerbations	Blood eosinophil >150 cells/μl at screening or ≥300 cells/μl in previous year	+++
	Mepolizumab [10]	Reduction in prednisolone dose	Blood eosinophil ≥150 cells/μl at optimization[b] or ≥300 cells/μl in previous year.	+++
	Reslizumab [12]	Exacerbations	Blood eosinophil ≥400 cells/μl	+++
	Reslizumab [13]	Change in FEV_1	Blood eosinophil ≥400 cells/μl	+++
	Benralizumab [71]	Exacerbations	All blood eosinophil levels recruited[c]	+++
	Benralizumab [72]	Exacerbations	All blood eosinophil levels recruited[c]	+++
	Dupilumab [78]	Exacerbations	All blood eosinophil levels recruited	0[d]

Peters MC et al., Curr Allergy Asthma Rep (2016) 16: 71

PRACTALL consensus report

Precision medicine in patients with allergic diseases: Airway diseases and atopic dermatitis—PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology

Antonella Muraro, MD,[a] Robert F. Lemanske, Jr, MD,[b] Peter W. Hellings, MD,[c] Cezmi A. Akdis, MD,[d] Thomas Bieber, MD,[e] Thomas B. Casale, MD,[f] Marek Jutel, MD,[g] Peck Y. Ong, MD,[h] Lars K. Poulsen, PhD,[i] Peter Schmid-Grendelmeier, MD,[j] Hans-Uwe Simon, MD,[k] Sven F. Seys, PhD,[l] and Ioana Agache, MD[m]
Padua, Italy, Madison, Wis, Leuven, Belgium, Davos and Bern, Switzerland, Bonn, Germany, Tampa, Fla, Wroclaw, Poland, Los Angeles, Calif, Copenhagen, Denmark, and Brasov, Romania



(J Allergy Clin Immunol 2016;137:1347-58)

Monoclonal Antibody Therapies Targeting Non-Th2 Asthma

Targeting IL-17

- BRODALUMAB
- SECUKINUMAB
- USTEKINUMAB

Targeting TNF-a

- ADALIMUMAB
- ETANERCEPT
- GOLIMUMAB
- INFLIXIMAB

Brodalumab is a human anti-IL-17RA immunoglobulin G2 (IgG2) monoclonal antibody that binds with high affinity to IL-17RA and blocks the biological activity of IL-17A, IL-17F, IL-17A/F heterodimer, and IL-25 . A study was conducted using brodalumab in moderate-to-severe asthmatics receiving regular ICS, and results showed improvements in ACQ scores, FEV_1, and symptom-free days

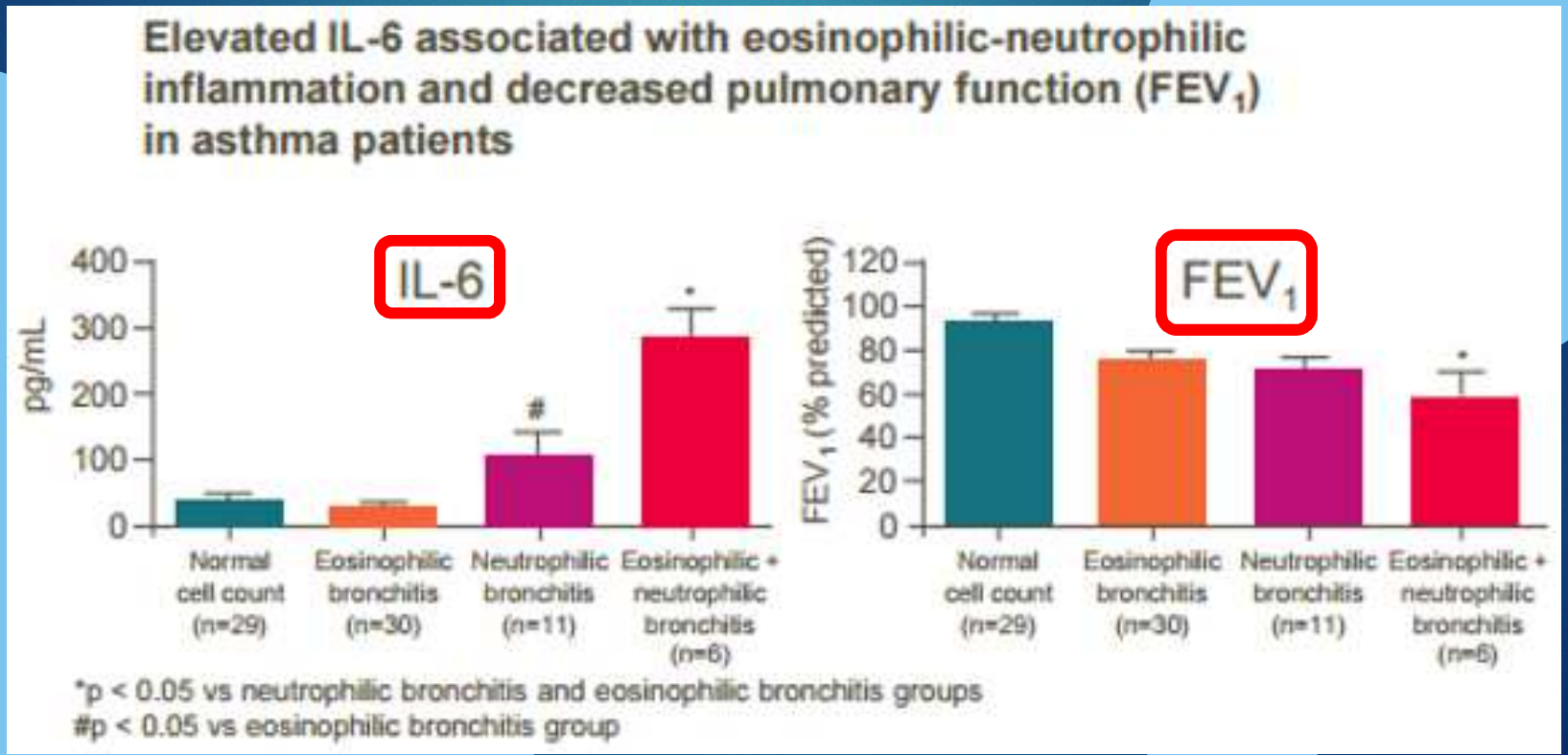
TNF-α receptor blockers such as etanercept and golimumab have not shown any clinical benefit in asthma. Holgate et al. performed a phase II randomized controlled trial of etanercept in moderate-to-severe asthmatics receiving high-dose ICS. Although etanercept was well tolerated, there were no improvements in FEV_1 (primary endpoint) or ACQ-5 scores (secondary endpoints) . Golimumab was studied in patients with uncontrolled persistent asthma receiving high-dose ICS and LABA but yielded no improvement in FEV_1 or exacerbation rates. Risk of malignancy and serious infection was increased with golimumab, and studies were subsequently ceased

- Conflicting results
- Serious infections
- Risk of malignancy

Peters MC et al., Curr Allergy Asthma Rep (2016) 16: 71

New MABS on the block for asthma : Non TH2 asthma / IL-6 mAb sirukumab

- Targets severe disease ineligible for Th2/eosinophilic directed mAbs (40% of severe asthma patients)
- IL-6: key inflammatory driver and genetic association of this pathway in asthma
- Expected to improve symptoms and exacerbations
- Phase II study start in 2016

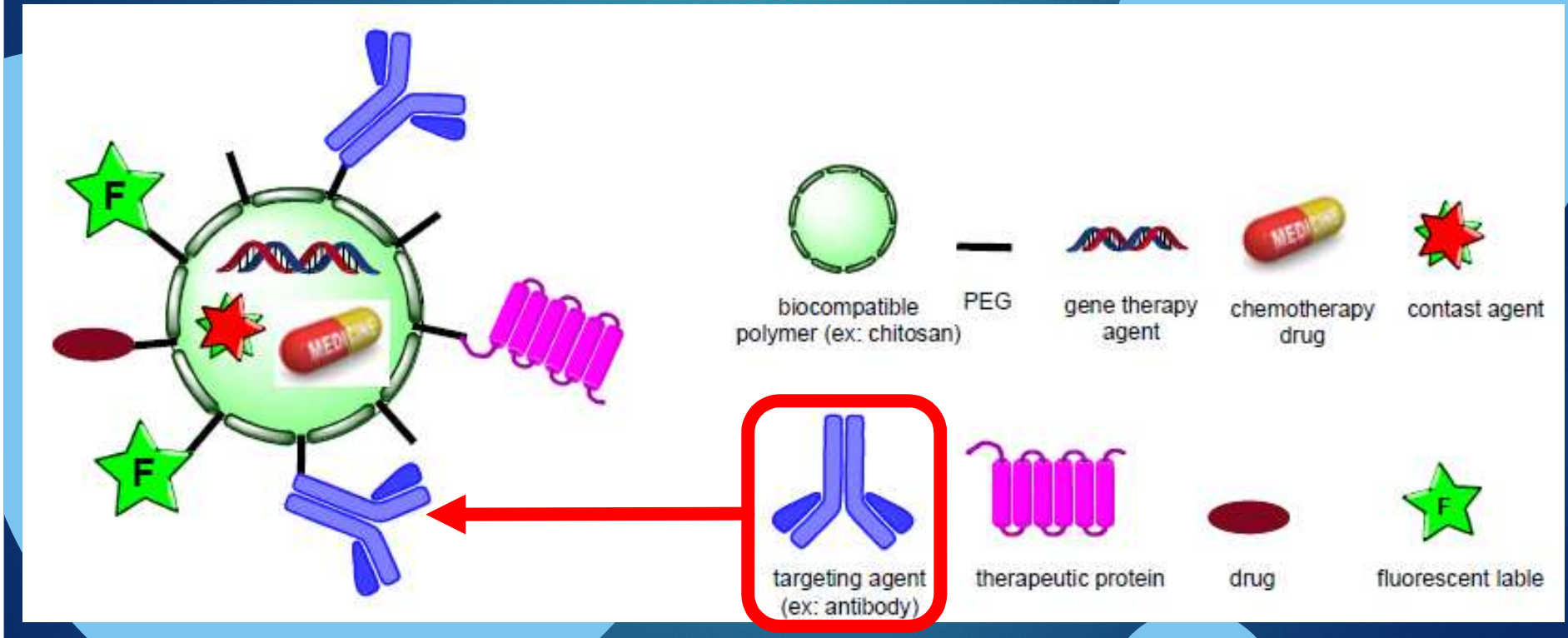


(Chu, Allergy Asthma & Clinical Immunology 2015; 11:14)

The future of research and development in biologicals is promising with the application of new knowledge and development in bioengineering and immunology, so that the designs of these therapeutics can be optimized and improved for clinical efficacy and cost-effective production.

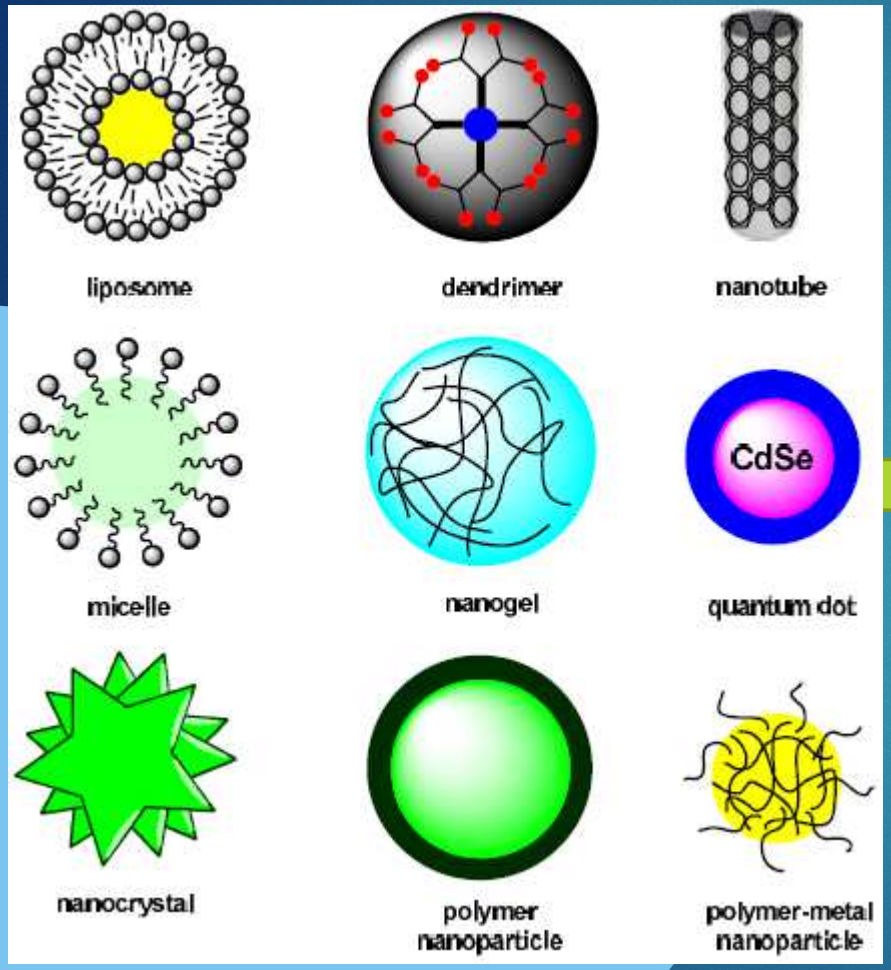
Alternative Approaches for the Treatment of Airway Diseases: Focus on Nanoparticle Medicine

The **surface** of nanoparticles can be functionalized with different agents to achieve targeted delivery, improved biocompatibility and high-resolution imaging. The **interior** of the nanoparticles can also be used to encapsulate various bioactive compounds, such as nucleic acids, drugs and imaging contrast agents.



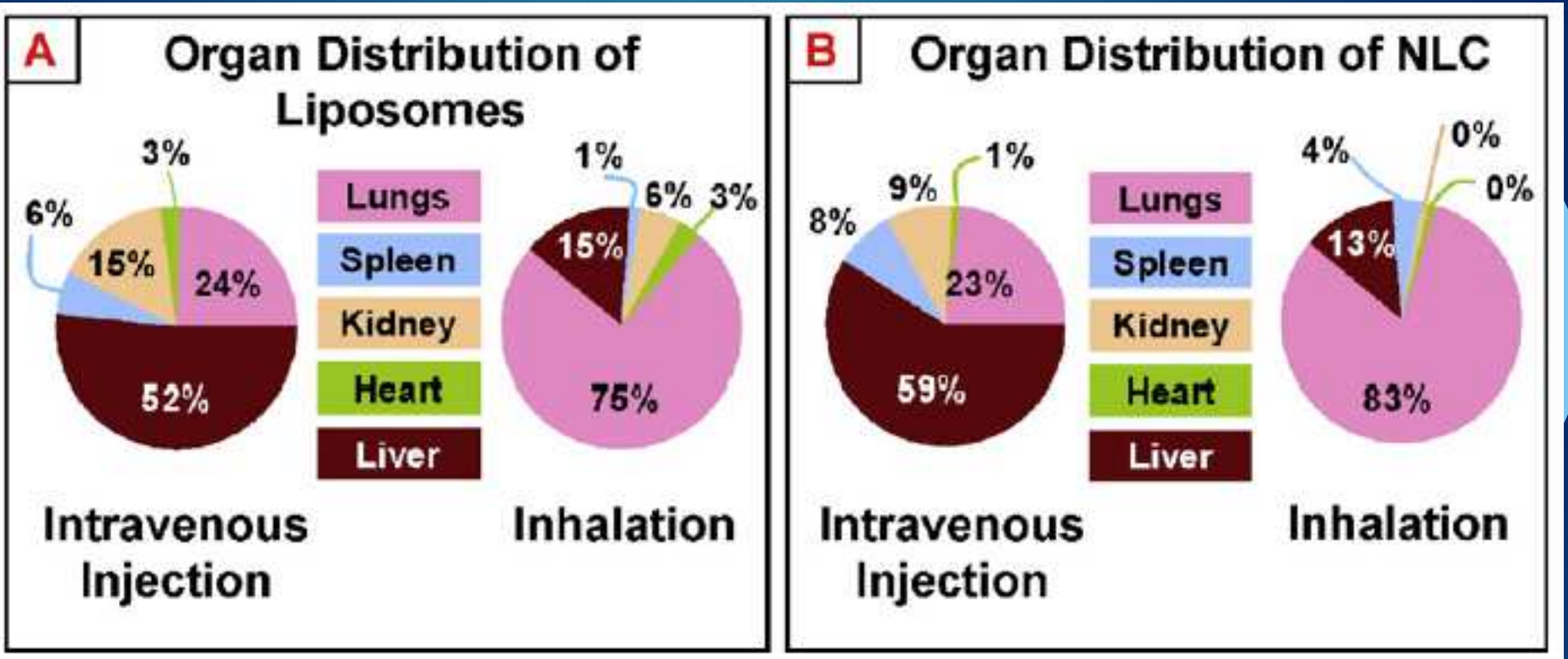
(Ratemi E., et al., Clinical Experimental Allergy 2016)

Advantages of using nanoparticles



(Ratemi E., et al., Clinical Experimental Allergy 2016)

Nanotechnology approaches for inhalation treatment of lung diseases



Advantages of inhalation drug delivery: improved organ distribution. Organ distribution of liposomes (A) and nanostructured lipid carriers (NLC, B) after intravenous and inhalation delivery.

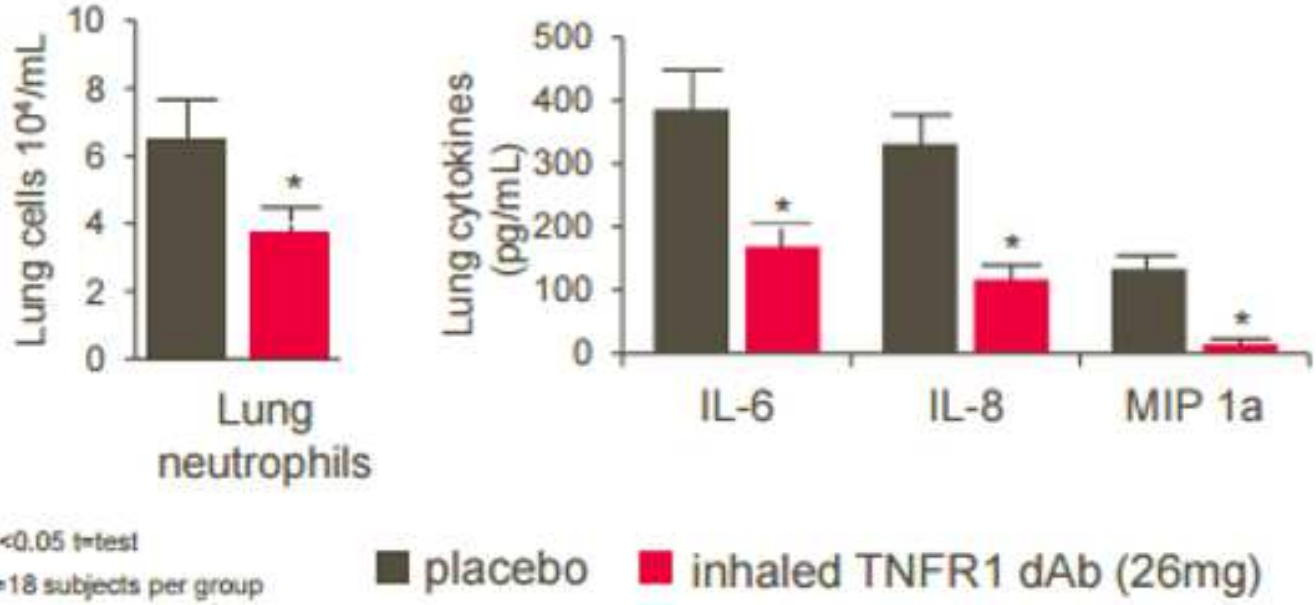
Kuzmov A & Minko T., Journal of Controlled Release 219 (2015) 500–518

New MABS on the block for asthma : TSLP dAb : Inhaled biologic

- Thymic Stromal Lymphopoietin (TSLP): key cytokine in epithelial immune response in asthma
- Inhaled domain antibody (dAb) directly targets site of action and reduces systemic exposure to improve risk:benefit profile
- Clinical proof of concept demonstrated for anti-TSLP approach
- Phase I start in 2016

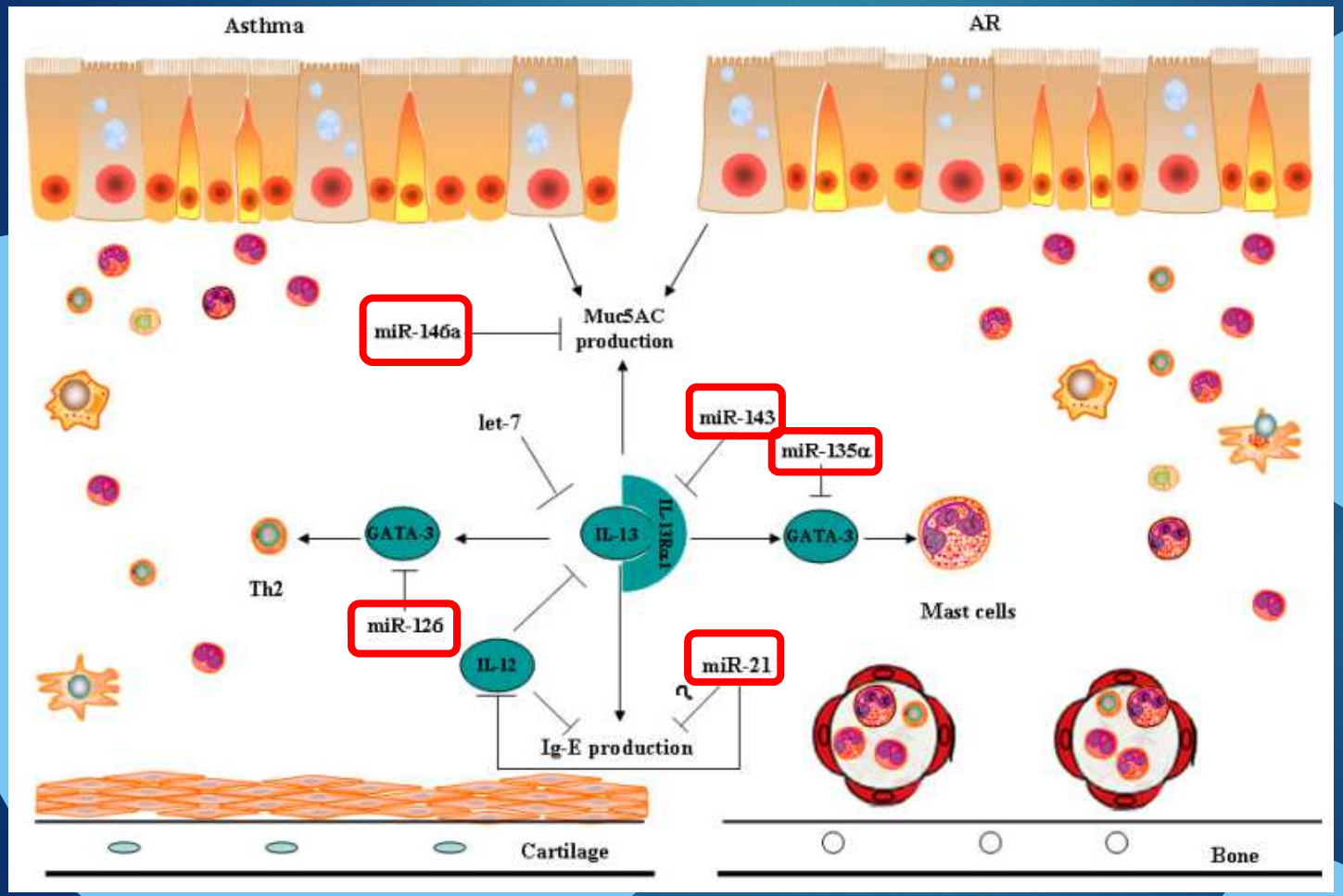
Target engagement after inhaled delivery of dAb: *exemplar*

Inhaled TNFR1 dAb reduced endotoxin (LPS) induced inflammation in healthy volunteers



(GSK data on file – study TFR116236)

Besides mAbs, other approaches that target RNAs are also advancing in this area .



Asthmatic patients demonstrated increased expression of several miRNAs (miR-143, miR-187, miR-498, miR-874 and miR-886-3p) and decreased expression of other miRNAs (let-7e, miR-18a, miR-126, miR-155 and miR-224)

(Liu et al., Int. J. Mol. Sci. 2016, 17, 716)

Besides mAbs, other approaches that target antisense molecules are also advancing in this area .

A review of antisense therapeutic interventions for molecular biological targets in asthma

Anti-mRNA approach in asthma can be achieved by using antisense oligonucleotides, ribozymes, and RNA interference.

Targeting mRNA rather than the protein itself is a more efficient approach to block a protein function, because multiple copies of a protein (approximately 5,000 copies) are produced by each mRNA molecule.

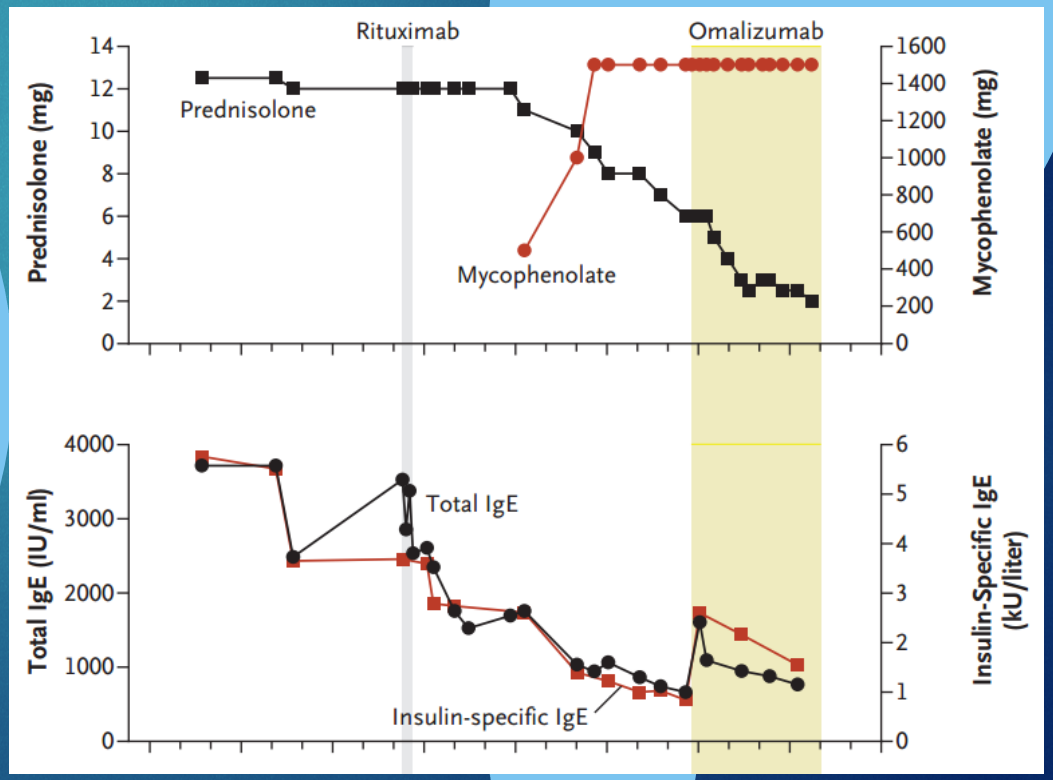
- Antisense oligonucleotides (ASO)
- Ribozymes (RZ)
- RNase P-associated external guide sequence (EGS)
- RNA interference (RNAi)
- RNAi triggered by siRNA
- Antagomirs

(Popescu FD et al., Biologics: Targets & Therapy 2007:1(3) 271–283)

The combined use of biologicals are being considered as viable therapeutic strategies, for example, treatment by combining mAbs to IgE and mAbs to B cell CD20 .

Yong PF et al., NEJM 2009; 360 (10): 1045-7

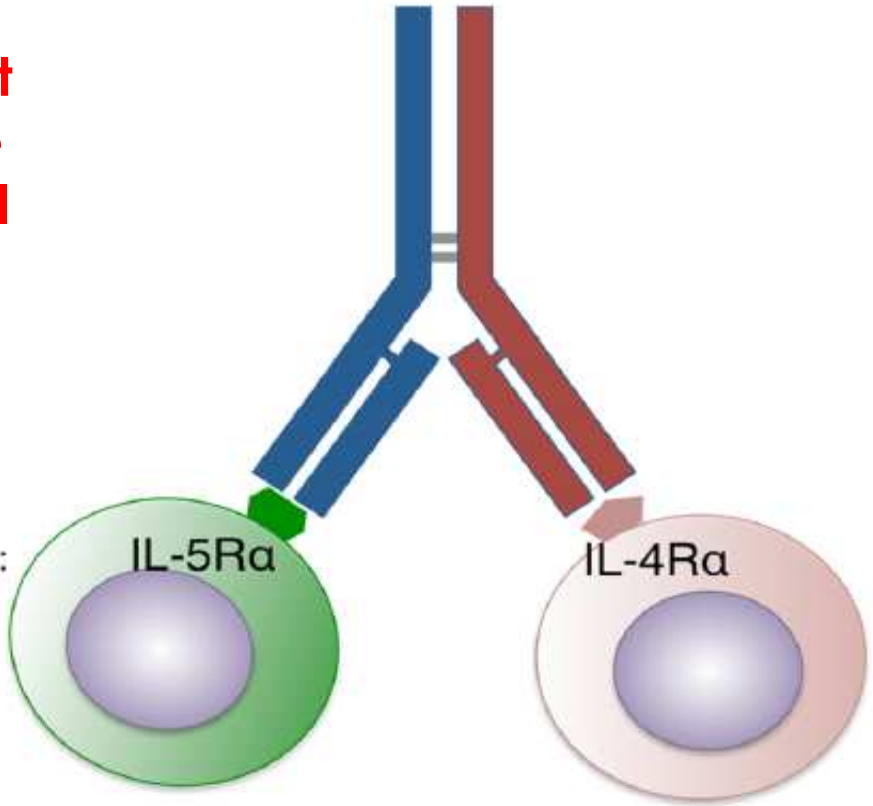
Rituximab and Omalizumab in Severe, Refractory Insulin Allergy



Creating bispecific antibodies that target more than one cell or receptor is an innovative approach for the future; for example, a bispecific antibody can be developed that has affinity for both IL-5 receptor and IL-4 receptor.

An example of a bispecific antibody that targets more than one cell or receptor.

Bispecific Antibody
IL-5Rα x IL-4Rα

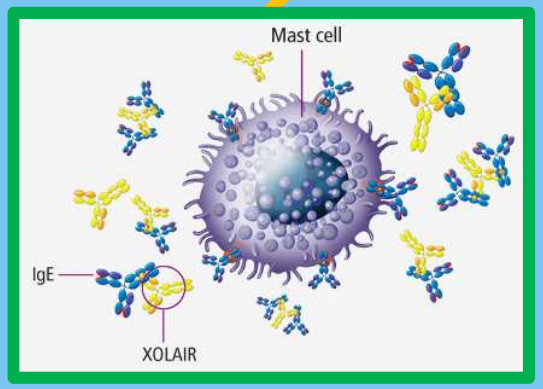


IL-5Rα is expressed on:
- eosinophils
- basophils
- B cells

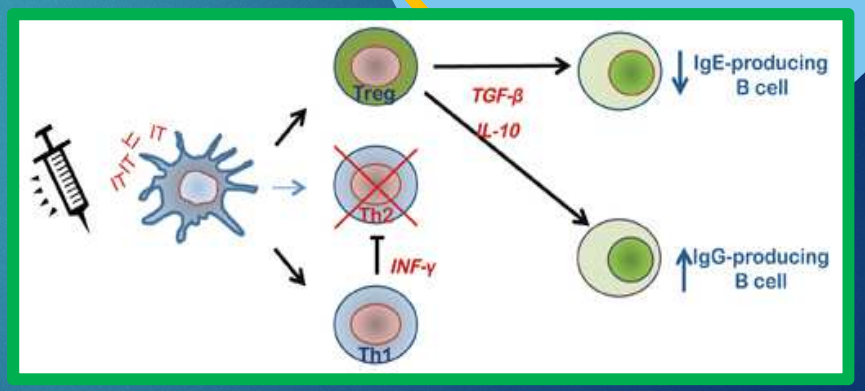
IL-4Rα is mainly expressed on:
- T cells
- B cells
- macrophages
- lung epithelial cells
- airway goblet cells
- smooth muscle cells

In addition, the combination of biological agents with allergen-specific immunotherapy may also enhance the efficiency of immunomodulation of allergic diseases.

omalizumab



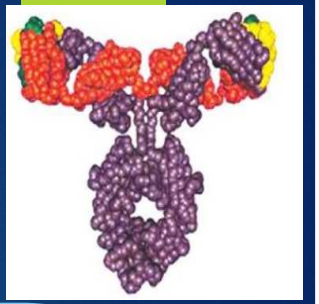
Allergen-specific immunotherapy



time

Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma

Marc Massanari, PharmD,[a] Harold Nelson, MD,[b] Thomas Casale, MD,[c] William Busse, MD,[d] Farid Kianifard, PhD,[a] Gregory P. Geba, MD, MPH,[a] and Robert K. Zeldin, MD[a] *East Hanover, NJ, Denver, Colo, Omaha, Neb, and Madison, Wis*



Objective: To evaluate omalizumab's effect on the tolerability of specific immunotherapy in patients with symptomatic persistent asthma not adequately controlled with inhaled corticosteroids.

multicenter, double-blind, parallel-group randomized study [248 pts]

3 perennial aeroallergens (cat, dog, and house dust mite)
4-week, 18-injection cluster regimen, followed by 7 weeks of maintenance therapy

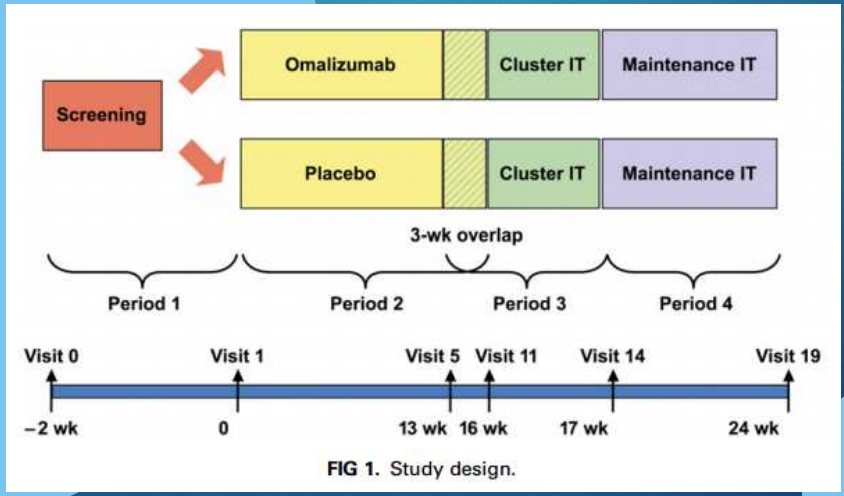
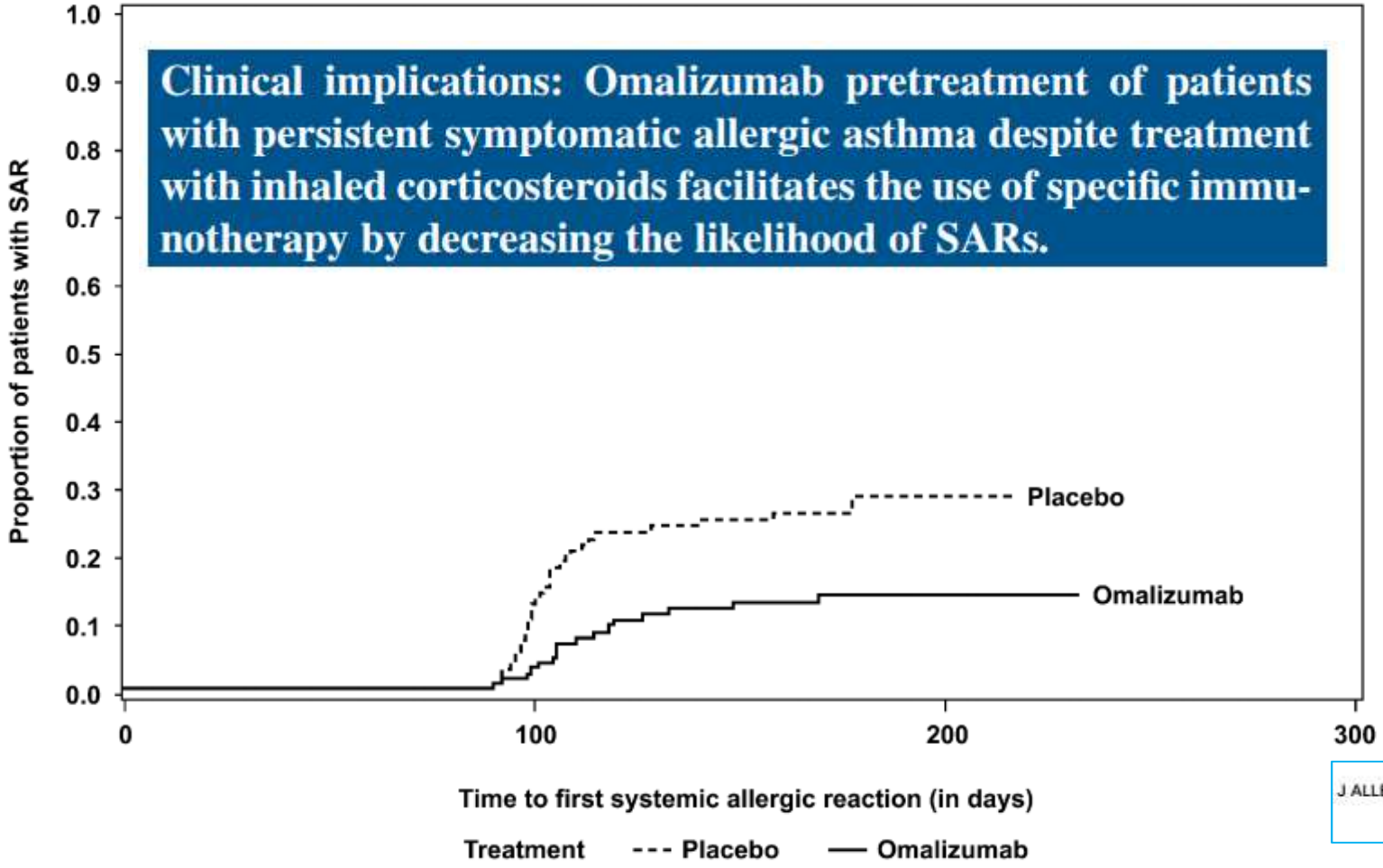


FIG 1. Study design.

J ALLERGY CLIN IMMUNOL
FEBRUARY 2010

Severity of first SAR*	Placebo n = 32	Omalizumab n = 17
Grade 1 (skin symptoms)	6	7
Grade 2 (gastrointestinal symptoms)	0	2
Grade 3 (respiratory symptoms)	24	6
Grade 4 (cardiovascular symptoms)	2	2

Clinical implications: Omalizumab pretreatment of patients with persistent symptomatic allergic asthma despite treatment with inhaled corticosteroids facilitates the use of specific immunotherapy by decreasing the likelihood of SARs.



J ALLERGY CLIN IMMUNOL
FEBRUARY 2010

Biologics for asthma treatment : UNMET NEEDS

- How long must continue the treatment
- Identification of «responders» / the best biomarker
- Impact on co-morbidities
- Long-term effects
- Long-term safety and tolerability aspects
- Impact on pharma-economic aspects
- Shift between a biological agent and the others

Grazie per l'attenzione!

carlo.lombardi@poliambulanza.it