MEDICINA DI PRECISIONE: ASMA E AGENTI BIOLOGICI

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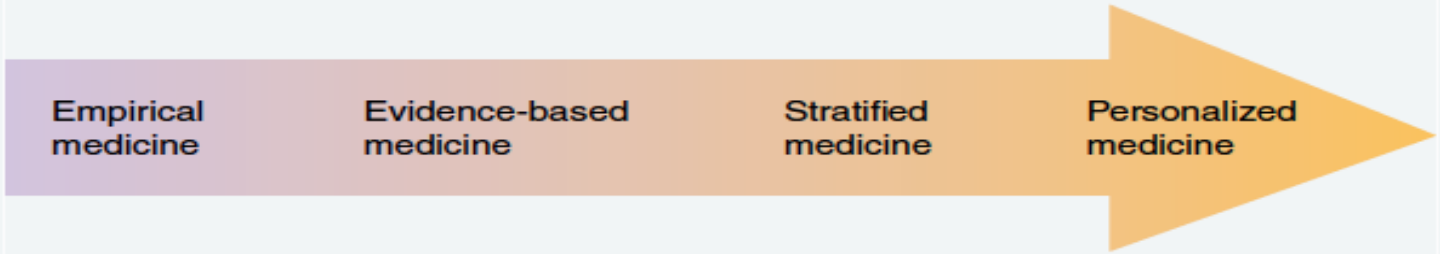
Stratified Medicine

A New Challenge for Academia, Industry, Regulators and Patients

Stratified medicine: a new era in the therapeutic approach

Figure 1.3. Spectrum of the current medicine.



Note that personalized medicine is the extreme, since it is based on the use of single and personal tissue probes for the design of an individual and tailored therapeutic approach.

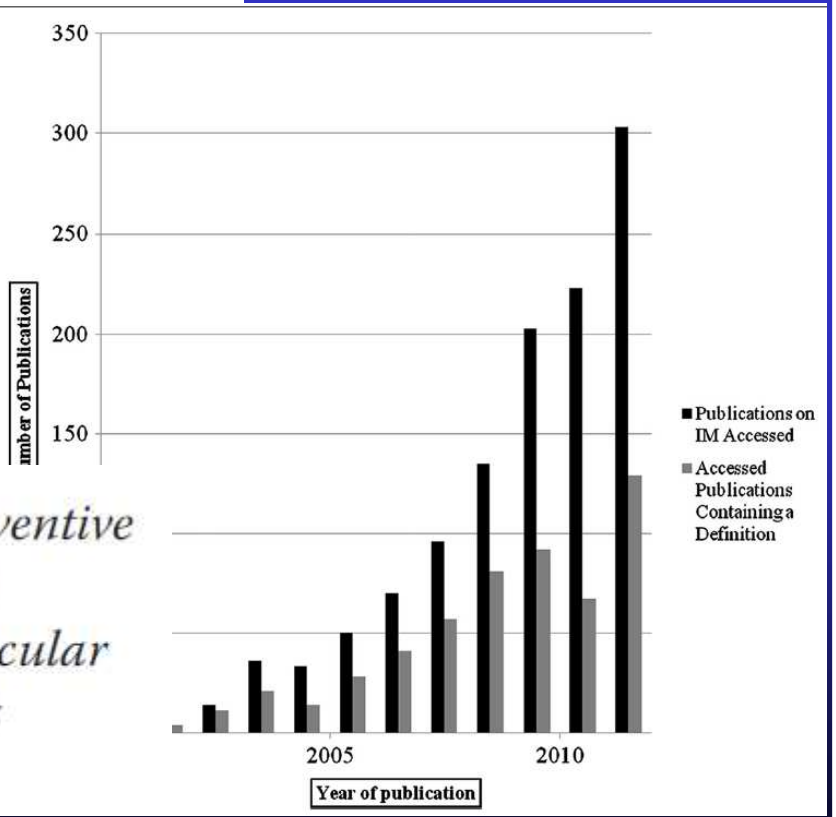
Bieber T. 2013

What is personalized medicine: sharpening a vague term based on a systematic literature review

Sebastian Schleidgen[1*], Corinna Klingler[1], Teresa Bertram[1], Wolf H Rogowski[2,3] and Georg Marckmann[1]

BMC Medical Ethics

"The purpose of personalized medicine is to identify the optimal treatment for each individual patient to maximize treatment benefit and minimize adverse effects. To achieve this goal, informative biomarkers need to be identified to stratify patients for specific therapies"



PM seeks to improve tailoring and timing of preventive and therapeutic measures by utilizing biological information and biomarkers on the level of molecular disease pathways, genetics, proteomics as well as metabolomics.

Il sottoscritto GIOVANNI PASSALACQUA

ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

Allergofarma
ALK-Abellò
Anallergo
AstraZeneca
Chiesi
GSK
HAL
Lofarma
Menarini
MSD
Novartis
Sanofi
Stallergenes-Greer
TEVA

- ..chronic inflammatory diseases of repiratory airways
- Inflammation of airways in which eosinophils, mast-cells
- and lymphocytes
- Recurrent episodes of wheezing, cough and dyspnoea
- Airways flow obstruction, that is diffused, variable
- and reversible, associated with bronchial
- hyperresponsiveness.

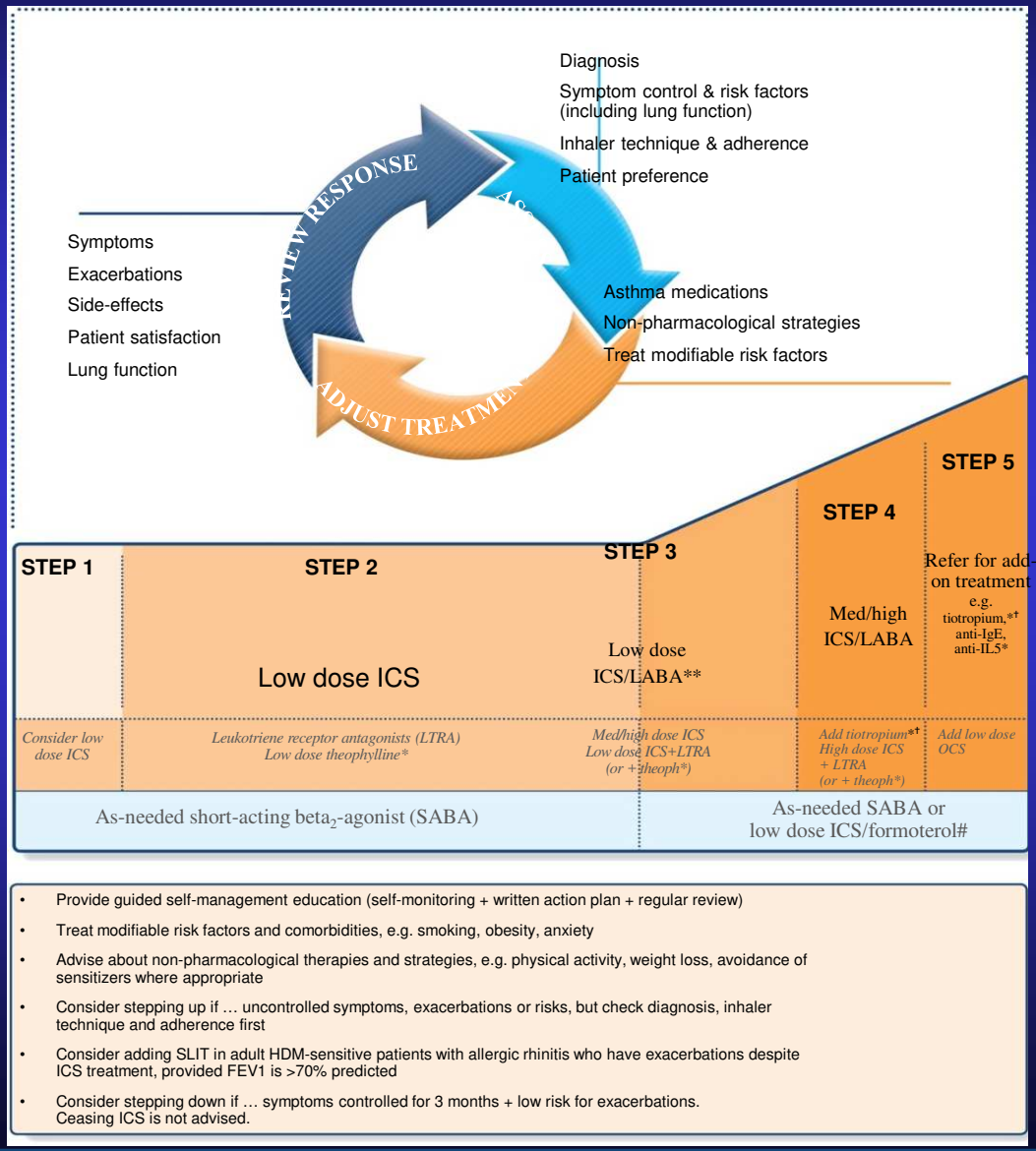
GINA 2006

KEY POINTS

- Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.
- Recognizable clusters of demographic, clinical and/or pathophysiological characteristics are often called 'asthma phenotypes'; however, these do not correlate strongly with specific pathological processes or treatment responses.
- The diagnosis of asthma should be based on the history of characteristic symptom patterns and evidence of variable airflow limitation. This should be documented from bronchodilator reversibility testing or other tests.
- Asthma is usually associated with airway hyperresponsiveness and airway inflammation, but these are not necessary or sufficient to make the diagnosis.

GINA 2017

Stepwise approach to control asthma symptoms and reduce risk



SLIT added as an option

MOLECOLA	NOME	DITTA	DEVICE	DOSE/INAL *	TIMING	INDICAZIONE **
LONG-ACTING BETA2 AGONISTS (LABA)						
Salmeterolo	Serevent Salmetedur	GSK Menarini	Diskus/MDI Diskus/MDI	50/25 50	Bid Bid	A/B A/B
Formoterolo	Foradil	Novartis	MDI/DPI	50	Bid	A/B
Indacaterolo	Hirobriz Onbrez	Novartis Novartis	Breezhaler capsule	150/300 150/300	Od Od	B B
Olodaterolo	Striverdi (1)	Boehringer I	Respimat	2.5	2/Od	B
LONG ACTING ANTIMUSCARINIC (LAMA)						
Tiotropio	Spiriva	Boehringer	DPI (capsule) handihaler Mist respihaler	18 9	Od Od	B B
ICS+LABA						
Fluticasone+salmeterolo	Seretide Aliflus	GSK Menarini	Diskus e MDI	100/50; 250/50; 500/50 50/25: 125/25 250/25	Bid	A/B
Fluticasone + vilanterolo	Relvar Revinty	GSK Menarini	DPI	92/22	Bid	A/B
Beclometasone+ formoterolo	Foster Formodual Inuver	Chiesi Chiesi Novartis	DPI, MDI DPI DPI	100/6	Bid	A
Budesonide + formoterolo	Symbicort Sinestic Assieme Duoresp	Astrazeneca Sigmatau Simesa Teva	Turbuhaler Turbuhaler Turbuhaler Respimax	160/4.5 320/9 160/4.5	Bid	A/B
Fluticasone + formoterolo	Abriff Flutiformo	 Mundifarma	DPI DPI	125/5; 250/10	Bid	A/B

*** mcg/dose; ** A= asma, B= BPCO; (1) necessario piano terapeutico**

ASTHMA?

CLINICAL PHENOTYPE
- Intermittent
- Persistent
- Brittle
- Steroid resistant
- Near fatal
- Late onset

AETIOLOGY
- Allergens
- Occupational
- Aspirin
- Exercise
- Infectious
- Vasculitis
- Aspergyllosis

BIOLOGIC PHENOTYPE
- Neutrophilic
- Eosinophilic/TH2
- Mixed
- Pauci-granulocytic

PATHOGENESIS

IgE-MEDIATED	NON IgE-MEDIATED
Inhalants	Occupational
Occupational	Viral
Aspergyllosis	Intrinsic
	Exercise

PRESENTATION

ISOLATED	EPIPHENOMENON
Inalants	Vasculitis
Occupational	Aspergyllosis
Exercise	
Aspirin	

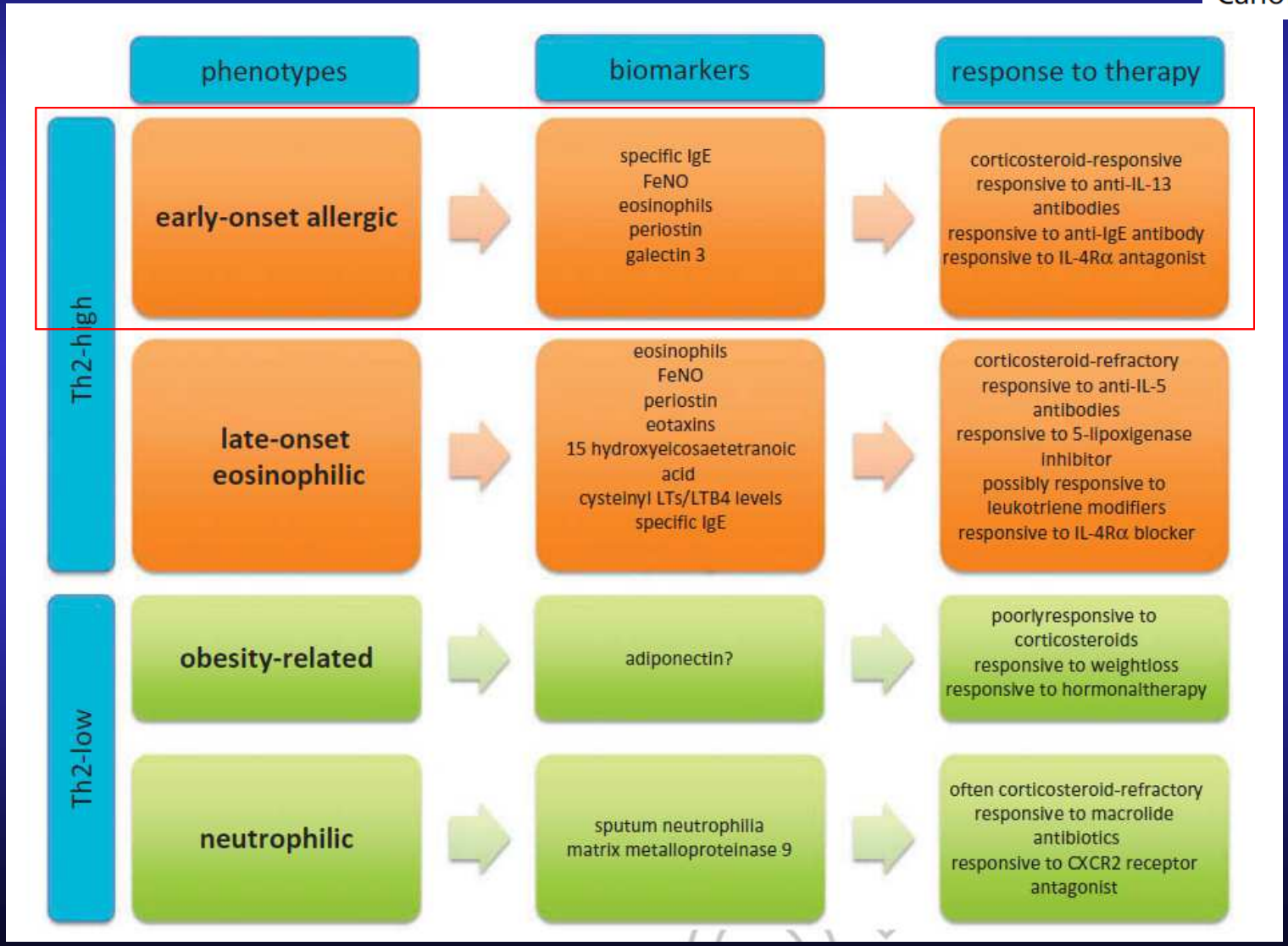
EXPERT REVIEWS

Molecular phenotyping and biomarker development: are we on our way towards targeted therapy for severe asthma?

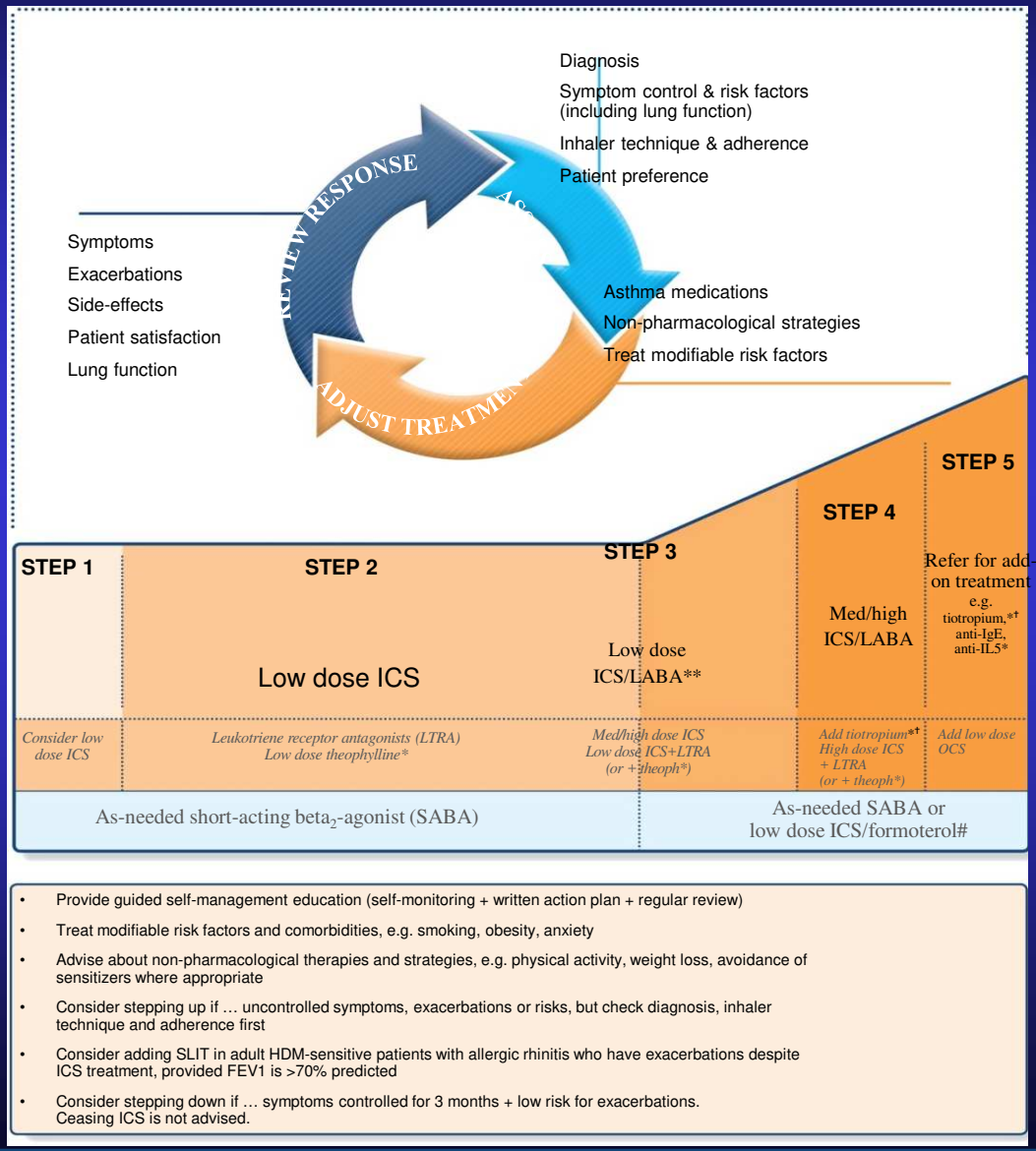
Expert Rev. Respir. Med. 00(00), 1-10 (2015)

Expert Rev Respir Med 2015

Laura De Ferrari‡, Alessandra Chiappori‡, Diego Bagnasco, Anna Maria Riccio, Giovanni Passalacqua and Giorgio Walter Canonica*



Stepwise approach to control asthma symptoms and reduce risk



SLIT added as an option

Perché la ricerca di nuove terapie?

Circa il 25% dei pazienti con asma, non sono controllati dalla terapia standard ottimale.

Effetti collaterali dei farmaci in uso

Facilità di uso/aderenza alla terapia

Nessuno dei farmaci è in grado di modificare il disordine immunologico alla base dell'asma.

Malattia unica o diversi fenotipi?

L'asma grave?

PROBLEMA: la definizione di asma grave

ENFUMOSA (**European Network For Understanding Mechanisms Of Severe Asthma**)

Almeno una riacutizzazione nell'ultimo anno nonostante dosi di steroide inalatorio >1200 mcg beclometasone (o equivalenti) e/o ricorso a steroide orale

TENOR (**The Epidemiology and Natural History, Outcome and Treatment Regimens**)

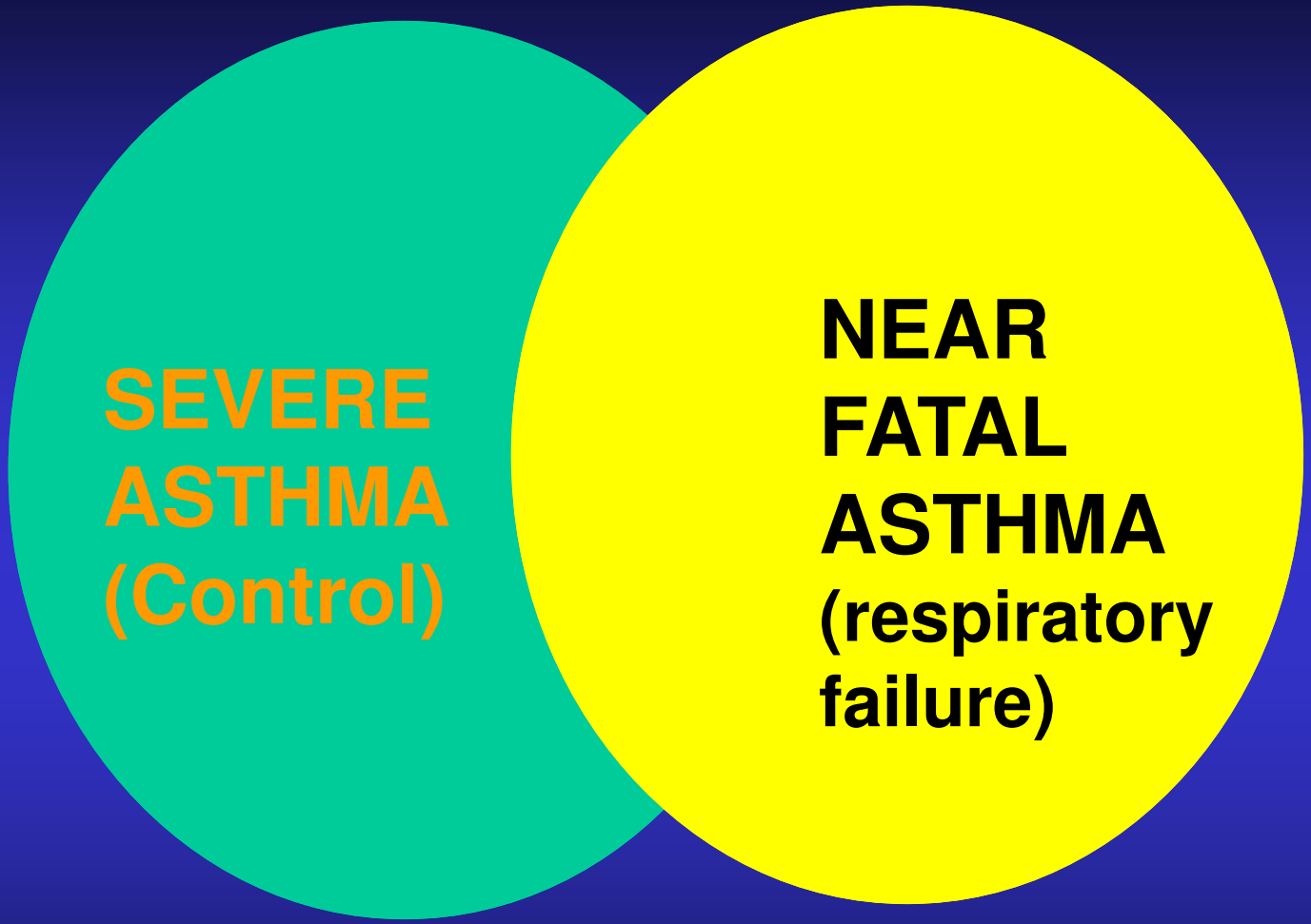
>1 esacerbazioni nell'ultimo anno o >1 terapie con steroide orale o >1 visite extra nonostante l'uso di almeno 3 farmaci per l'asma

American Thoracic Society

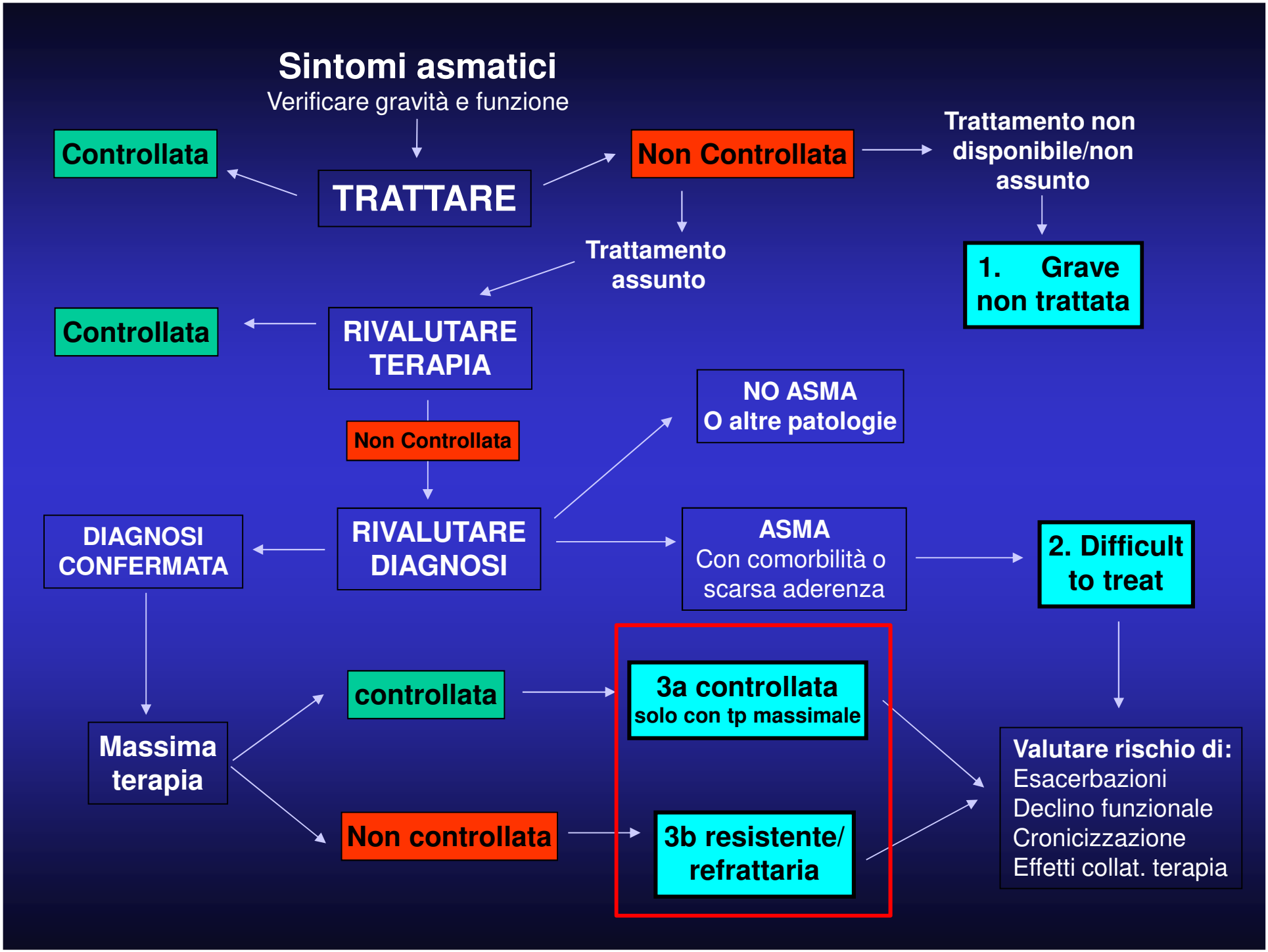
1 criterio maggiore tra: steroide orale per >50% dell'anno o uso di dose massimale di steroide inalatorio.

2 criteri minori tra: uso quotidiano di salbutamolo; 1 episodio di asma quasi fatale; VEMS<80%; almeno un altro farmaco oltre a steroide inalatorio; rapido peggioramento se riduzione del 25% dello steroide inalatorio

Severe asthma is different from near-fatal asthma



Near-fatal asthma (NFA) is described as acute asthma associated with a respiratory failure, or arrest, or arterial carbon dioxide tension greater than 50 mmHg, with or without altered consciousness


Sintomi asmatici
Verificare gravità e funzione
TRATTARE
Controllata
Non Controllata
Trattamento non disponibile/non assunto
1. Grave non trattata
Trattamento assunto
RIVALUTARE TERAPIA
Controllata
Non Controllata
NO ASMA O altre patologie
RIVALUTARE DIAGNOSI
DIAGNOSI CONFERMATA
ASMA
Con comorbilità o scarsa aderenza
2. Difficult to treat
Massima terapia
controllata
3a controllata
solo con tp massimale
Non controllata
3b resistente/ refrattaria
Valutare rischio di:
Esacerbazioni
Declino funzionale
Cronicizzazione
Effetti collat. terapia

EXPERT REVIEWS

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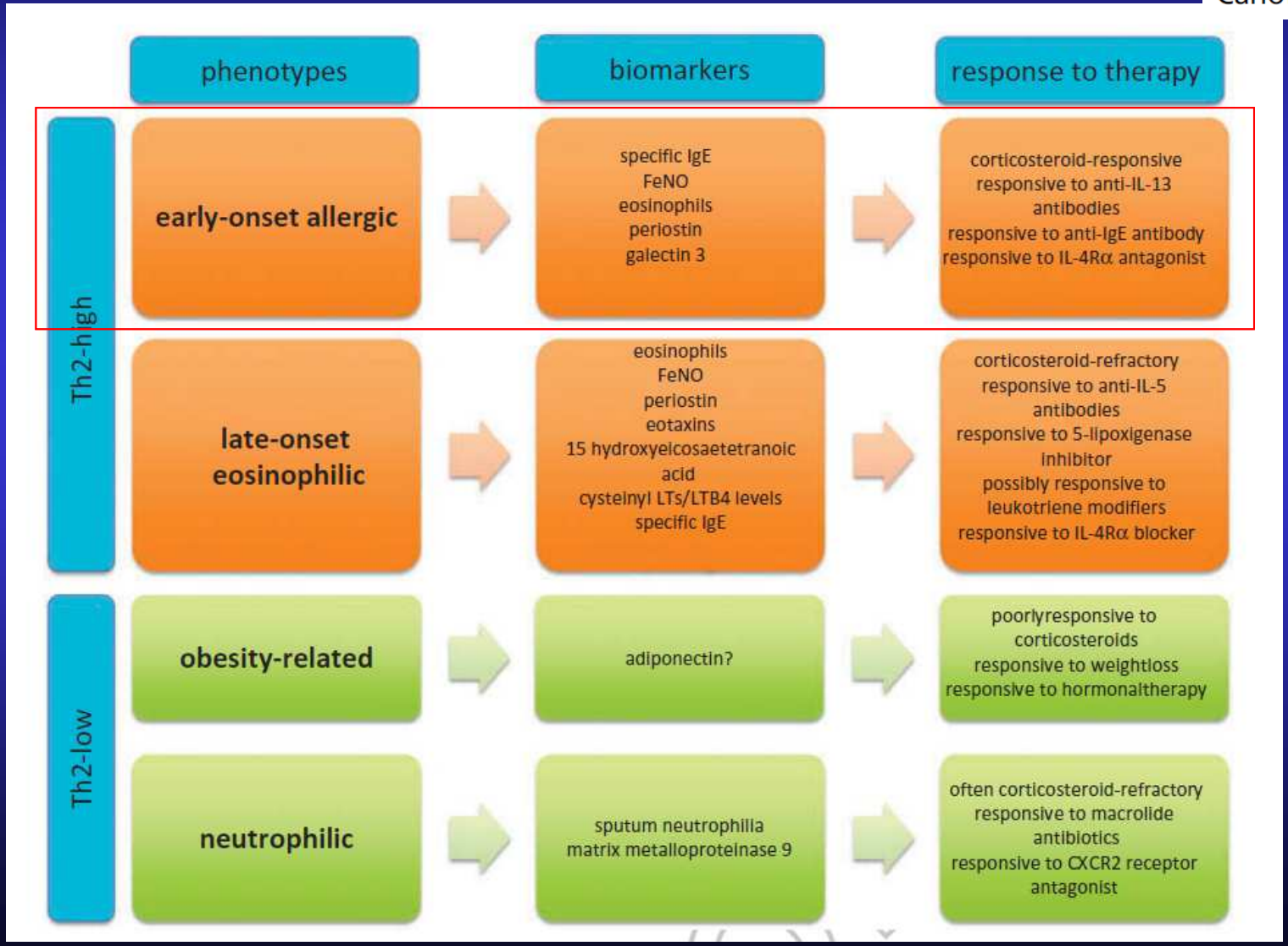
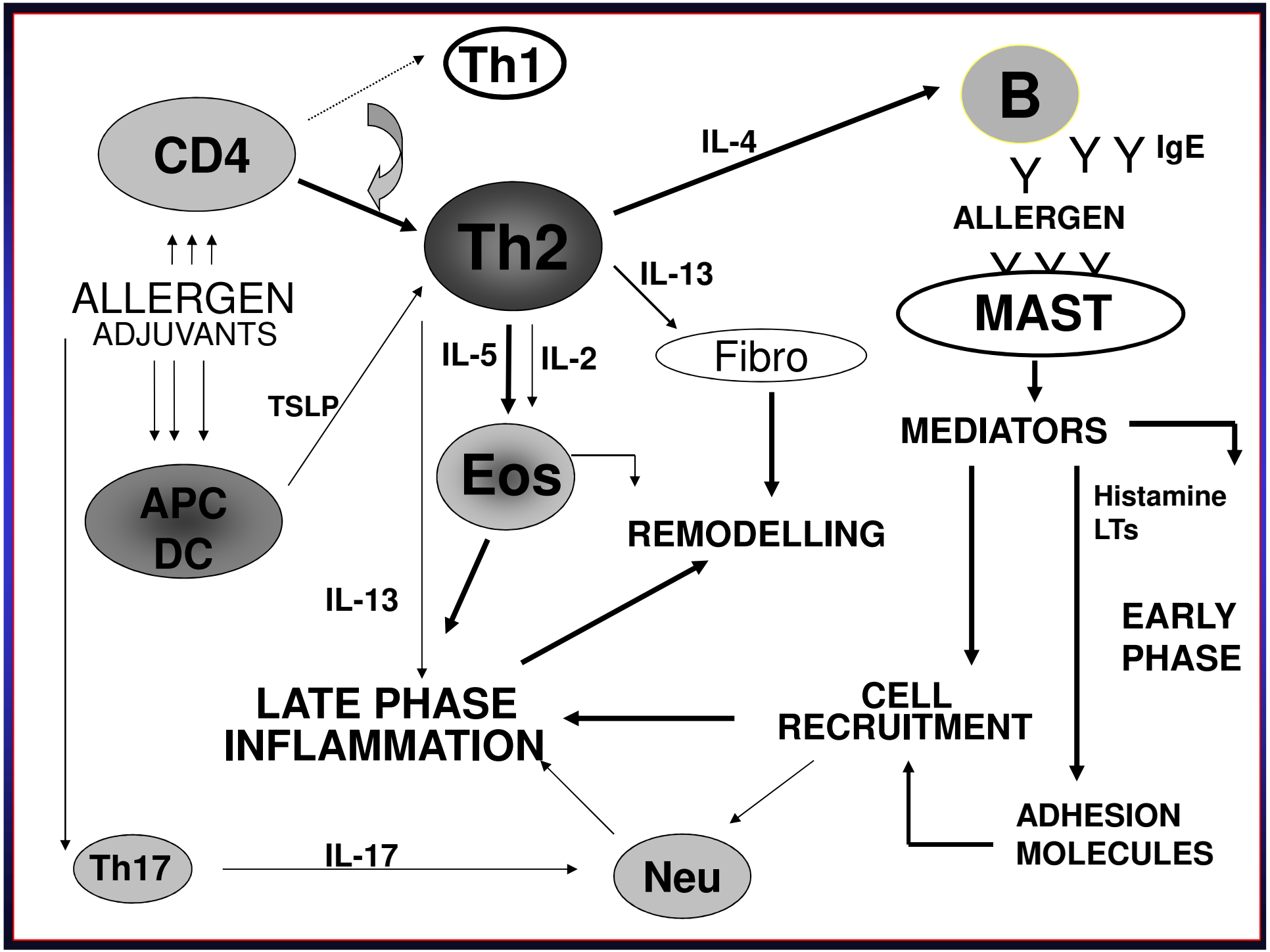
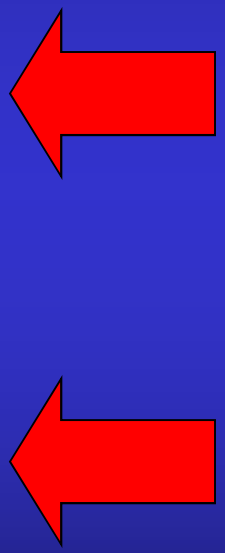



Th1
CD4
B
IL-4
IgE
ALLERGEN
Th2
IL-13
ALLERGEN
ADJUVANTS
MAST
IL-5
IL-2
Fibro
TSLP
MEDIATORS
Eos
APC
DC
REMODELLING
Histamine
LTs
IL-13
EARLY
PHASE
LATE PHASE
INFLAMMATION
CELL
RECRUITMENT
ADHESION
MOLECULES
Th17
IL-17
Neu

EVOLUTION OF TREATMENTS

Development of knowledge:

Receptors
Mediators
Interleukins
Adhesion mol.
Kinins
Neuropeptides
Endothelins



Development of approaches

Mediator antagonists

Monoclonal Antibodies

SOME EXAMPLES

BIOLOGICAL

Anti IgE
(omalizumab)

Anti TNF
(infliximab)

Recombinant
Insulin

NON-BIOLOGICAL

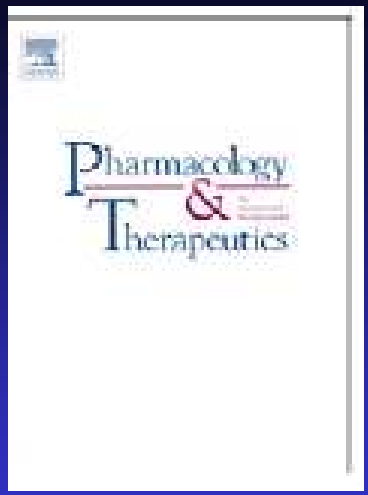
Antihistamines

Beta-blockers

Antimuscarinic

Thyroid hormone

Monoclonal antibody	MOA	IgG format affinity for target (K_d)	Effect on eosinophils	Clinical effects
Omalizumab (Xolair®)	Anti-IgE	Humanized IgG_1 $K_d = 2.7$ nM (Meno-Tetang & Lowe, 2005; Arm et al., 2014) $K_d = 7.7$ nM (Arm et al., 2014)	Sputum: • Reduction post allergen challenge but not statistically significant compared with placebo (Fahy et al., 1997) • Reduction in patients with mild to moderate allergic asthma (Djukanović et al., 2004) • Nonsignificant reduction compared with placebo in patients with severe allergic asthma (Takaku et al., 2013) Lung tissue: • Statistically significant reduction in lung tissue eosinophils in patients with mild to moderate asthma (Djukanović et al., 2004) and in patients with severe allergic asthma (Riccio et al., 2012) Blood: • Reduction in blood eosinophils post allergen challenge (Fahy et al., 1997) and in patients with moderate to severe allergic asthma (Massanari et al., 2010)	Statistically significant reduction in the number of asthma exacerbations, improvements in lung function and symptoms for patients with moderate to severe allergic asthma (Busse et al., 2001; Solèr et al., 2001)
Mepolizumab (Nucala®)	Anti-IL-5	Humanized IgG_1 $K_d = 100$ pM (Nucala package insert)	Sputum: • Reduction post allergen challenge in patients with mild asthma (Leckie et al., 2000) • Reduction in patients with severe asthma with eosinophilic inflammation (Haldar et al., 2009; Nair et al., 2009; Pavord et al., 2012) BAL: • Reduction (Flood-Page et al., 2003b) Lung tissue: • Reduction in tissue eosinophils in patients with mild asthma (Flood-Page et al., 2003b) and patients with severe asthma with an eosinophilic inflammation (Haldar et al., 2009) Blood: • Reduction in patients with mild allergic asthma (Leckie et al., 2000; Flood-Page et al., 2003b) and in patients with severe asthma with eosinophilic inflammation (Haldar et al., 2009; Nair et al., 2009; Pavord et al., 2012; Ortega et al., 2014) Bone marrow: • Reduction (Flood-Page et al., 2003b)	Statistically significant reduction in exacerbations, improvement in FEV_1, ACQ-5, and SGRQ for patients with severe, uncontrolled asthma with eosinophilic inflammation (Ortega et al., 2014)
Reslizumab (Cinqair®)	Anti-IL-5	Humanized IgG_4 $K_d = 20$ pM (Egan et al., 1999; Wechsler et al., 2012) $K_d = 81$ pM (Walsh, 2013)	Sputum: • Reduction in patients with moderate to severe asthma (Castro et al., 2011) Blood: • Reduction in blood eosinophils (Kips et al., 2003; Castro et al., 2015)	Statistically significant reductions in exacerbations and improvements in lung function, ACQ and AQLQ for patients with severe asthma with eosinophilic inflammation by blood eosinophils ≥ 400/μL (Castro et al., 2015)
Benralizumab	Anti-IL-5Rα with ADCC	Humanized IgG_1 $K_d = 11$ pM (Kolbeck et al., 2010)	Sputum: • Reduction in patients with mild to moderate asthma (Laviolette et al., 2013) Lung tissue: • Reduction in patients with mild to moderate asthma (Laviolette et al., 2013) Blood: • Reduction in patients with mild (Busse et al., 2010), mild to moderate (Laviolette et al., 2013) and moderate to severe asthma (Castro et al., 2014) Bone marrow: • Reduction in patients with mild to moderate asthma (Laviolette et al., 2013)	Statistically significant reductions in exacerbations and improvements in lung function, asthma symptoms, ACQ-6 and AQLQ in patients with moderate to severe, uncontrolled asthma with eosinophilic inflammation by blood eosinophils ≥ 300/μL (Castro et al., 2014; Bleecker et al., 2016; FitzGerald et al., 2016)
Lebrikizumab	Anti-IL-13	Humanized IgG_4 $K_d < 10$ pM (Ultsch et al., 2013)	Blood: • Increase in patients with moderate to severe uncontrolled asthma (Corren et al., 2011; Hanania et al., 2015)	Statistically significant reduction in exacerbations and improvement in lung function for patients with moderate to severe asthma and greater concentrations of serum periostin. High blood eosinophils at baseline (≥240/μL) were also predictive of efficacy (Hanania et al., 2015)
Tralokinumab	Anti-IL-13	Fully human IgG_4	Sputum:	Statistically significant reduction in exacerbations and



Monoclonal antibody therapy for the treatment of asthma and chronic obstructive pulmonary disease with eosinophilic inflammation

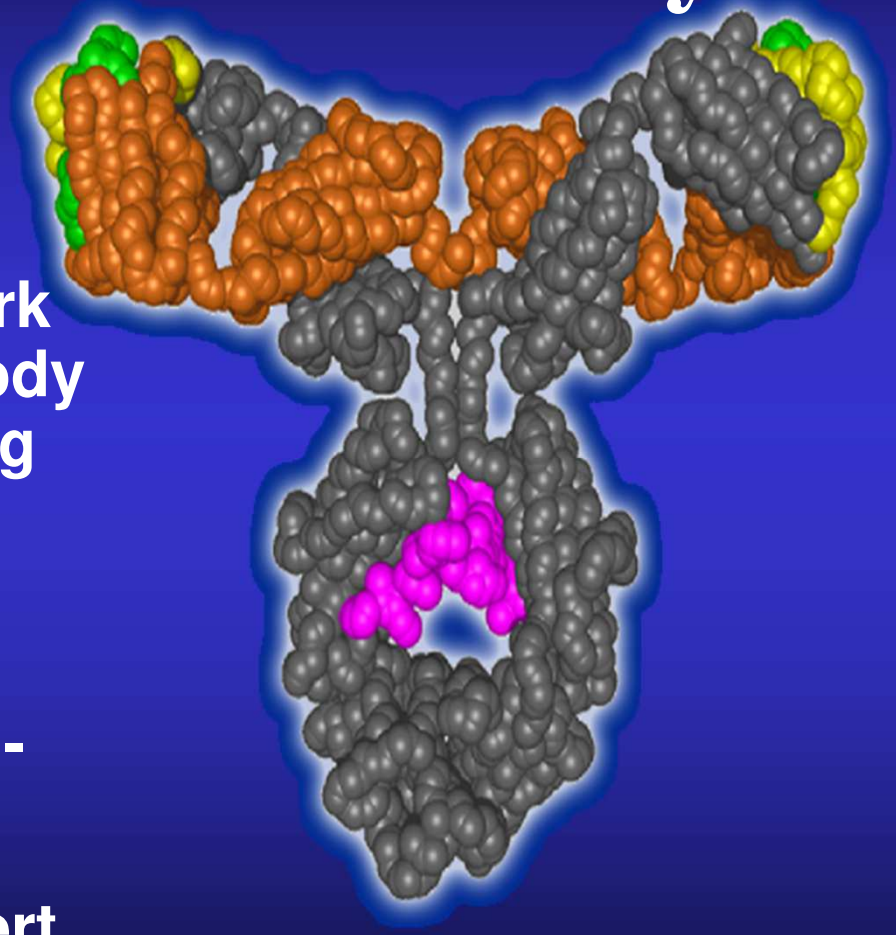
John Nixon [a], Paul Newbold [b], Tomas Mustelin [b], Gary P. Anderson [c], Roland Kolbeck [b,*]

Benralizumab	Anti-IL-5Rα with ADCC	Humanized IgG_1 K_d = 11 pM (Kolbeck et al., 2010)	Sputum: • Reduction in patients with mild to moderate asthma (Laviolette et al., 2013) Lung tissue: • Reduction in patients with mild to moderate asthma (Laviolette et al., 2013) Blood: • Reduction in patients with mild (Busse et al., 2010), mild to moderate (Laviolette et al., 2013) and moderate to severe asthma (Castro et al., 2014) Bone marrow: • Reduction in patients with mild to moderate asthma (Laviolette et al., 2013)	Statistically significant reductions in exacerbations and improvements in lung function, asthma symptoms, ACQ-6 and AQLQ in patients with moderate to severe, uncontrolled asthma with eosinophilic inflammation by blood eosinophils ≥ 300/μL (Castro et al., 2014; Bleecker et al., 2016; FitzGerald et al., 2016)
Lebrikizumab	Anti-IL-13	Humanized IgG_4 K_d < 10 pM (Ultsch et al., 2013)	Blood: • Increase in patients with moderate to severe uncontrolled asthma (Corren et al., 2011; Hanania et al., 2015)	Statistically significant reduction in exacerbations and improvement in lung function for patients with moderate to severe asthma and greater concentrations of serum periostin. High blood eosinophils at baseline (≥240/μL) were also predictive of efficacy (Hanania et al., 2015)
Tralokinumab	Anti-IL-13	Fully human IgG_4	Sputum:	Statistically significant reduction in exacerbations and

Table 1 (*continued*)

Monoclonal antibody	MOA	IgG format affinity for target (K_d)	Effect on eosinophils	Clinical effects
		K_d = 165 pM (May & Fung., 2015; May et al., 2012; Monk et al., 2005)	• No detectable effect in patients with moderate to severe asthma (Piper et al., 2013) Blood: • Increase in blood eosinophils in patients with moderate to severe asthma (Piper et al., 2013; Brightling et al., 2015a)	improvements in lung function, ACQ-6 and AQLQ for patients with severe asthma with high serum periostin or dipeptidyl peptidase 4 (Brightling et al., 2015)
Dupilumab	Anti-IL-4Rα	Fully human IgG_4 K_d = 68–94 pM (Martin et al., 2009)	Blood: • Overall increase in blood eosinophils in patients with moderate to severe asthma which did not reach statistical significance (Wenzel et al., 2013)	Reduction in exacerbations, improvement in lung function, ACQ-5 and asthma symptom score for patients with moderate to severe asthma with eosinophilic inflammation while tapering ICS therapy (Wenzel et al., 2013)
AMG157/MEDI-9929	Anti-TSLP	Fully human IgG_2 K_d = 15.8–29.2 pM (Gauvreau et al., 2014)	Sputum: • Reduction post allergen challenge in patients with mild asthma (Gauvreau et al., 2014) Blood: • Reduction pre and post allergen challenge in patients with mild asthma (Gauvreau et al., 2014)	Currently in Phase II evaluating the efficacy in patients with moderate to severe asthma
Bertilimumab	Anti-eotaxin-1 (CCL11)	Fully human IgG_4 K_d = 80 pM (Main et al., 2006)	No clinical data to date	No clinical data to date

Xolair® (omalizumab) anti-IgE monoclonal antibody



- IgG1 kappa human framework containing 5% murine antibody complementarity-determining regions (M_W ~150kD)
- Binds circulating free IgE
- Prevents IgE binding to high- and low-affinity receptors
- Forms small, biologically inert omalizumab:IgE complexes

Omalizumab for asthma in adults and children (Review)

Normansell R, Walker S, Milan SJ, Walters EH, Nair P

Cochrane 2014

) 2 Subcutaneous omalizumab + steroid versus placebo + steroid (steroid reduction) Outcome 1 Number of participants with exacerbation.

Review: Omalizumab for asthma in adults and children

Comparison: 2 Subcutaneous omalizumab + steroid versus placebo + steroid (steroid reduction)

Outcome: 1 Number of participants with exacerbation

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Moderate to severe asthma					
Busse 2001	57/268	83/257		30.9 %	0.57 [0.38, 0.84]
Milgrom 2001	41/216	42/101		21.5 %	0.33 [0.20, 0.55]
Sol r 2001	43/274	81/272		31.8 %	0.44 [0.29, 0.67]
Subtotal (95% CI)	**758**	**630**		**84.2 %**	**0.46 [0.36, 0.59]**
Total events: 141 (Treatment), 206 (Control)					
Heterogeneity: Chi^2 = 2.71, df = 2 (P = 0.26); I^2 =26%					
Test for overall effect: Z = 6.11 (P < 0.00001)					
2 Severe asthma					
Holgate 2004a	17/126	25/120		10.3 %	0.59 [0.30, 1.16]
Subtotal (95% CI)	**126**	**120**		**10.3 %**	**0.59 [0.30, 1.16]**
Total events: 17 (Treatment), 25 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.52 (P = 0.13)					
3 Severe (ICS and OCS users)					
Holgate 2004b	21/50	19/42		5.6 %	0.88 [0.38, 2.01]
Subtotal (95% CI)	**50**	**42**		**5.6 %**	**0.88 [0.38, 2.01]**
Total events: 21 (Treatment), 19 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.31 (P = 0.76)					
Total (95% CI)	**934**	**792**		**100.0 %**	**0.49 [0.39, 0.62]**
Total events: 179 (Treatment), 250 (Control)					
Heterogeneity: Chi^2 = 5.23, df = 4 (P = 0.26); I^2 =23%					
Test for overall effect: Z = 6.12 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 2.48, df = 2 (P = 0.29), I^2 =19%					

0.1 0.2 0.5 1 2 5 10

Favours Omalizumab Favours control

RIASSUNTO DELLE CARATTERISTICHE DEL PAZIENTE

Età maggiore di 6 anni

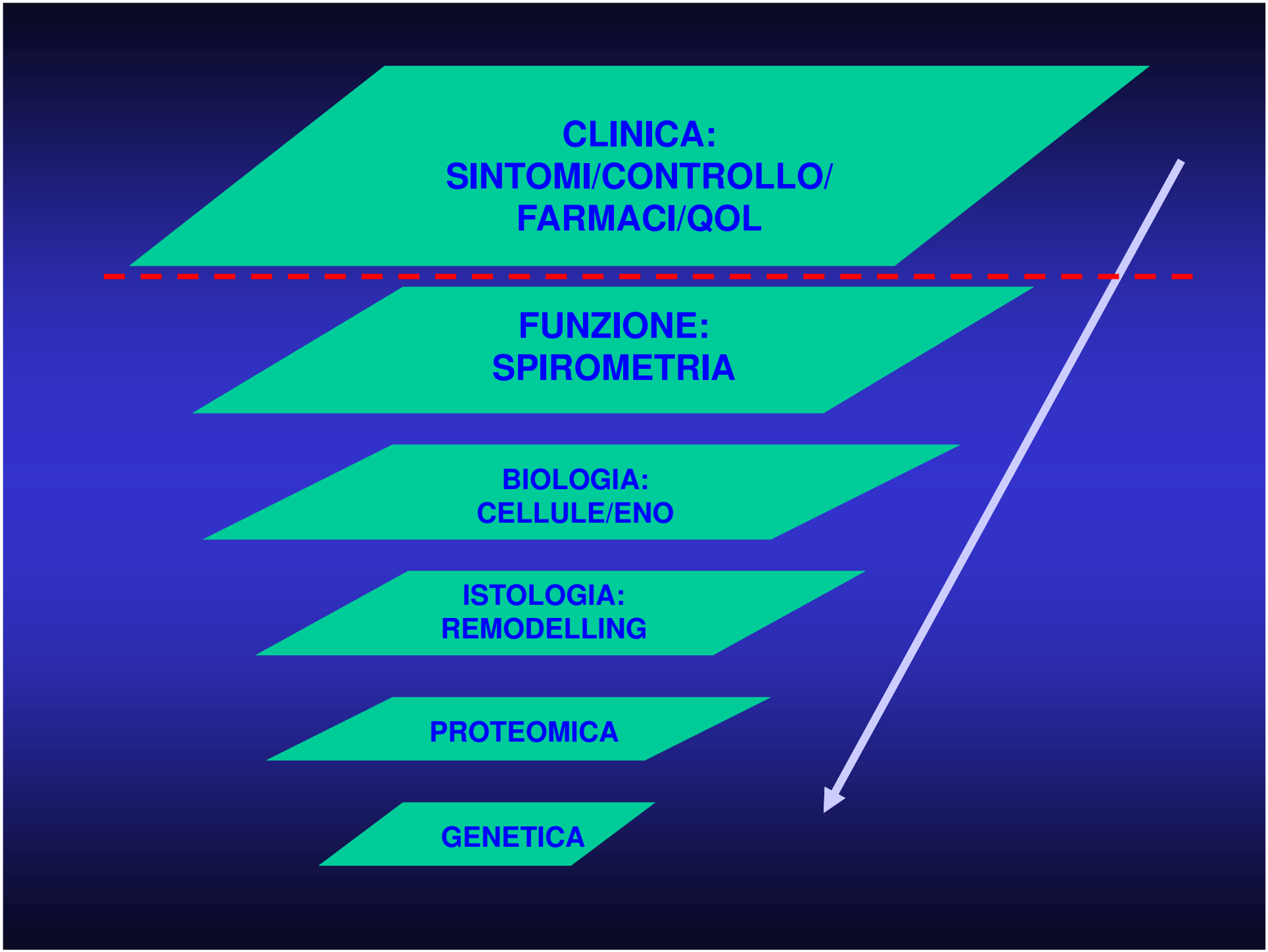
Asma allergica moderata-grave, non controllata dalla terapia

Utilizzo di ICS ad alte dosi (≥ 1000 mcg BDP o equivalente) e LABA

Esacerbazioni e/o ricoveri nell'ultimo anno

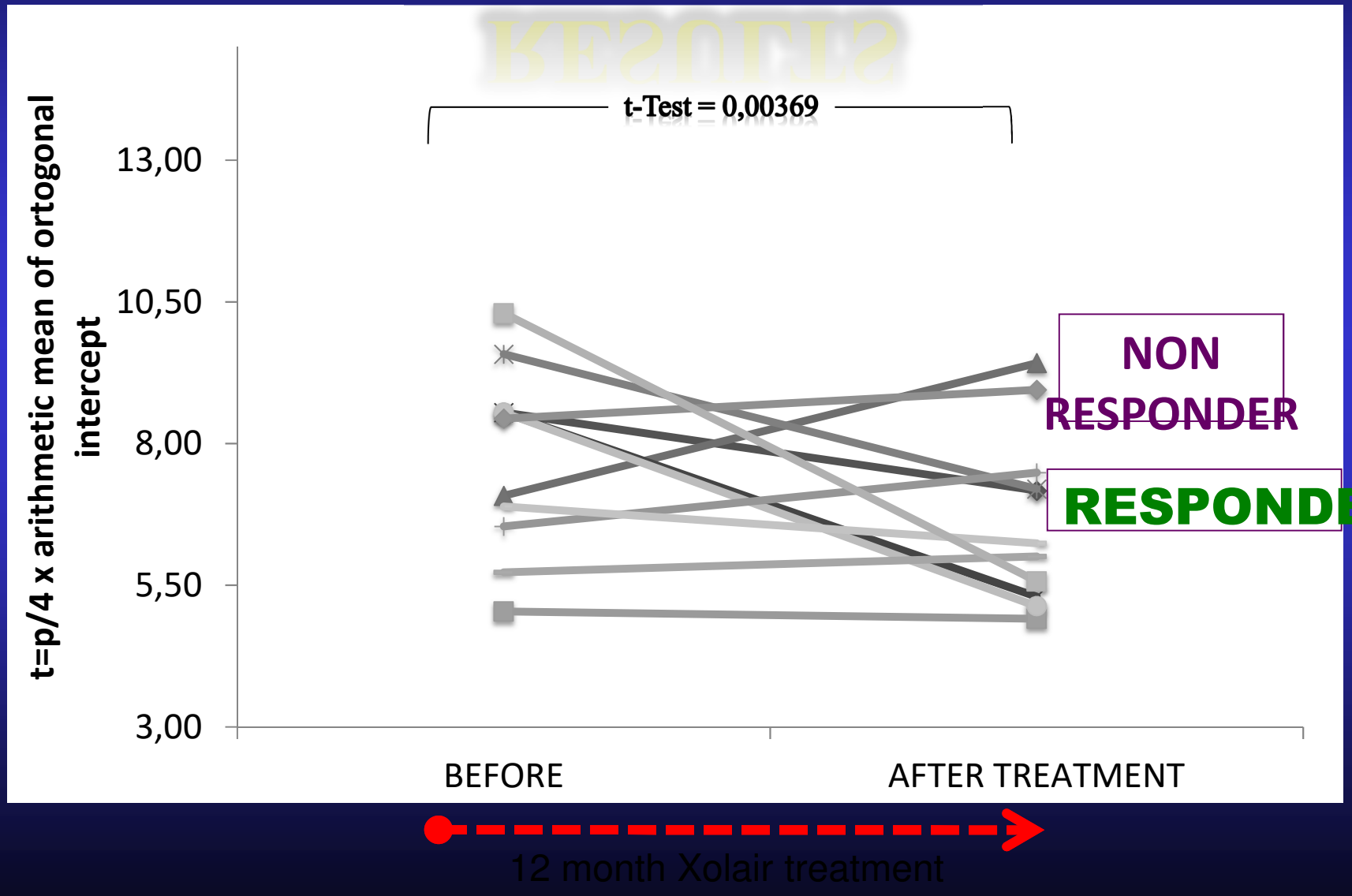
IgE totali (PRIST) comprese tra 30 e 1300 kU/L

Sensibilizzazione ad almeno un allergene perenne


CLINICA:
SINTOMI/CONTROLLO/
FARMACI/QOL
FUNZIONE:
SPIROMETRIA
BIOLOGIA:
CELLULE/ENO
ISTOLOGIA:
REMODELLING
PROTEOMICA
GENETICA

Riccio, Dal Negro et al.,Int.J.Immunopathol. & Pharmacol.2012

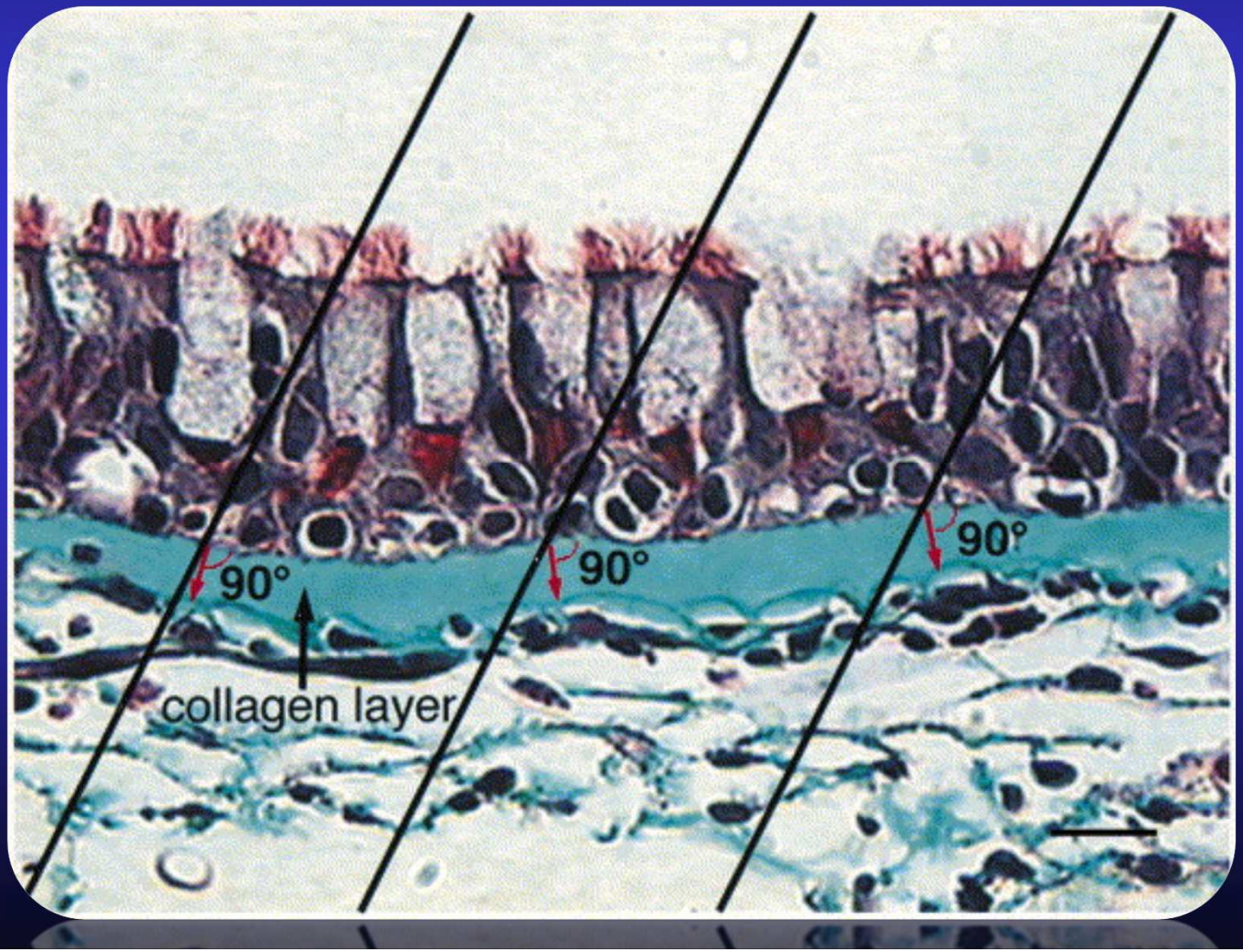
RESULTS



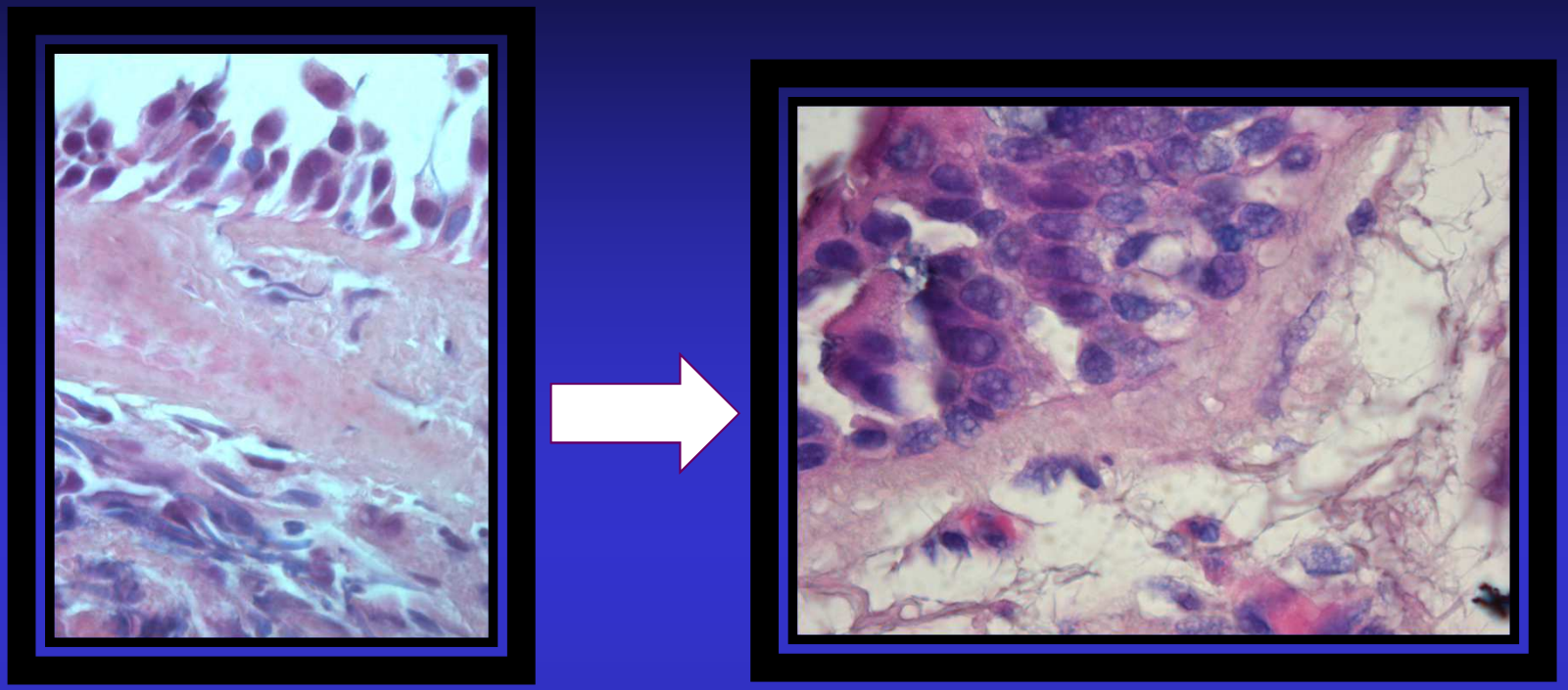
Riccio, Dal Negro et al.,Int.J.Immunopathol. & Pharmacol.2012

MORPHOMETRIC ANALYSIS

The orthogonal intercept method for measurement of BM zone thickness.



CASE 1

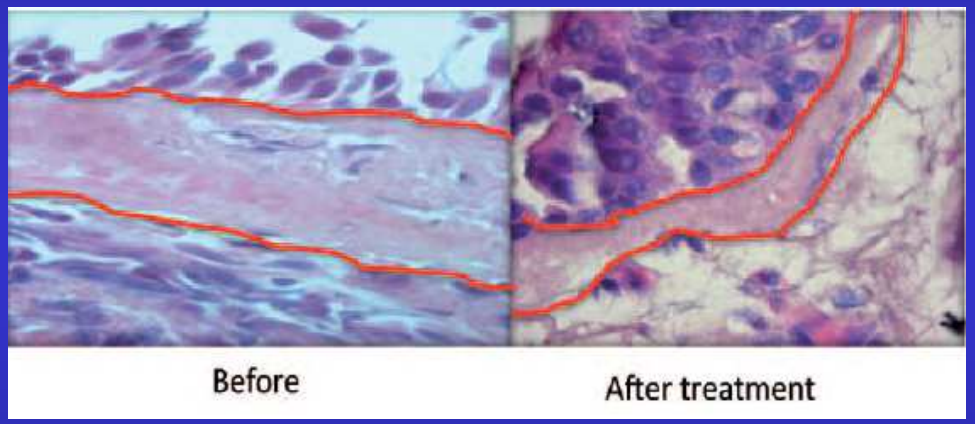


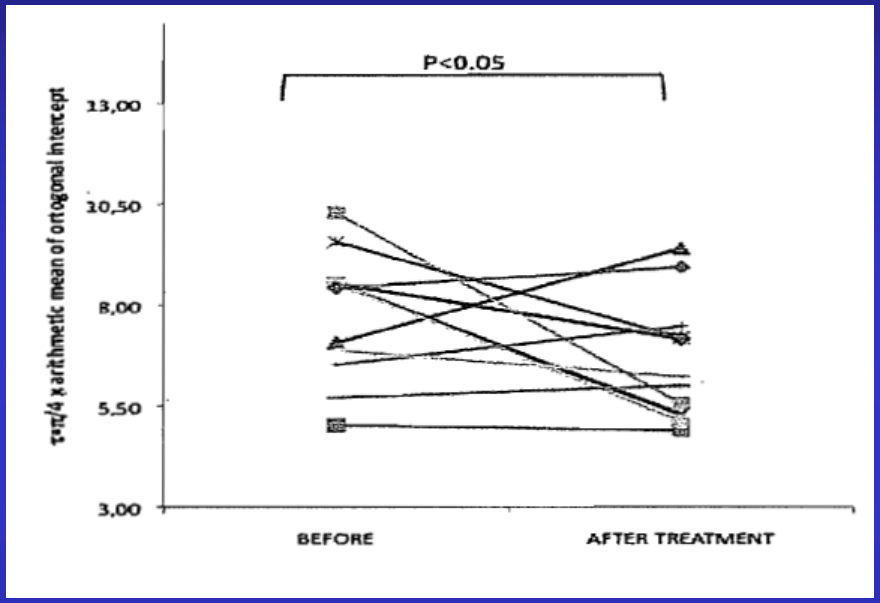
RBM thickness reduced after 12 month Xolair Therapy

Riccio, Dal Negro et al.,Int.J.Immunopathol. & Pharmacol.2012

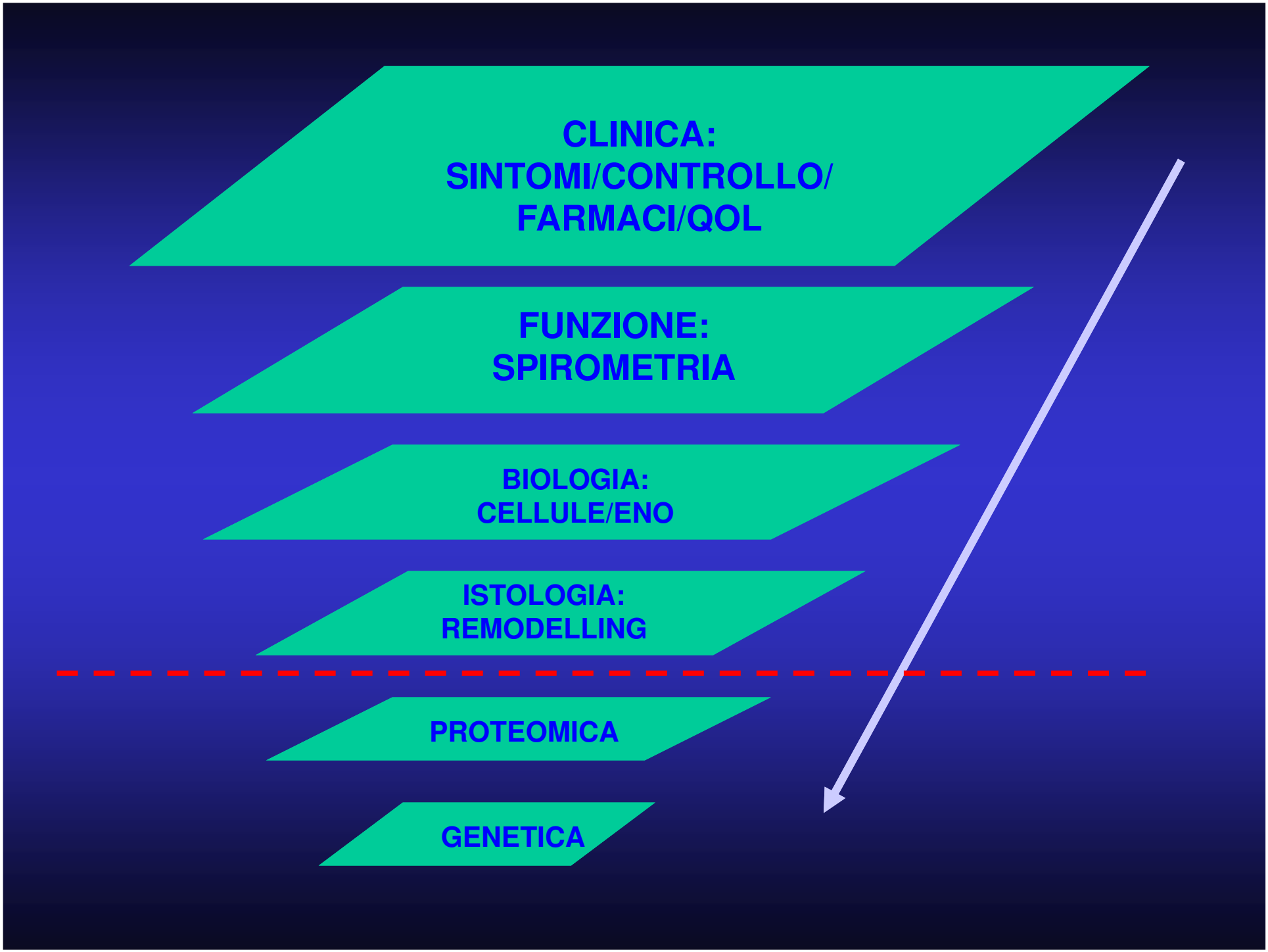
Evidence on Airway Remodeling

Effect on reticular basement membrane
Riccio et al Int J Imm Pharm 2012





Effect s on airway wall thickening
Hoshino M & Ohtawa J. Respiration 2012

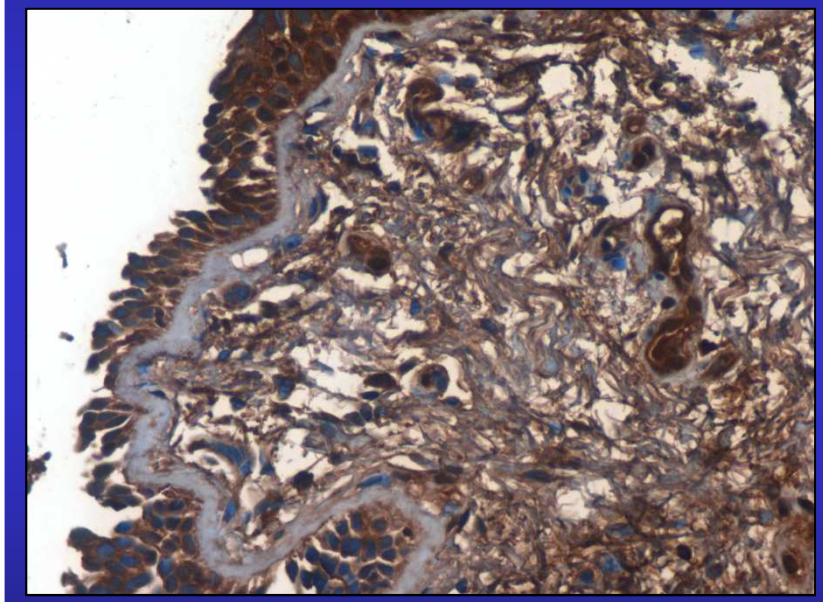

CLINICA:
SINTOMI/CONTROLLO/
FARMACI/QOL
FUNZIONE:
SPIROMETRIA
BIOLOGIA:
CELLULE/ENO
ISTOLOGIA:
REMODELLING
PROTEOMICA
GENETICA

Galactin 3

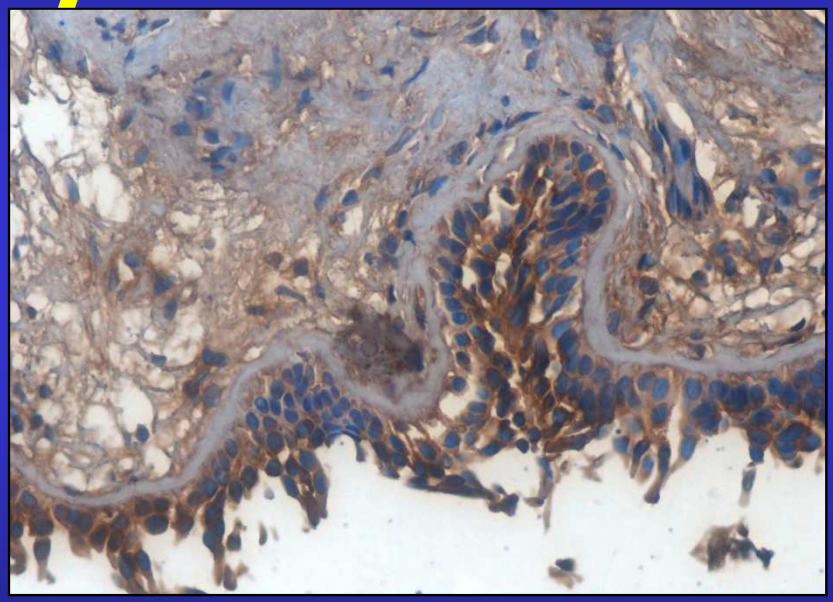
in biopsies

of

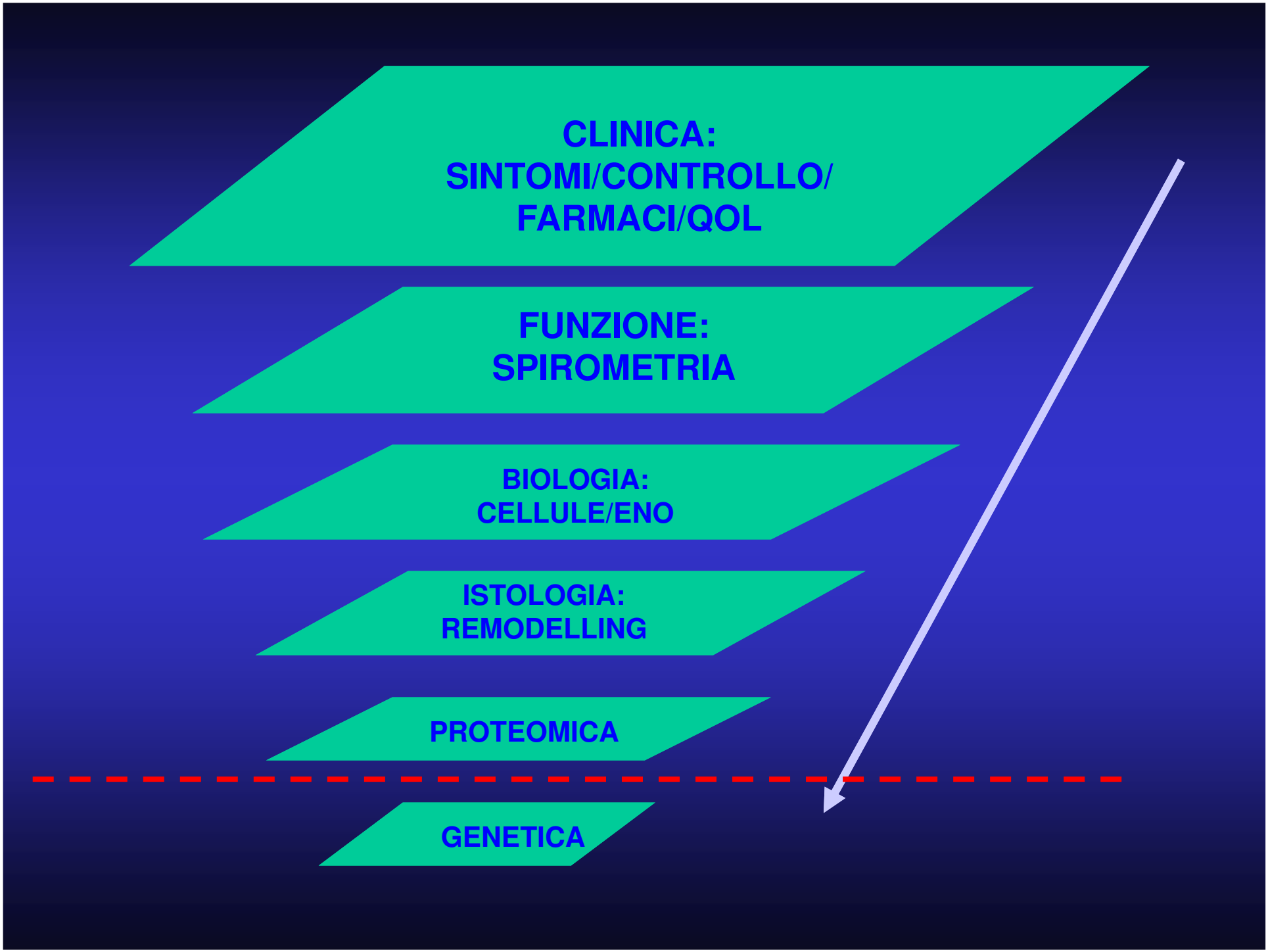
Xolair treated patients



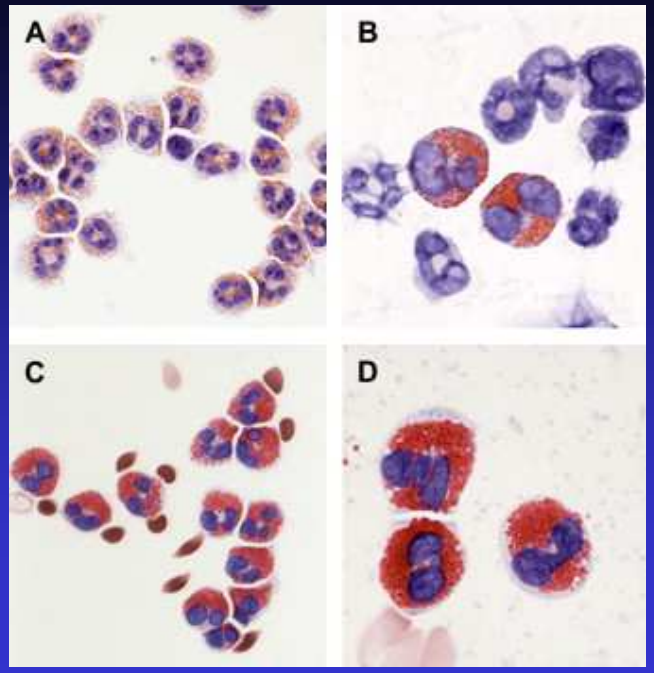
Responder



Non Responder


CLINICA:
SINTOMI/CONTROLLO/
FARMACI/QOL
FUNZIONE:
SPIROMETRIA
BIOLOGIA:
CELLULE/ENO
ISTOLOGIA:
REMODELLING
PROTEOMICA
GENETICA

Interleukin-5



IL-5 is primarily produced by activated Th2 cells, but also Mast cells and eosinophils.
It promotes:

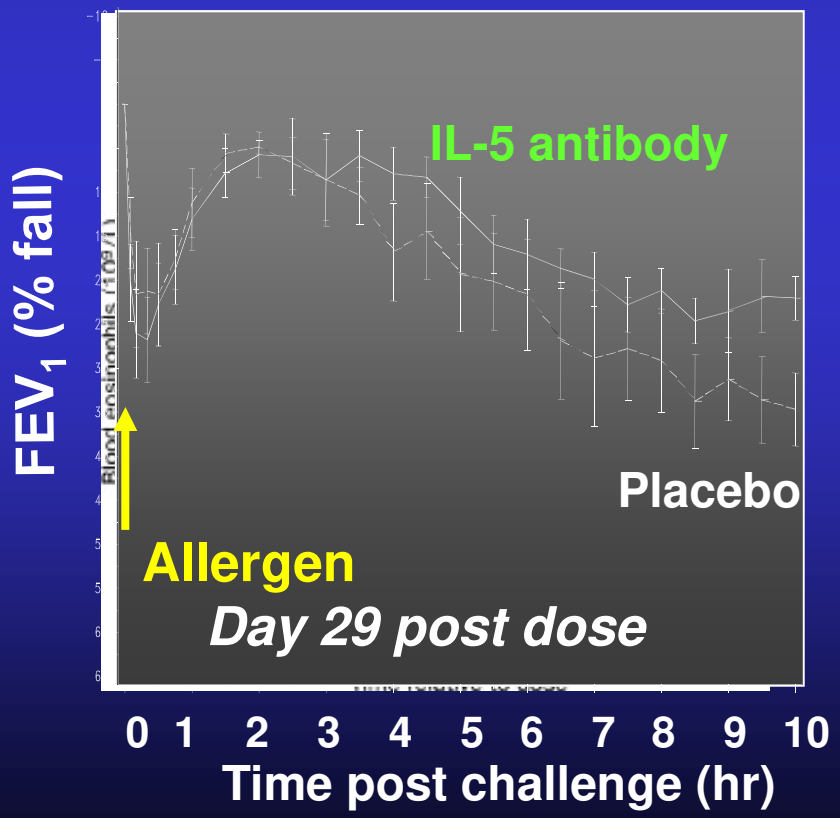
eosinophil maturation
eosinophil migration and chemotaxis
eosinophil activation and survival

EFFECT OF ANTI-IL5 Mab (Mepolizumab) IN ASTHMA

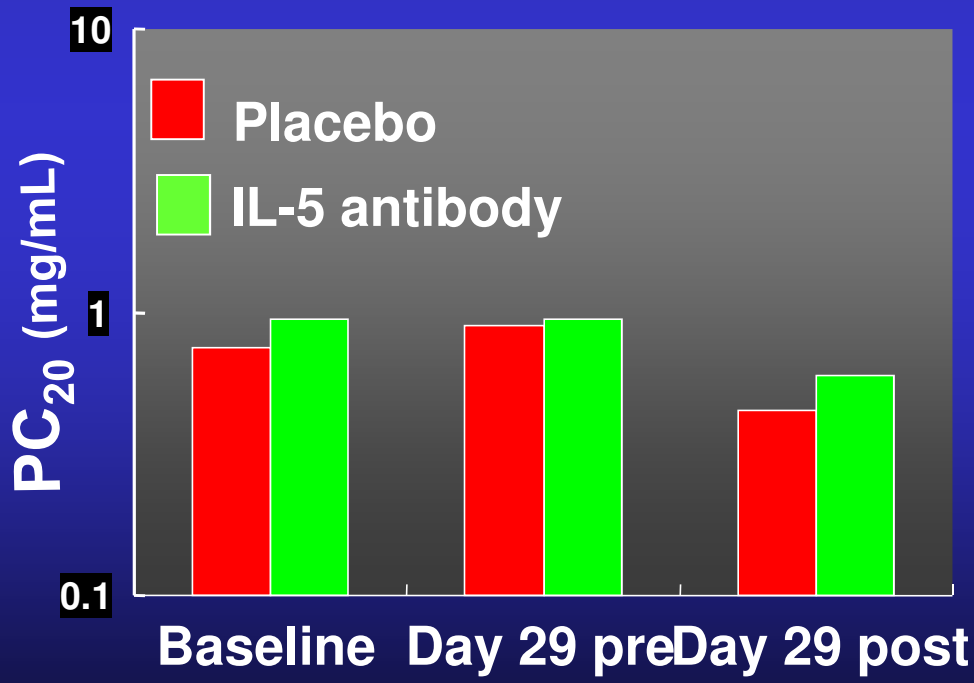
Asthmatic patients (n=8)

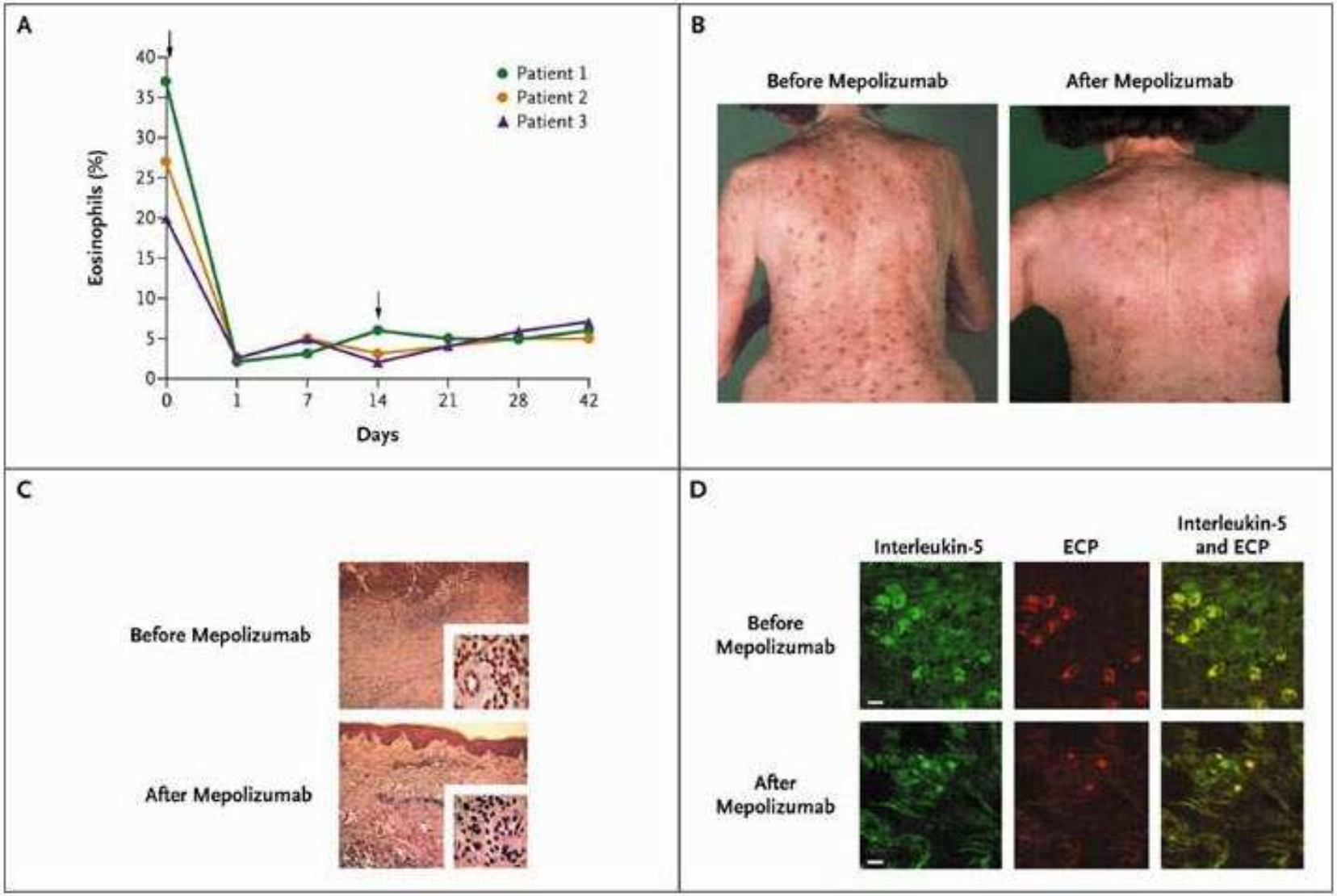
Humanised monoclonal IL-5 antibody (10 mg/kg i.v.)

Allergen challenge



Methacholine challenge




A
Eosinophils (%)
40
35
30
25
20
15
10
5
0
0
1
7
14
21
28
42
Days
Patient 1
Patient 2
Patient 3
B
Before Mepolizumab
After Mepolizumab
C
Before Mepolizumab
After Mepolizumab
D
Interleukin-5
ECP
Interleukin-5 and ECP
Before Mepolizumab
After Mepolizumab

ORIGINAL ARTICLE

Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia

Parameswaran Nair, M.D., Ph.D., Marcia M.M. Pizzichini, M.D., Ph.D.,

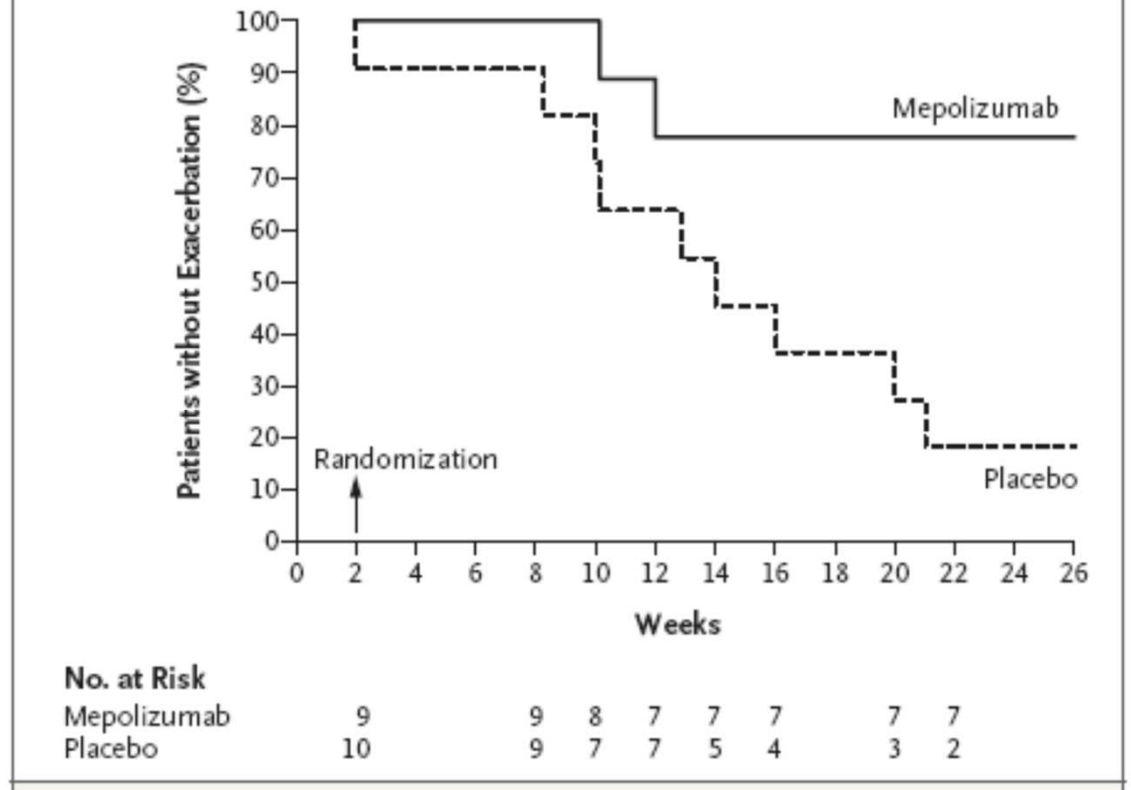


Figure 2. Kaplan–Meier Analysis of the Proportion of Patients without an Asthma Exacerbation during the Study.

66.6±18.3	74.3±17.9
63.8±16.2	65.9±13.1
16.6	4.0
1.6–54.3	0–35.3
10.0	10.0
5.0–25.0	2.5–20.0

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

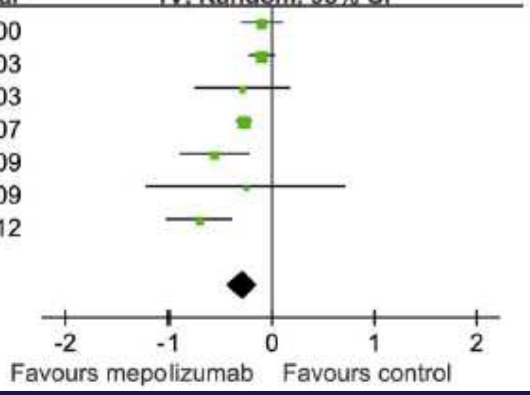
Yao Liu, Song Zhang, Dao-wei Li, Shu-juan Jiang*

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

	mepolizumab			Placebo				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Leckie	-0.32	0.11	8	-0.22	0.27	8	18.2%	-0.10 [-0.30, 0.10]	2000
Flood-Page PT	-0.22	0.115	11	-0.12	0.2	13	22.8%	-0.10 [-0.23, 0.03]	2003
Bűttner	-0.42	0.26	5	-0.13	0.55	7	7.4%	-0.29 [-0.76, 0.18]	2003
Flood-Page P	-0.309	0.25	112	-0.035	0.33	119	25.7%	-0.27 [-0.35, -0.20]	2007
Nair	-0.61	0.47	9	-0.05	0.23	10	11.3%	-0.56 [-0.90, -0.22]	2009
Haldar	-0.28	2.08	29	-0.03	1.74	32	2.2%	-0.25 [-1.22, 0.72]	2009
Pavord	-0.885	1.25	156	-0.18	1.56	155	12.3%	-0.71 [-1.02, -0.39]	2012
Total (95% CI)			**330**			**344**	**100.0%**	**-0.29 [-0.44, -0.14]**	

Heterogeneity: Tau² = 0.02; Chi² = 19.05, df = 6 (P = 0.004); I² = 69%

Test for overall effect: Z = 3.80 (P = 0.0001)



Liu et al , PLOSone 2013

Therapeutics and Clinical Risk Management

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REVIEW

Role of biologics in severe eosinophilic asthma – focus on reslizumab

Girolamo Pelaia[1]
Alessandro Vatrella[2]
Maria Teresa Busceti[1]
Luca Gallelli[3]
Mariaimmacolata Preianò[3]
Nicola Lombardo[1]
Rosa Terracciano[3]
Rosario Maselli[1]

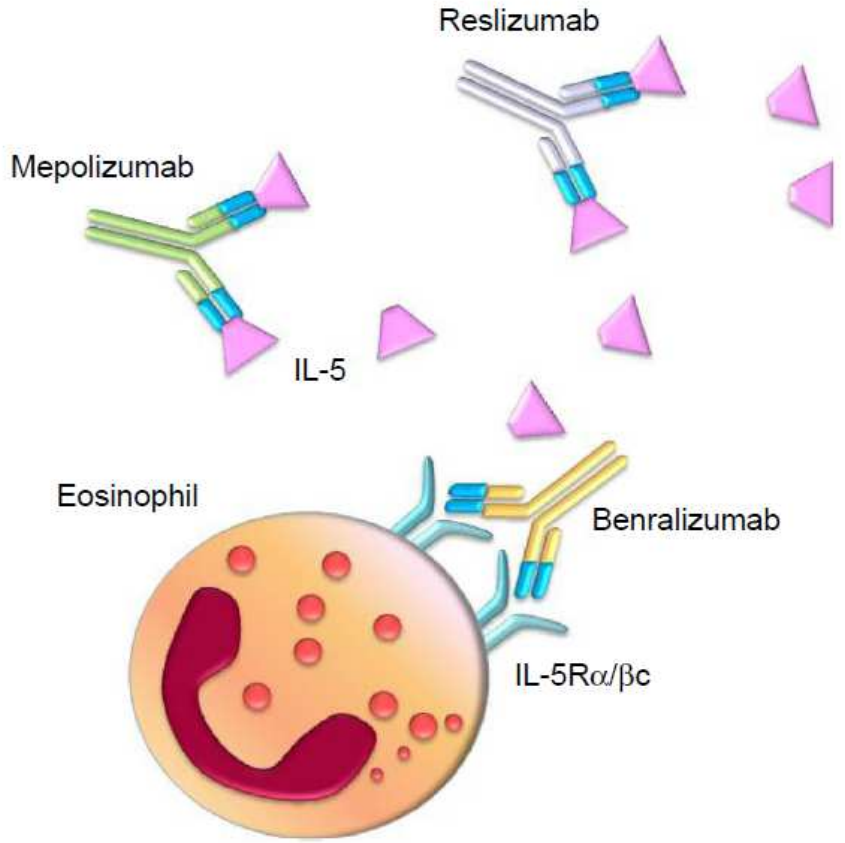


Figure 2 Anti-IL-5/IL-5R biologic therapies.
Notes: Monoclonal antibodies aimed to inhibit eosinophil functions include mepolizumab and reslizumab, which bind to and neutralize IL-5, as well as benralizumab, which targets and blocks IL-5Rα.
Abbreviation: IL-5, interleukin-5.

Reslizumab

Table 2. Clinical trials of reslizumab in asthma (SCH55700 – anti-interleukin-5, IgG_4 – Cephalon Inc.)

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	53	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%

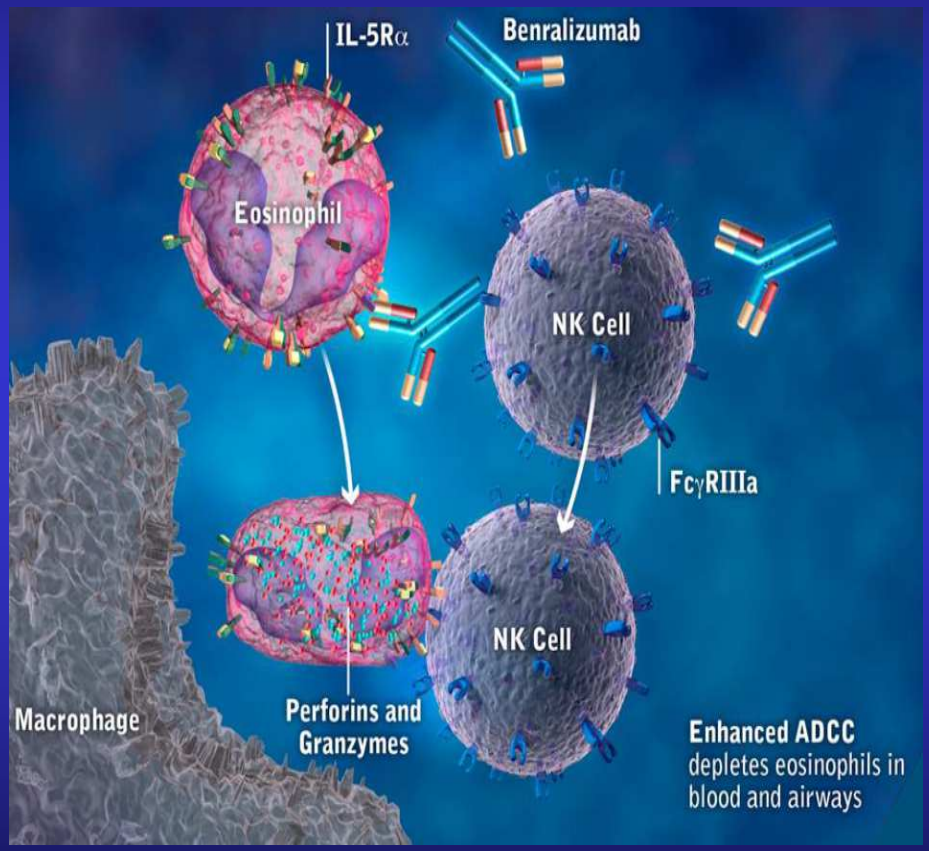
Benralizumab

Table 3. Clinical trials of benralizumab in asthma (MEDI-563, Anti-interleukin-5a, IgG_1 – Medimmune)

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 [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

Benralizumab: Eosinophil Depletion Via Antigen Dependent Cell-mediated Cytotoxicity

- **Benralizumab** leads to antibody-dependent cellular cytotoxicity (**ADDC**) caused by Fc receptor binding on NK cells to the anti-IL-5Ra antibody on eosinophils[1,2]
- Key property of benralizumab antibody: **afucosylation**[3]
  - Removal of the fucose sugar residue in the CH2 region

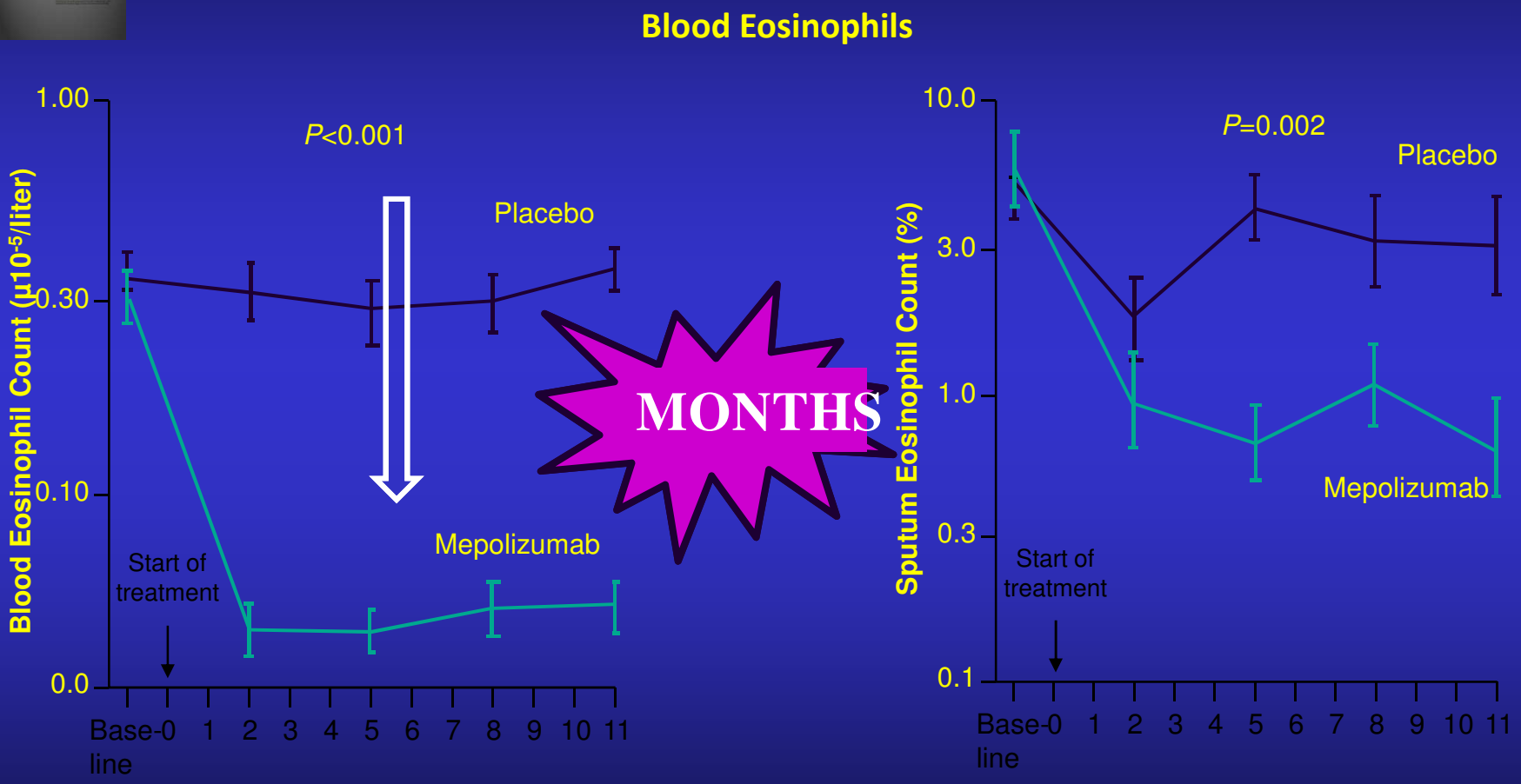


Afucosylation enhances ability of benralizumab to engage with FcγRIIIa on effector cells (eg, NK cells and macrophages)[2,3]

IL-interleukin; NK=natural killer.

1. Molfino NA et al. *Clin Exp Allergy.* 2011;42:712-737. 2. Kolbeck R et al. *J Allergy Clin Immunol.* 2010;125:1344-1353. 3. Tan LD et al. *J Asthma Allergy.* 2016;9:71-81.

Mepolizumab Speed of Onset

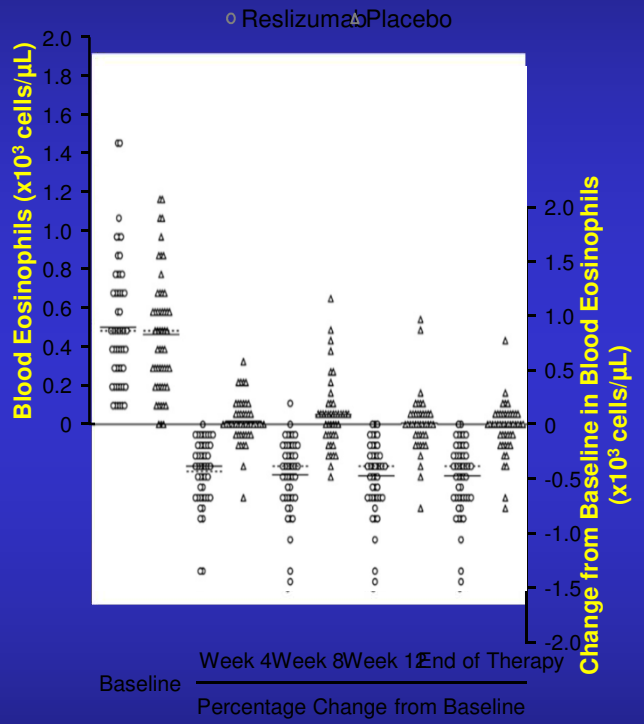


Results from a randomized, double-blind study on the effect of monthly intravenous infusions of 750 mg mepolizumab for 1 year, on clinical outcome measures in 61 patients who had refractory eosinophilic asthma and a history of recurrent severe exacerbations.

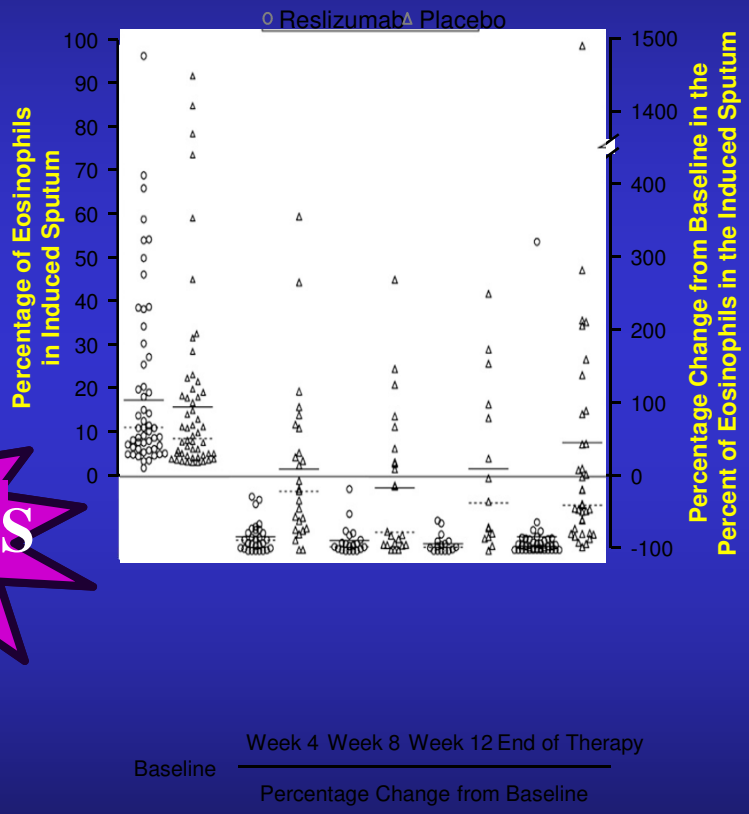
Haldar P et al. *N Engl J Med.* 2009;360:973-984.

Reslizumab Speed of Onset

Blood Eosinophils



% Eos in Induced Sputum



WEEKS

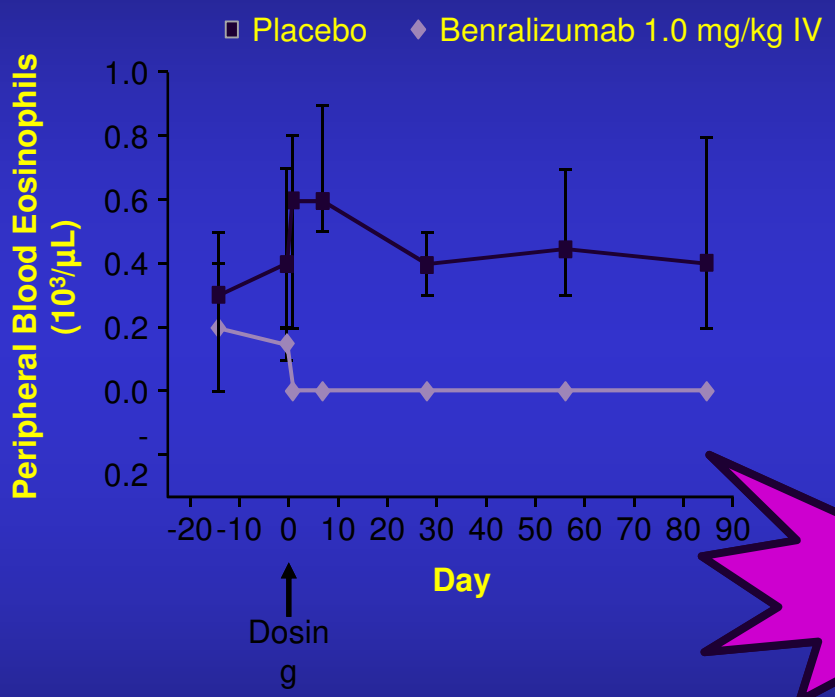
Results from a randomized, double-blind, placebo-controlled study on the effect of three intravenous infusions of 3.0 mg/kg reslizumab at 4 weeks intervals, on the change from baseline in the ACQ score in 106 patients with eosinophilic asthma that is poorly controlled wih high-dose inhaled corticosteroid.

ACQ=asthma control questionnaire.

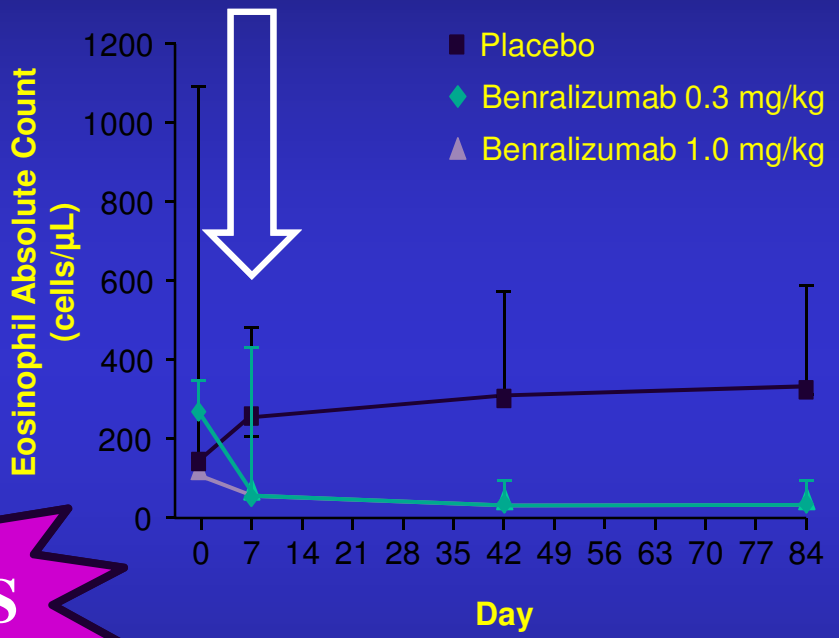
Castro M et al. *Am J Respir Crit Care Med.* 2011;184:1125-1132.

Benralizumab Speed of Onset

Blood Eosinophils[1,a]



Blood Eosinophils[2,b]



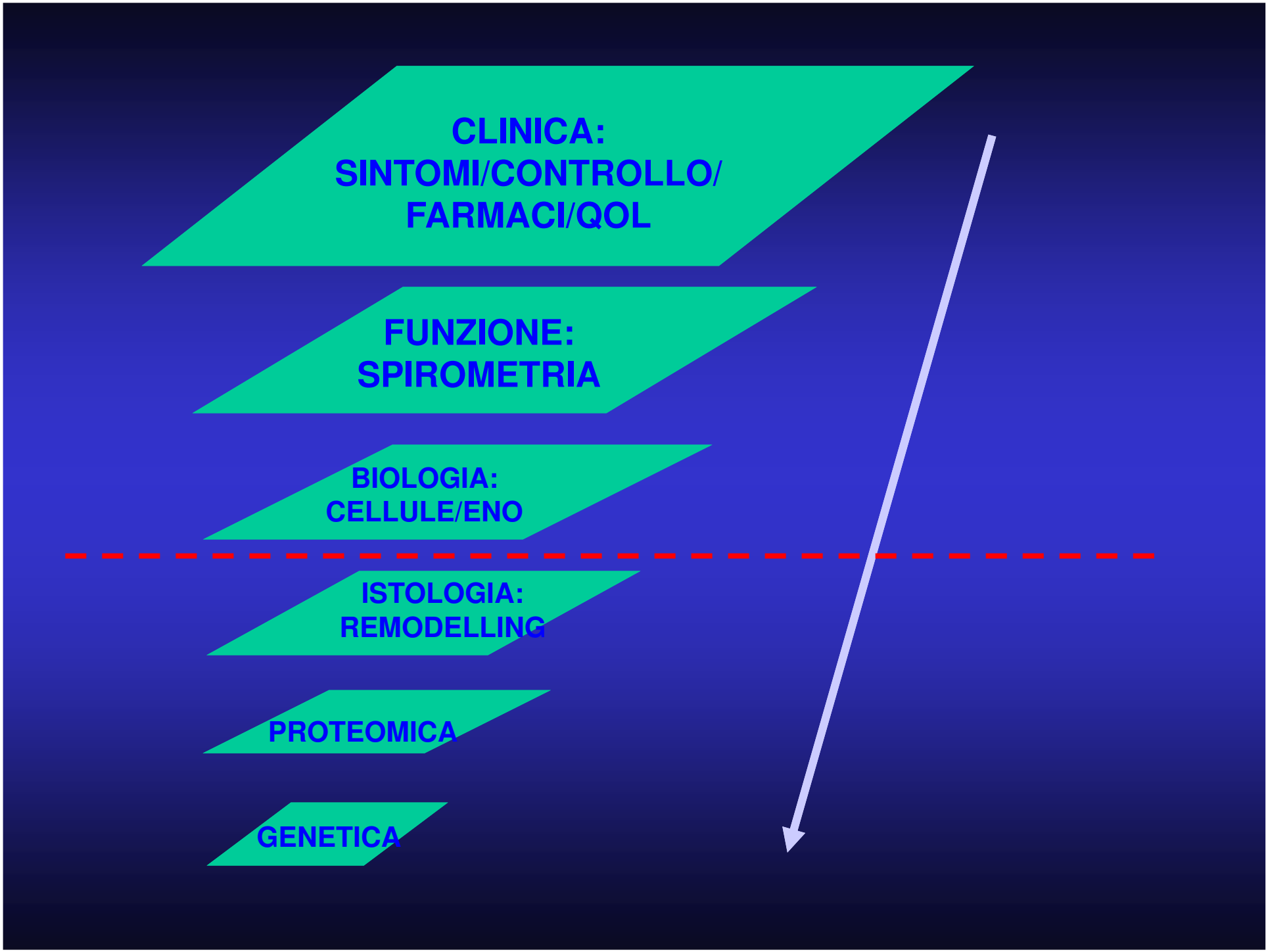
DAYS

- **Benralizumab patients exhibited decreases at Day 1 that persisted until Day 84[2,3]**

[a]Results from a multicenter, double-blind, placebo-controlled phase I study on the safety of a single intravenous infusion of 1 mg/kg or three monthly subcetaneous doses of 100 mg or 200 mg benralizumab, in 54 adult patients with eosinophilic asthma.

[b]Results from a randomised, double-blind, placebo-controlled study on the effect of 1 dose of 0.3 or 1.0 mg/kg intravenous infusions of benralizumab, on asthma exacerbation rate at 12 weeks in patients who presented to the emergency department with acute asthma.

1. Laviolette M et al. *J Allergy Clin Immunol.* 2013;132(5):1086-1096.e5. 2. Nowak RM. *Am J Emerg Med.* 2015;33(1):14-20. 3. Pham TH et al. *Respir Med.* 2016;111:21-29.


CLINICA:
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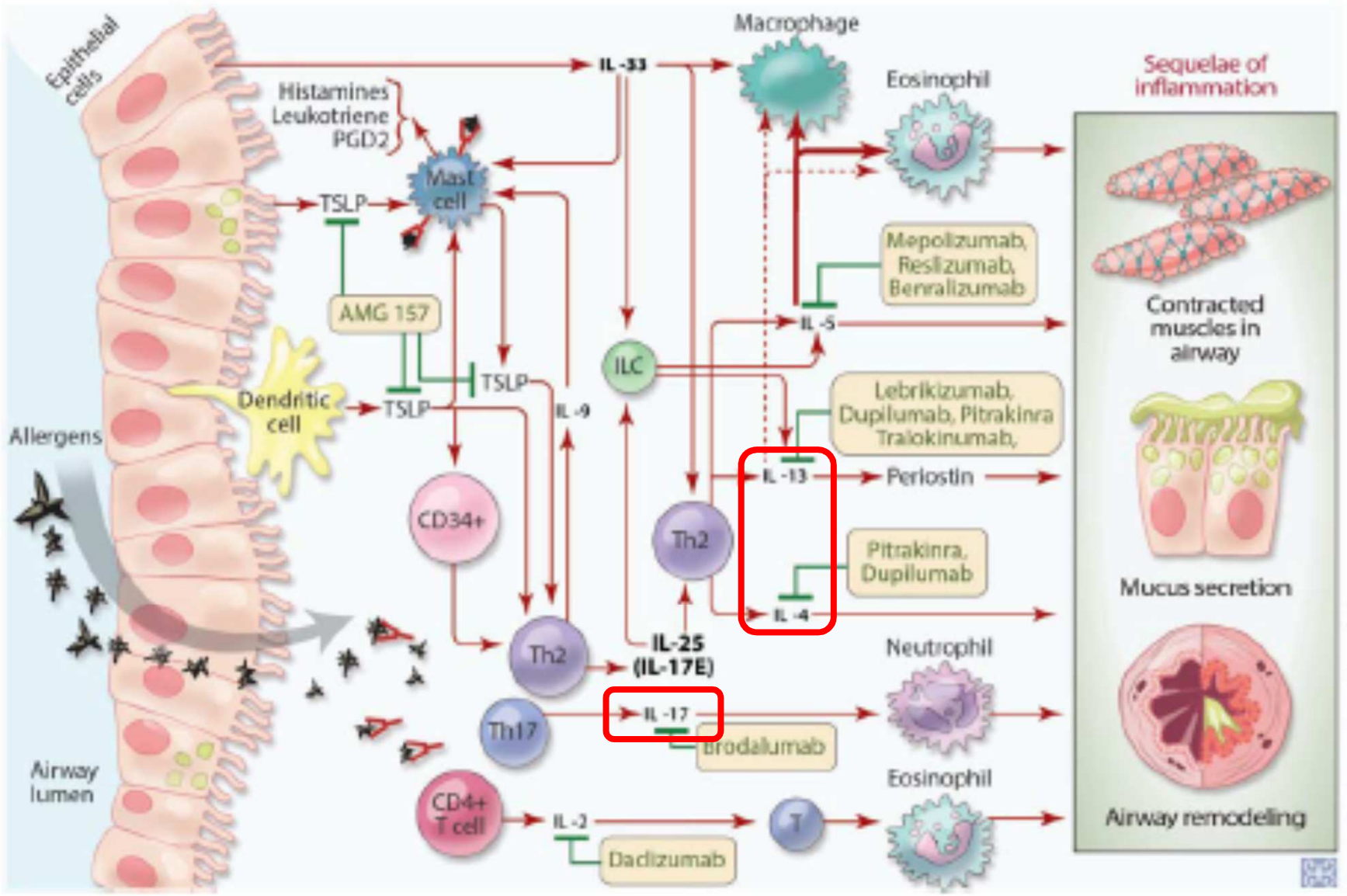
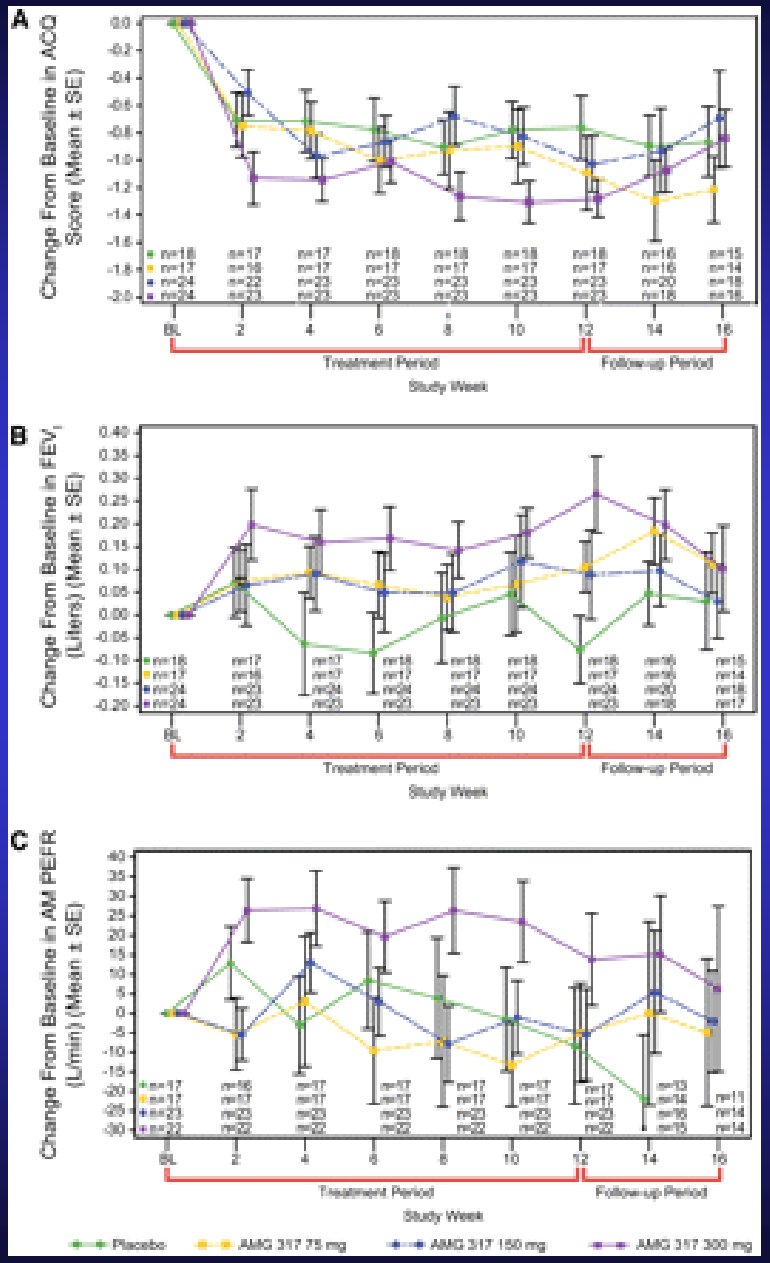
FARMACI/QOL
FUNZIONE:
SPIROMETRIA
BIOLOGIA:
CELLULE/ENO
ISTOLOGIA:
REMODELLING
PROTEOMICA
GENETICA

Anti-interleukin Therapy in Asthma

RM Dunn[1] and ME Wechsler[1]

STATE OF THE ART

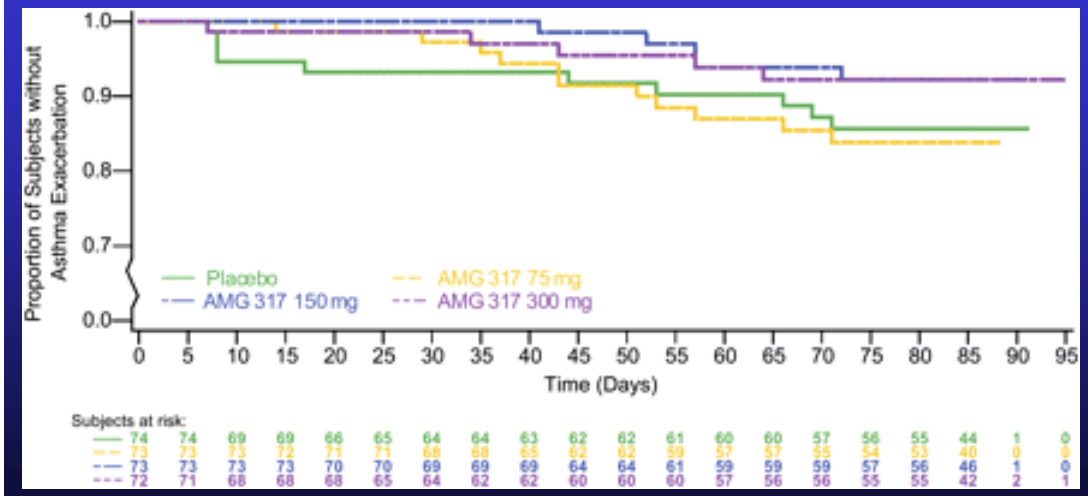




A randomized controlled phase II trial with AMG317, anti IL-4 Receptor in patients with asthma

Corren

Chest 2012



ORIGINAL ARTICLE

Lebrikizumab Treatment in Adu with Asthma

Jonathan Corren, M.D., Robert F. Lemanske, Jr., M.D., Nicola A. Ha

219 adult patients
40% < FEV1 < 80%
12% FEV1 reversibility
200 FP < 1000 mcg
ACQ > 1.5

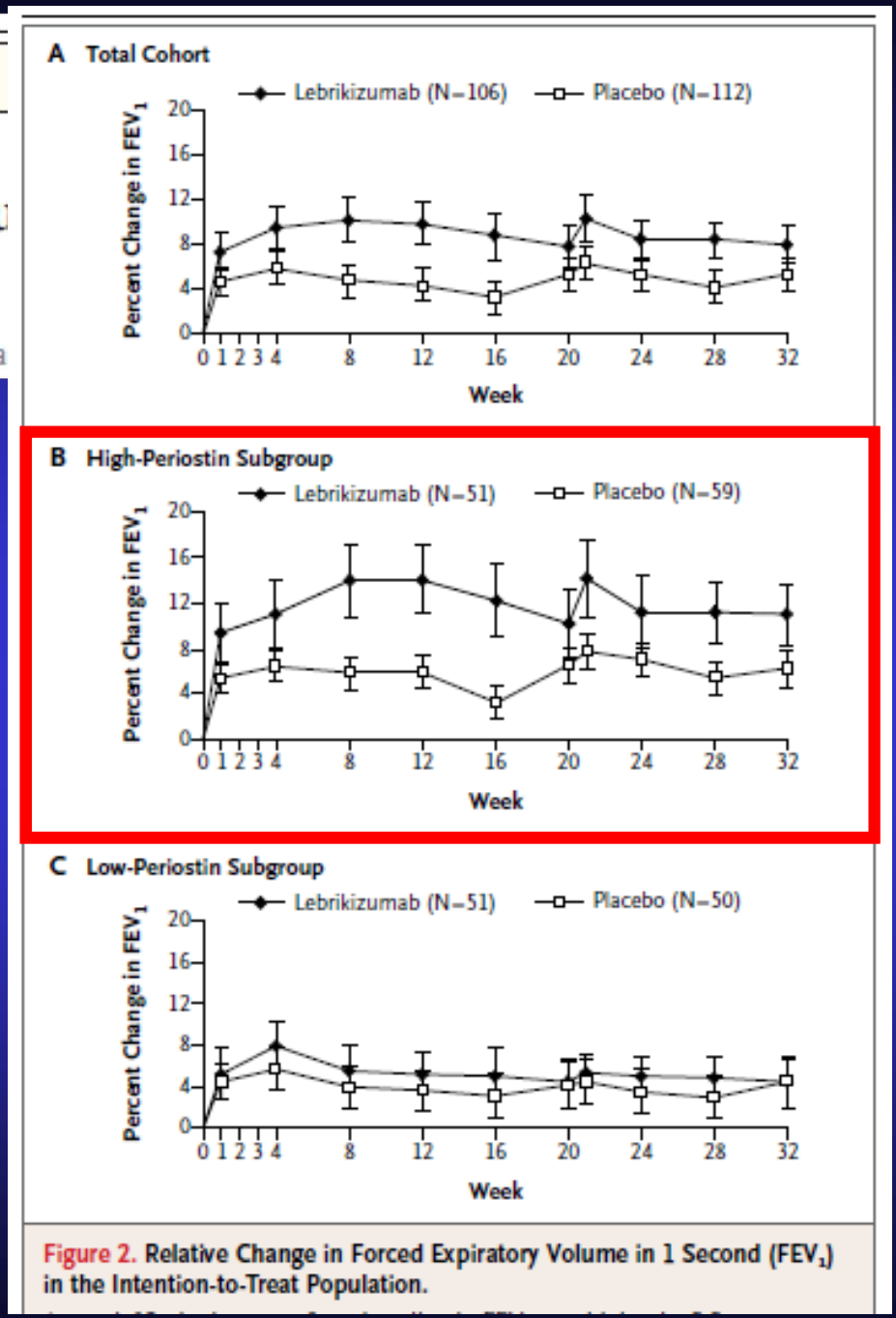
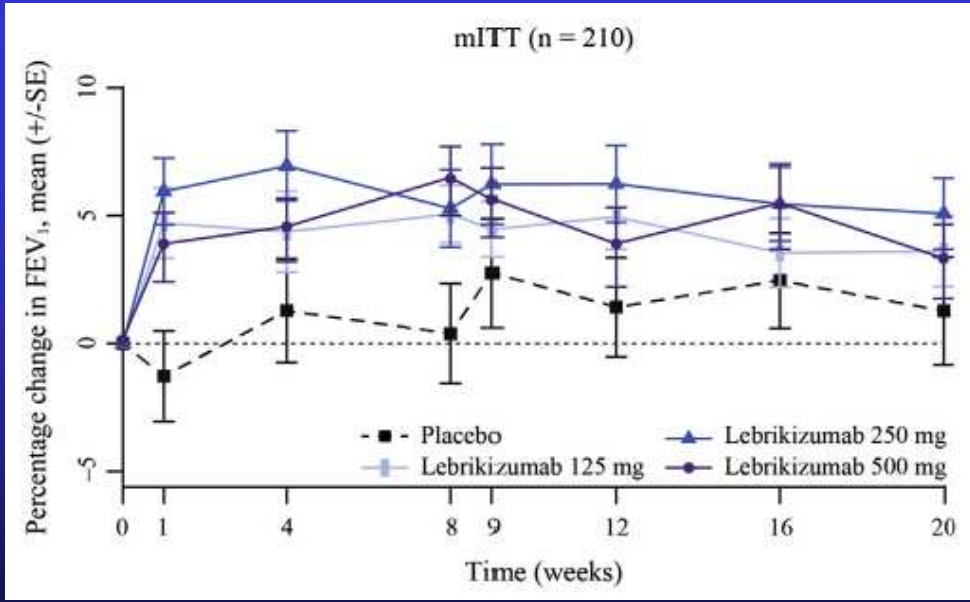


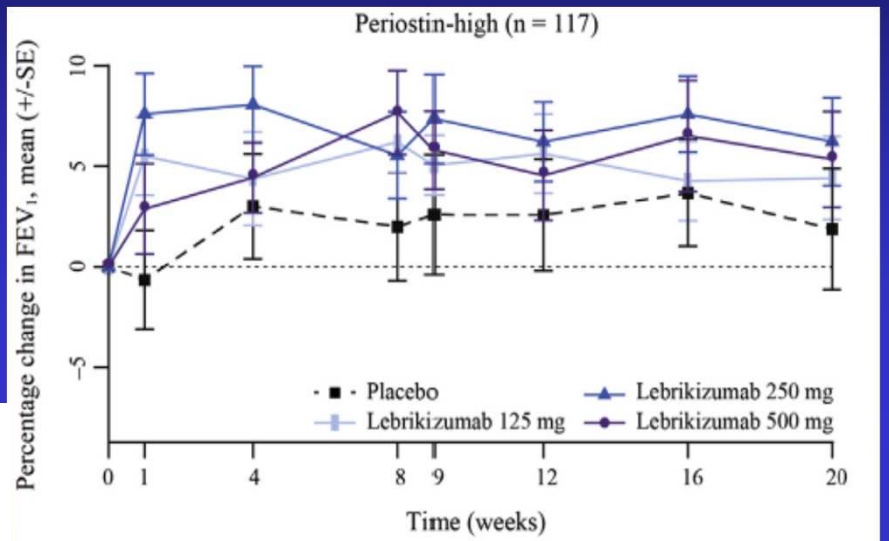
Figure 2. Relative Change in Forced Expiratory Volume in 1 Second (FEV_1) in the Intention-to-Treat Population.

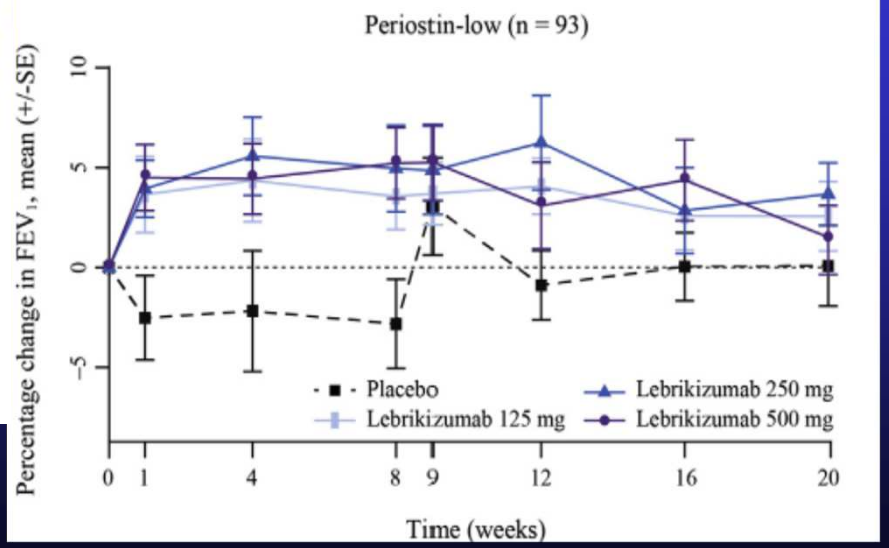
Corren NEJM 2011

Dose-ranging study of lebrikizumab in asthmatic patients not receiving inhaled steroids

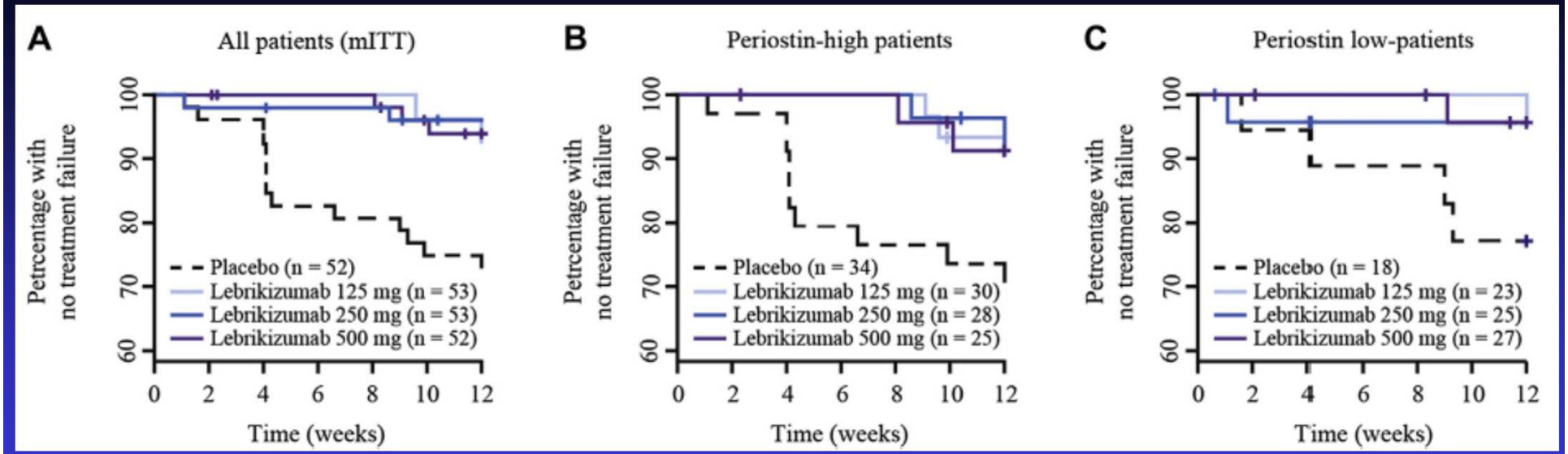
212 adult patients
FEV1 > 80%
15% FEV1 reversibility
No stable ICS

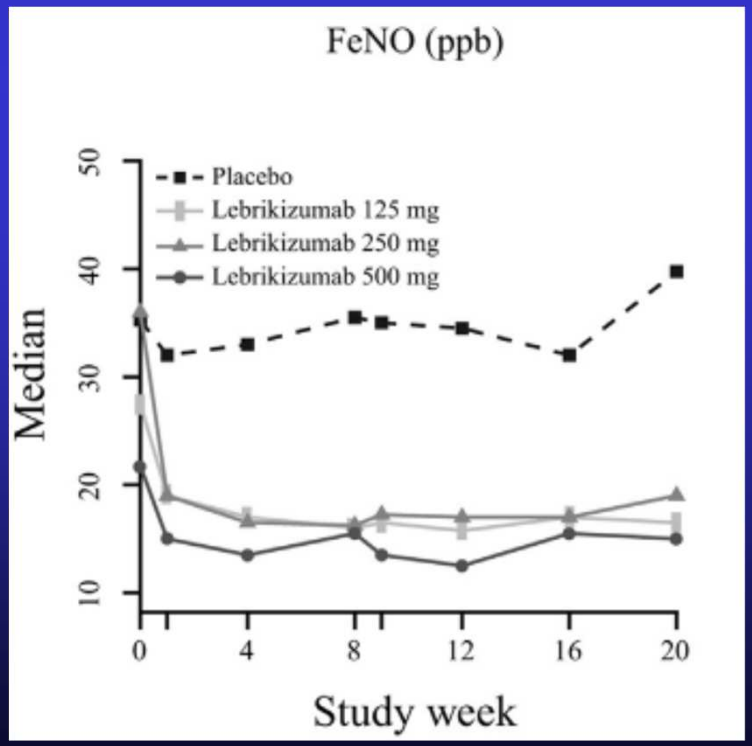


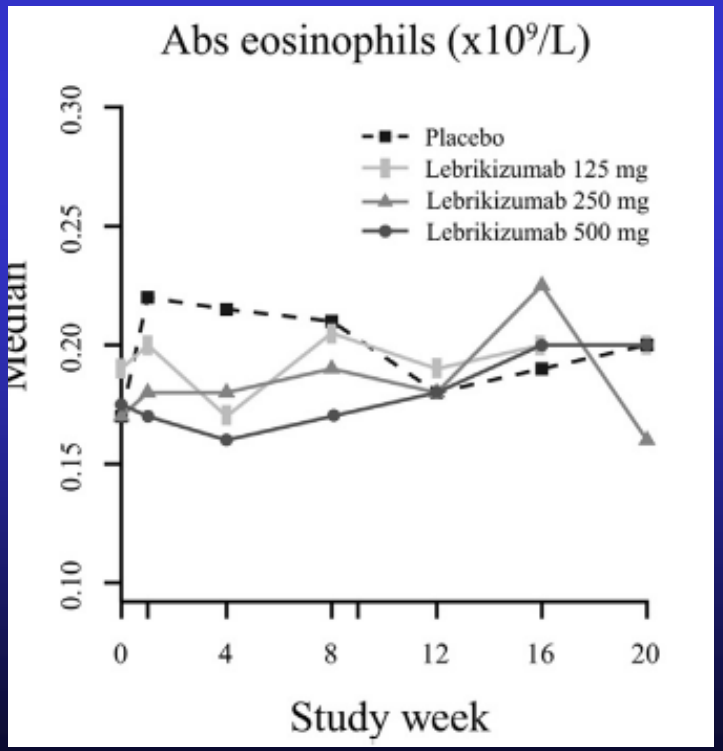




Noonan, JACI 2013


A
All patients (mITT)
Petrcentage with no treatment failure
100
90
80
70
60
0
2
4
6
8
10
12
Time (weeks)
Placebo (n = 52)
Lebrikizumab 125 mg (n = 53)
Lebrikizumab 250 mg (n = 53)
Lebrikizumab 500 mg (n = 52)
B
Periostin-high patients
Petrcentage with no treatment failure
Time (weeks)
Placebo (n = 34)
Lebrikizumab 125 mg (n = 30)
Lebrikizumab 250 mg (n = 28)
Lebrikizumab 500 mg (n = 25)
C
Periostin low-patients
Petrcentage with no treatment failure
Time (weeks)
Placebo (n = 18)
Lebrikizumab 125 mg (n = 23)
Lebrikizumab 250 mg (n = 25)
Lebrikizumab 500 mg (n = 27)


FeNO (ppb)
Median
50
40
30
20
10
0
4
8
12
16
20
Study week
Placebo
Lebrikizumab 125 mg
Lebrikizumab 250 mg
Lebrikizumab 500 mg


Abs eosinophils (x10⁹/L)
Median
0.30
0.25
0.20
0.15
0.10
0
4
8
12
16
20
Study week
Placebo
Lebrikizumab 125 mg
Lebrikizumab 250 mg
Lebrikizumab 500 mg

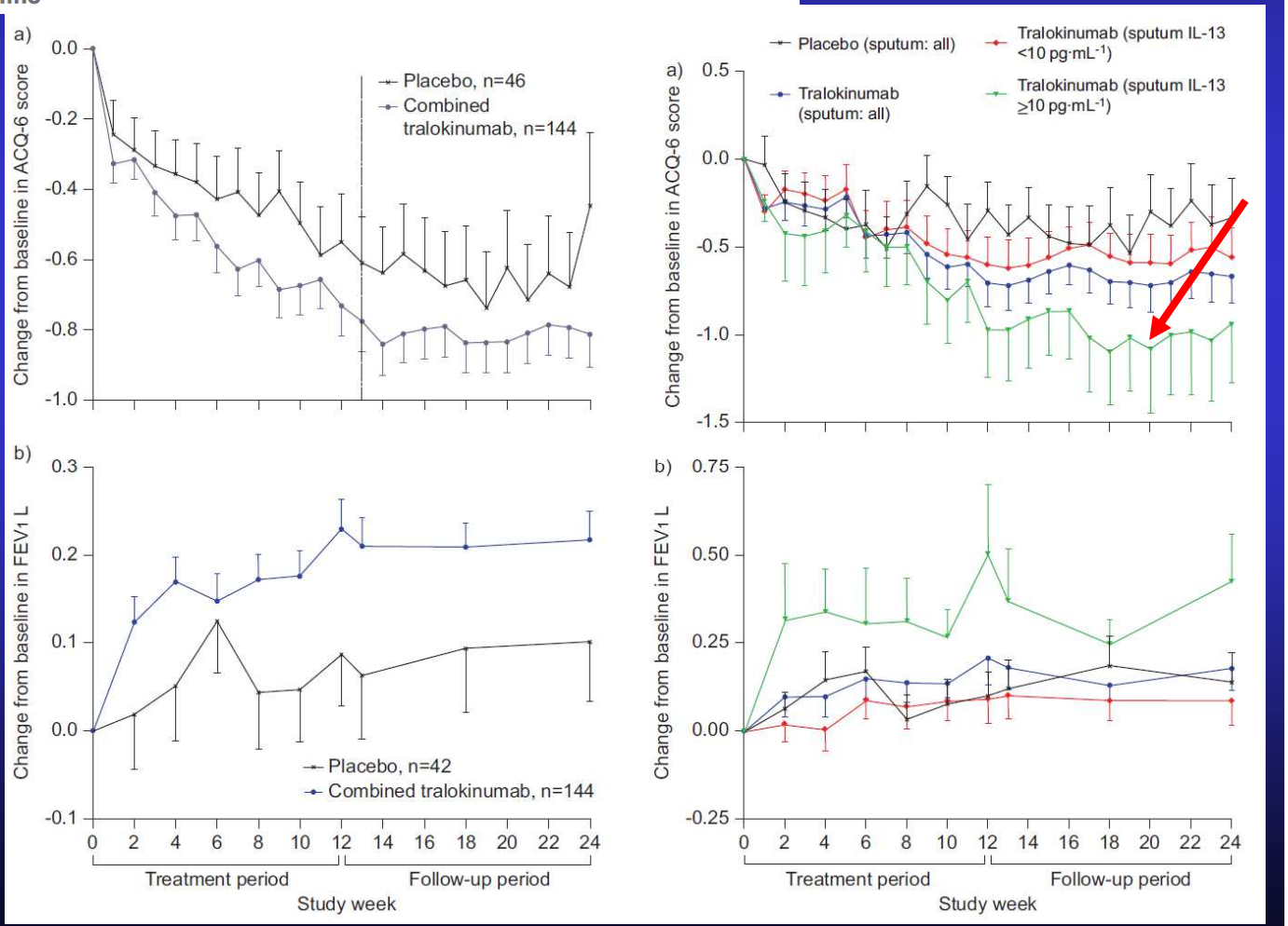
Eur Respir J 2013; 41: 330–338
DOI: 10.1183/09031936.00223411

A phase II placebo-controlled study of tralokinumab in moderate-to-severe asthma

Edward Piper*, Christopher Brightling#, Robert Niven¶, Chad Oh+, Raffaella Faggioni§, Kwai Poon*, Dewei She+, Chris Kell*, Richard D. May*, Gregory P. Geba+ and Nestor A. Molfino+

ERJ Open

194 adults
FEV1 > 40%
15% FEV1
ACQ> 1.5



International Archives of Allergy and Immunology

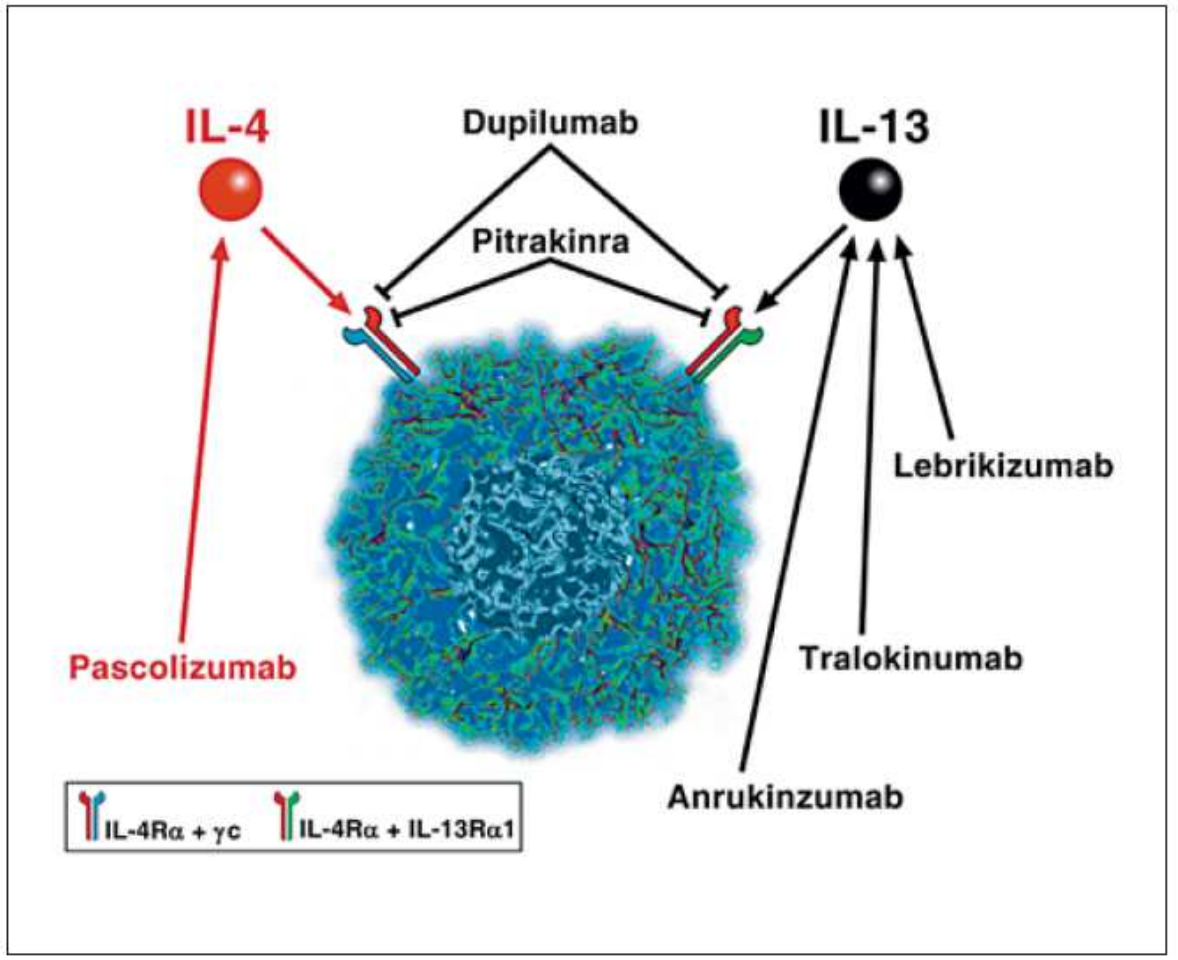
Review

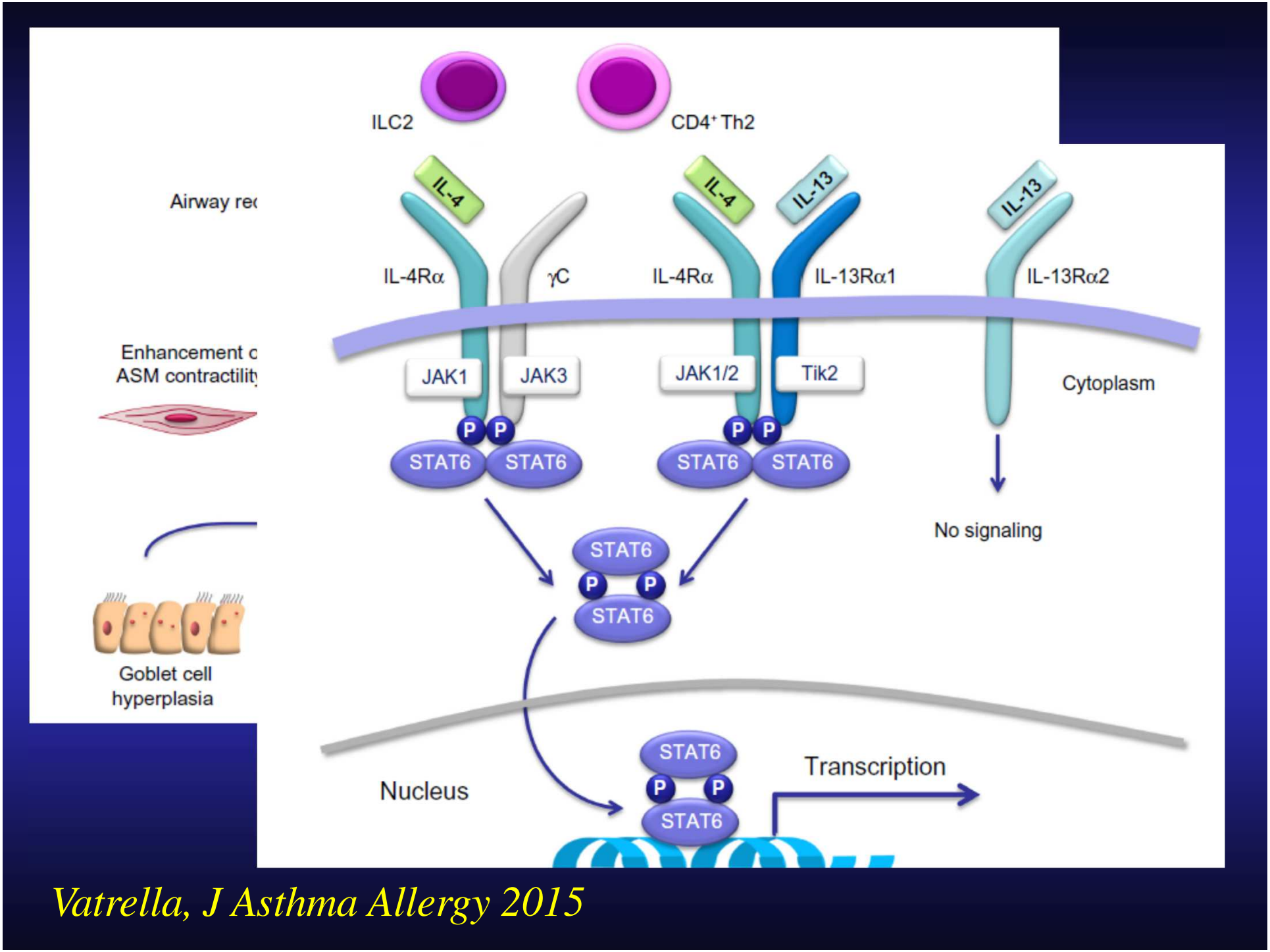
Int Arch Allergy Immunol 2016;170:122–131
DOI: 10.1159/000447692

Published online: August 3, 2016

A Critical Evaluation of Anti-IL-13 and Anti-IL-4 Strategies in Severe Asthma

Diego Bagnasco[a] Matteo Ferrando[a] Gilda Varricchi[b] Giovanni Passalacqua[a]
Giorgio Walter Canonica[a]





Vatrella, J Asthma Allergy 2015

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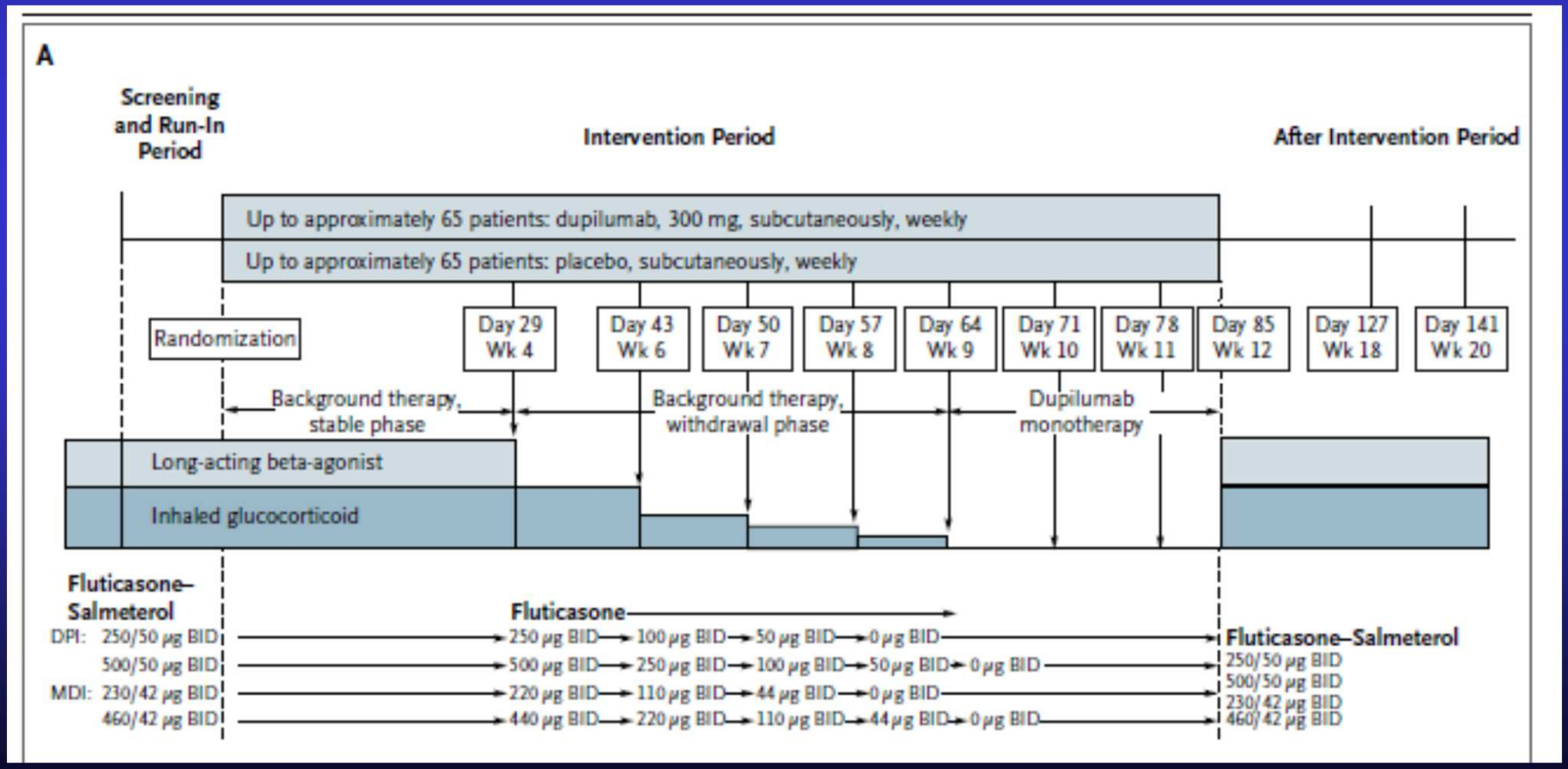
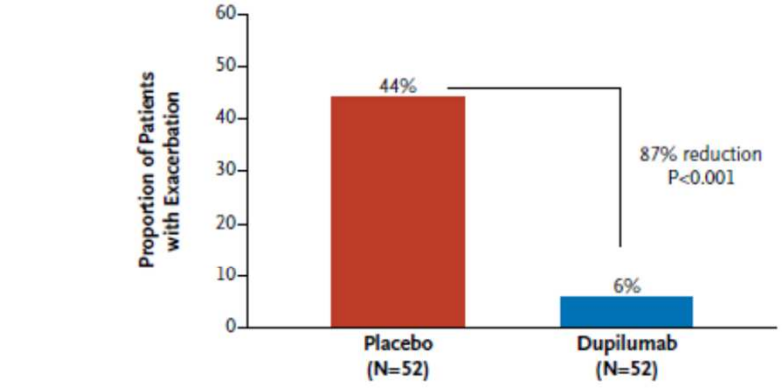
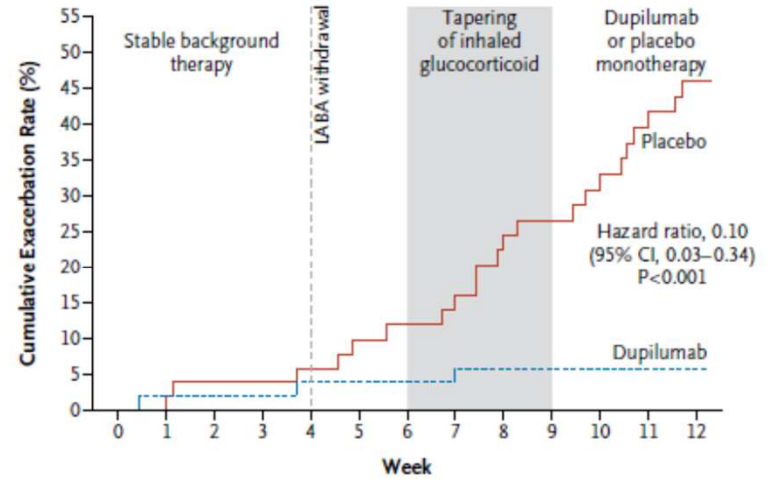
Dupilumab in Persistent Asthma with Elevated Eosinophil Levels

Sally Wenzel, M.D., Linda Ford, M.D., David Pearlman, M.D., Sheldon Spector, M.D., Lawrence Sher, M.D., Franck Skobieranda, M.D., Lin Wang, Ph.D., Stephane Kirkesseli, M.D., Ross Rocklin, M.D., Brian Bock, D.O., Jennifer Hamilton, Ph.D., Jeffrey E. Ming, M.D., Ph.D., Allen Radin, M.D., Neil Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., Neil Graham, M.D., and Gianluca Pirozzi, M.D., Ph.D.

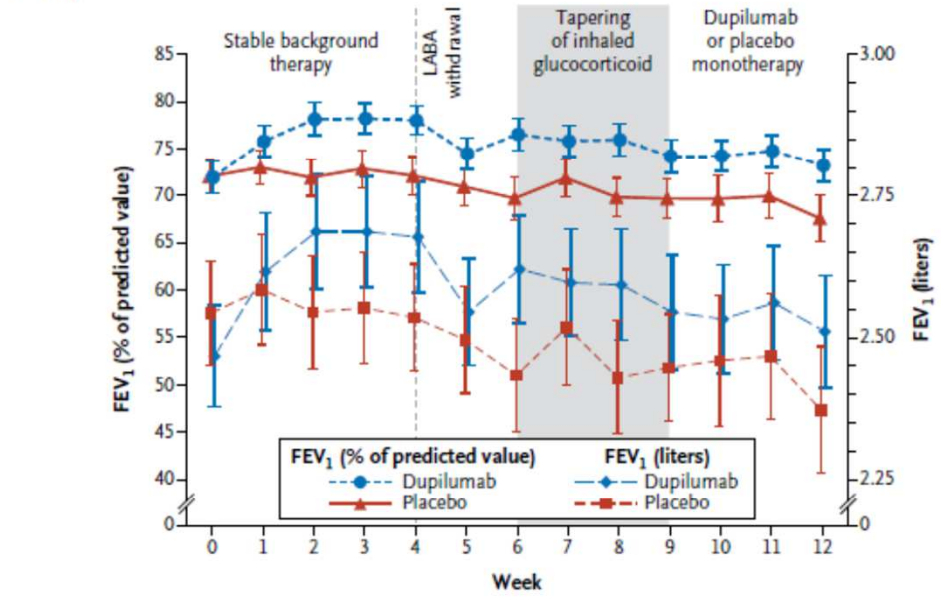






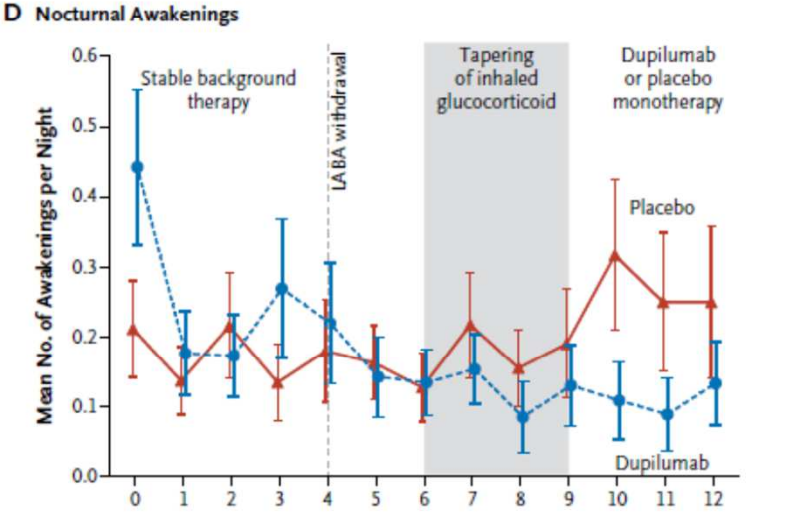
No. at Risk

Dupilumab	52	51	51	51	50	50	50	50	47	45	44	43	42
Placebo	52	52	50	50	48	44	43	41	37	35	32	28	24



No. of Patients

FEV_1 (% of predicted value)													
Dupilumab	52	51	52	52	50	49	52	52	47	46	46	45	45
Placebo	52	52	51	51	50	49	47	46	45	43	41	40	36
FEV_1 (liters)													
Dupilumab	52	51	52	52	50	49	52	52	47	46	46	45	45
Placebo	52	52	51	51	50	49	47	46	45	43	41	40	36



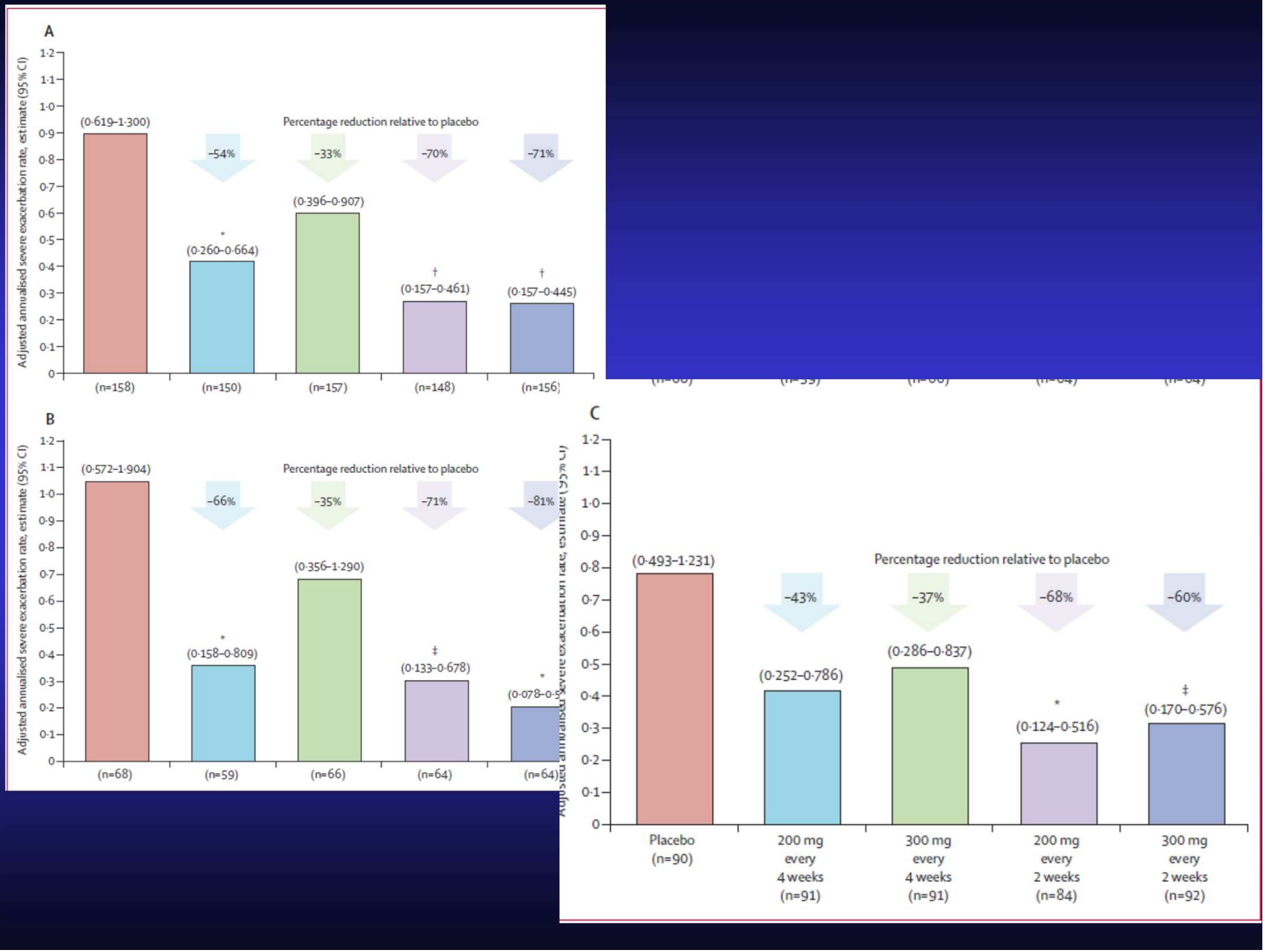
No. of Patients

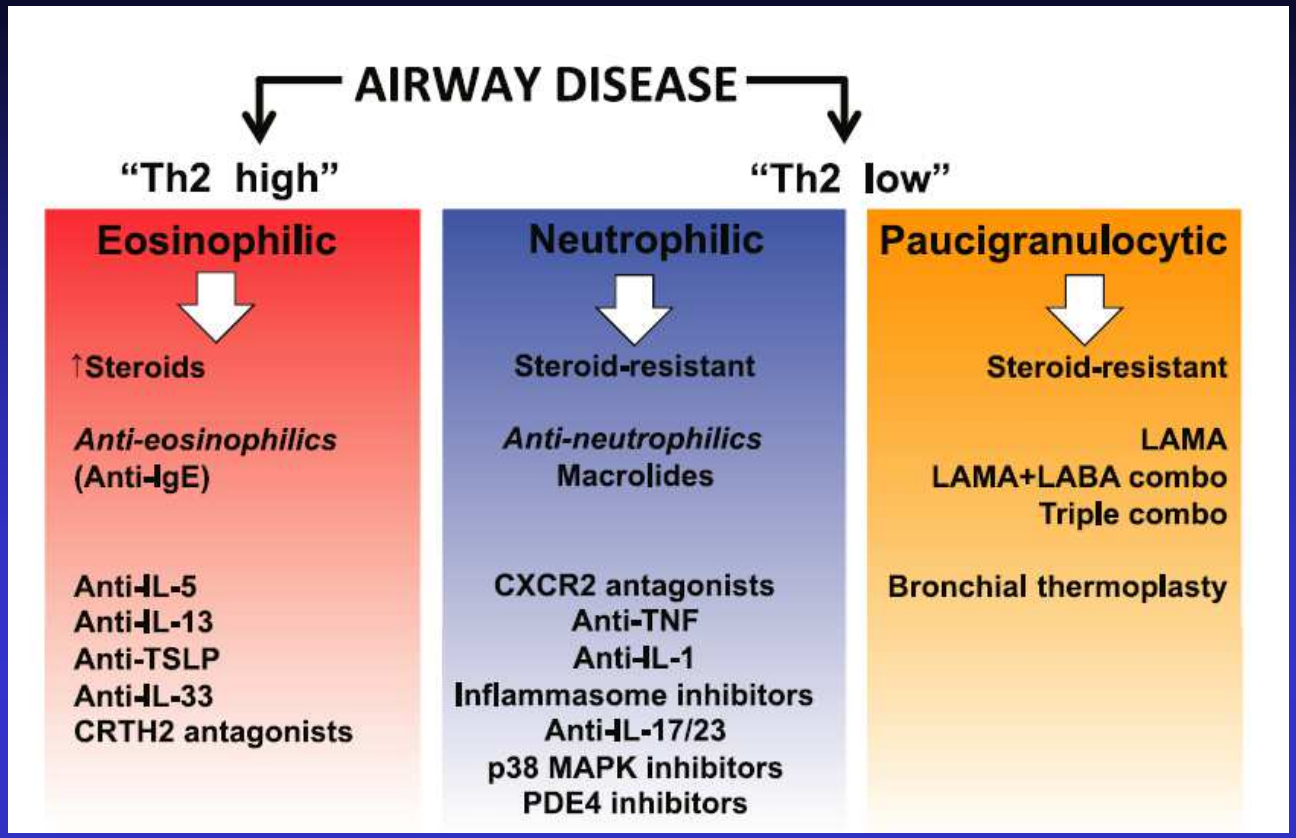
Dupilumab	52	51	52	52	50	49	52	52	47	46	46	45	45
Placebo	52	51	51	52	50	49	47	46	45	42	41	40	36

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

Wenzel et al.Lancet 2016

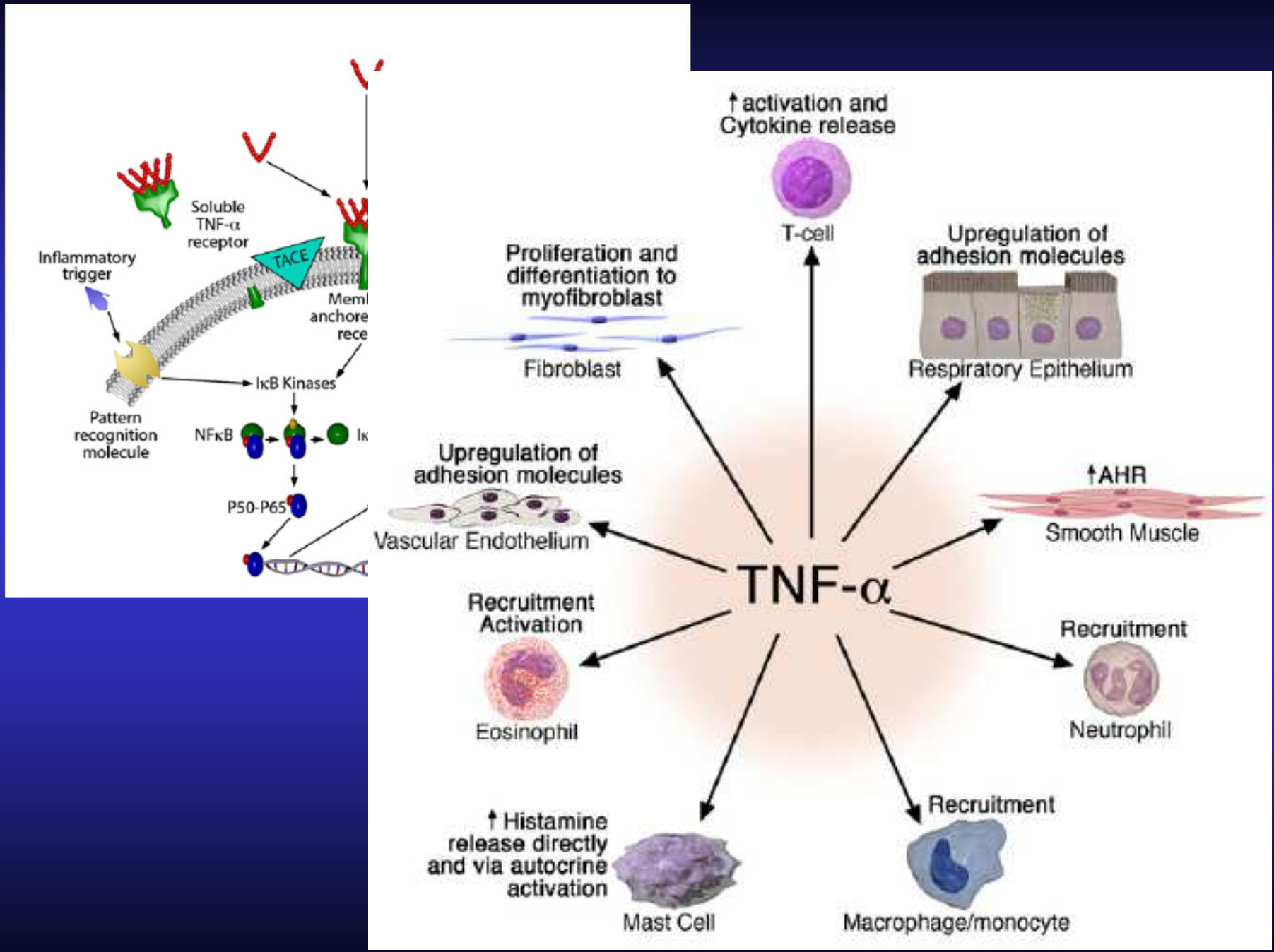

A
Adjusted annualised severe exacerbation rate, estimate (95% CI)
Percentage reduction relative to placebo
(0·619–1·300)
−54%
−33%
−70%
−71%
*
(0·260–0·664)
(0·396–0·907)
†
(0·157–0·461)
†
(0·157–0·445)
(n=158)
(n=150)
(n=157)
(n=148)
(n=156)
B
Adjusted annualised severe exacerbation rate, estimate (95% CI)
Percentage reduction relative to placebo
(0·572–1·904)
−66%
−35%
−71%
−81%
*
(0·158–0·809)
(0·356–1·290)
‡
(0·133–0·678)
*
(0·078–0·5
(n=68)
(n=59)
(n=66)
(n=64)
(n=64)
C
Adjusted annualised severe exacerbation rate, estimate (95% CI)
Percentage reduction relative to placebo
(0·493–1·231)
−43%
−37%
−68%
−60%
(0·252–0·786)
(0·286–0·837)
*
(0·124–0·516)
‡
(0·170–0·576)
Placebo (n=90)
200 mg every 4 weeks (n=91)
300 mg every 4 weeks (n=91)
200 mg every 2 weeks (n=84)
300 mg every 2 weeks (n=92)



Therapeutic approaches to asthma–chronic obstructive pulmonary disease overlap syndromes

Peter J. Barnes, FMedSci, FRS *London, United Kingdom*

JACI 2015


Soluble TNF-α receptor
Inflammatory trigger
TACE
Pattern recognition molecule
IκB Kinases
NFκB
P50-P65
↑activation and Cytokine release
T-cell
Proliferation and differentiation to myofibroblast
Fibroblast
Upregulation of adhesion molecules
Respiratory Epithelium
Upregulation of adhesion molecules
Vascular Endothelium
↑AHR
Smooth Muscle
TNF-α
Recruitment Activation
Eosinophil
Recruitment
Neutrophil
↑ Histamine release directly and via autocrine activation
Mast Cell
Recruitment
Macrophage/monocyte

Respiratory Medicine (2013) 107, 424–432

Available online at www.sciencedirect.com

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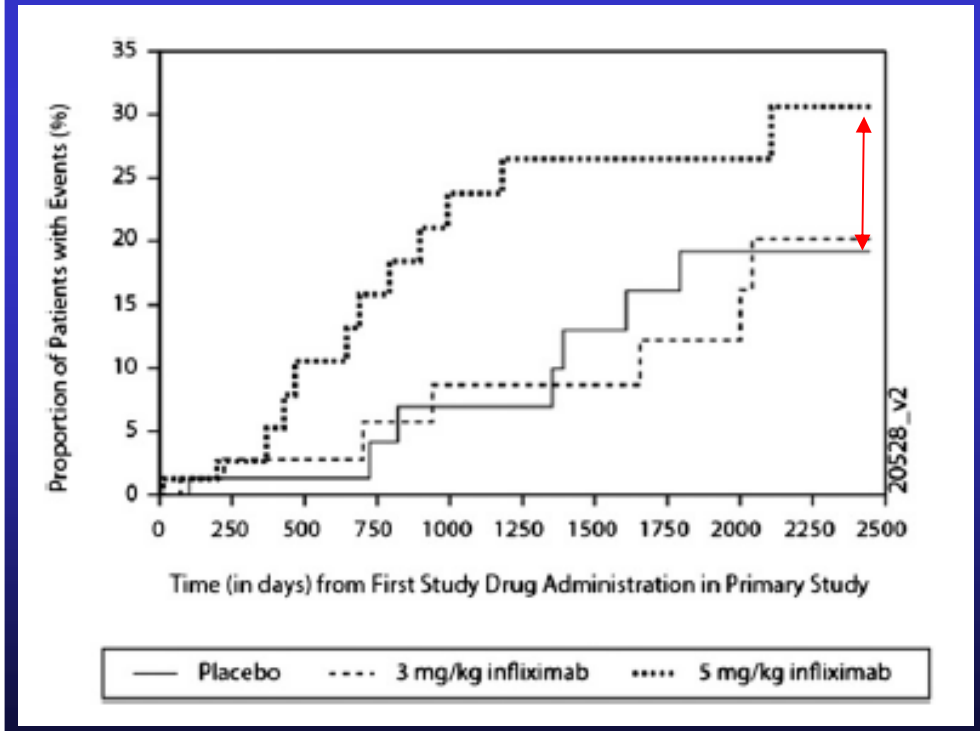
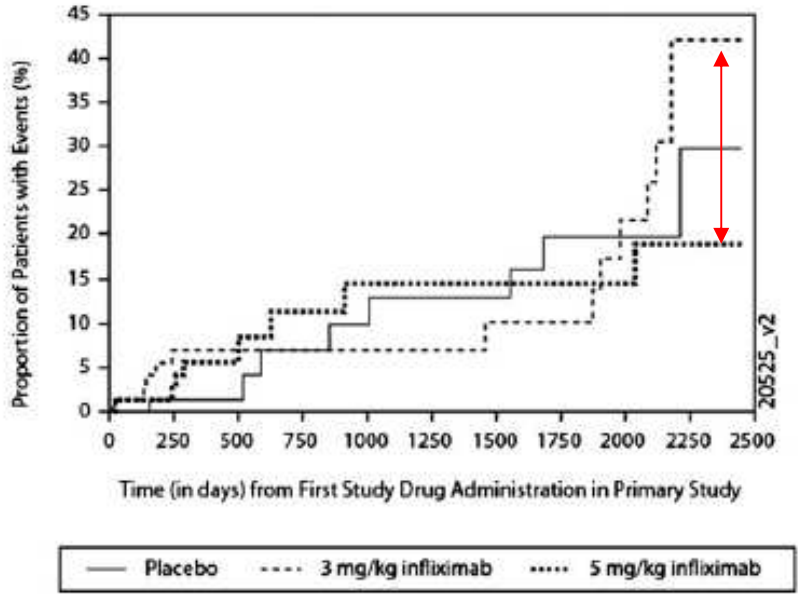
Long-term safety study of infliximab in moderate-to-severe chronic obstructive pulmonary disease

Stephen I. Rennard [a,*], Susan K. Flavin [b], Prasheen K. Agarwal [b], Kim Hung Lo [b], Elliot S. Barnathan [b]





Targeting TNF-α: A novel therapeutic approach for asthma

Christopher Brightling, PhD, MRCP,[a] Mike Berry, MD, MRCP,[b] and Yassine Amrani, PhD[a] *Leicester and Birmingham, United Kingdom*

TABLE I. Summary of clinical trials of anti–TNF-α therapy in asthma

	No./severity	Design	Treatment	Outcome	Result
Howarth et al[7]	15/GINA V	Open label uncontrolled	Etanercept 12 wk	1° ACQ	Improvement ACQ, FEV_1, AHR
				2° FEV_1, AHR	
Berry et al[8]	10/7 GINA V, 3 GINA IV	Randomized placebo controlled crossover	Etanercept 10 wk	1° AHR and AQLQ	Improvement AQLQ, FEV_1, AHR
					amine
Mor					mpared with
Erin		group			morning
				2° FEV_1, exacerbations, sputum markers	↓ PEF variability
					↓, exacerbations
Rouhani et al[60]	21/β-agonist only	Segmental allergen challenge	Etanercept 2 wk	Markers of inflammation AHR	Increased TNFR2 in BAL, no change in AHR

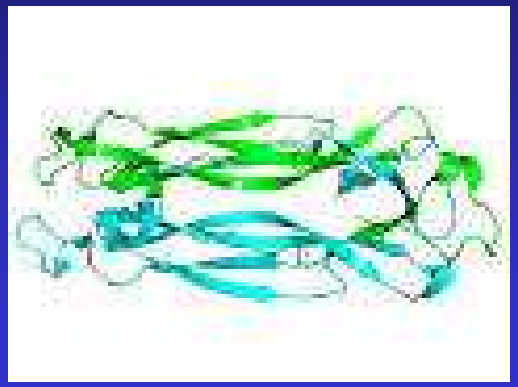
potential risks. A recent report on the administration of infliximab for 6 months in patients with chronic obstructive pulmonary disease showed no benefit and recorded 9 malignancies in 157 treated patients compared with 1 malignancy in 77 placebo-treated subjects, together with an increased risk of pneumonia.[62]

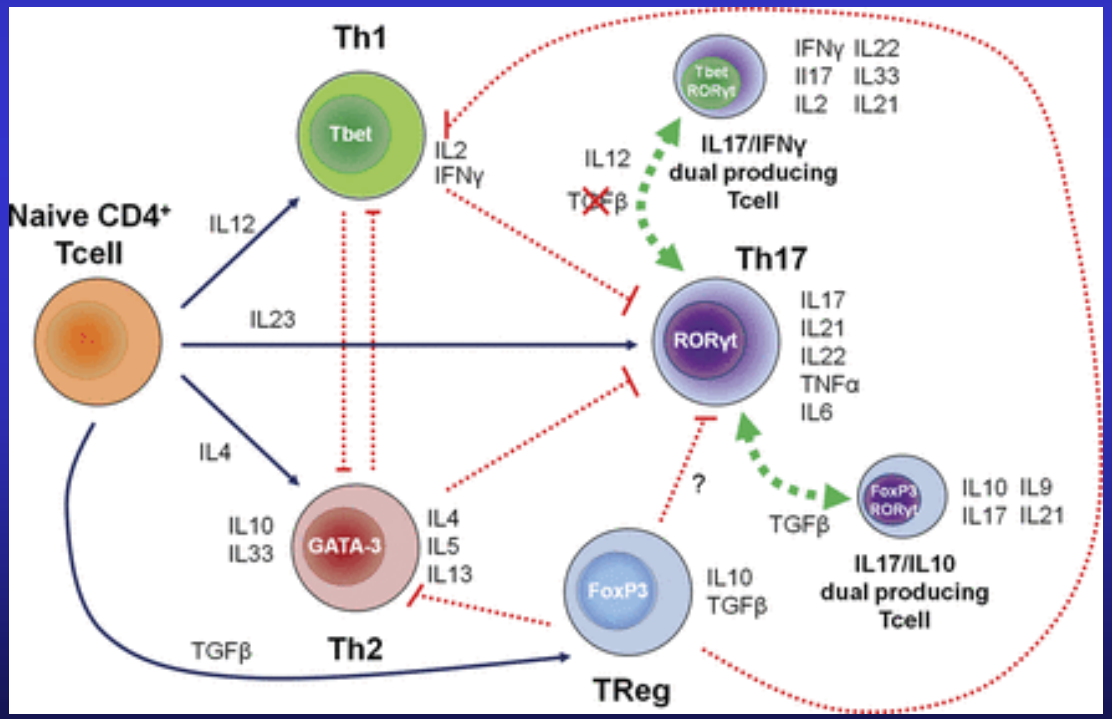
A Randomized, Double-blind, Placebo-controlled Study of Tumor Necrosis Factor-α Blockade in Severe Persistent Asthma

TABLE 2. SAFETY ASSESSMENTS FROM BASELINE THROUGH WEEK 76* BY MeDDRA PREFERRED TERM, TREATED PATIENTS

		Golimumab		
	Placebo	50 mg	100 mg	200 mg
N	78	75	78	78
Patients who discontinued study agent due to adverse events through Week 24	1 (1.3)	7 (9.1)	11 (14.5)	9 (11.5)
Patients with ≥1 adverse events	75 (96.2)	69 (92.0)	77 (98.7)	78 (100)
Patients with adverse events occurring ≥3% more frequently in the combined golimumab groups than placebo				
Sinusitis	9 (11.5)	19 (25.3)	17 (21.8)	10 (12.8)
Pneumonia	4 (5.1)	7 (9.3)	8 (10.3)	5 (6.4)
Nausea	1 (1.3)	2 (2.7)	6 (7.7)	3 (3.8)
Injection site erythema	0 (0)	2 (2.7)	4 (5.1)	4 (5.1)
Patients with ≥1 infections	54 (69.2)	50 (66.7)	55 (70.5)	56 (71.8)
Patients with ≥1 serious adverse events	16 (20.5)	24 (32.0)	24 (30.8)	22 (28.2)
Patients with common serious adverse events occurring in >2 patients in the combined golimumab groups				
Asthma exacerbation†	7 (9.0)	12 (16.0)	6 (7.7)	9 (11.5)
Pneumonia	1 (1.3)	3 (4.0)	5 (6.4)	2 (2.6)
Cellulitis	0 (0)	1 (1.3)	1 (1.3)	2 (2.6)
Sepsis	0 (0)	1 (1.3)	0 (0)	2 (2.6)
Chest pain	0 (0)	0 (0)	1 (1.3)	2 (2.6)

INTERLEUKIN 17?

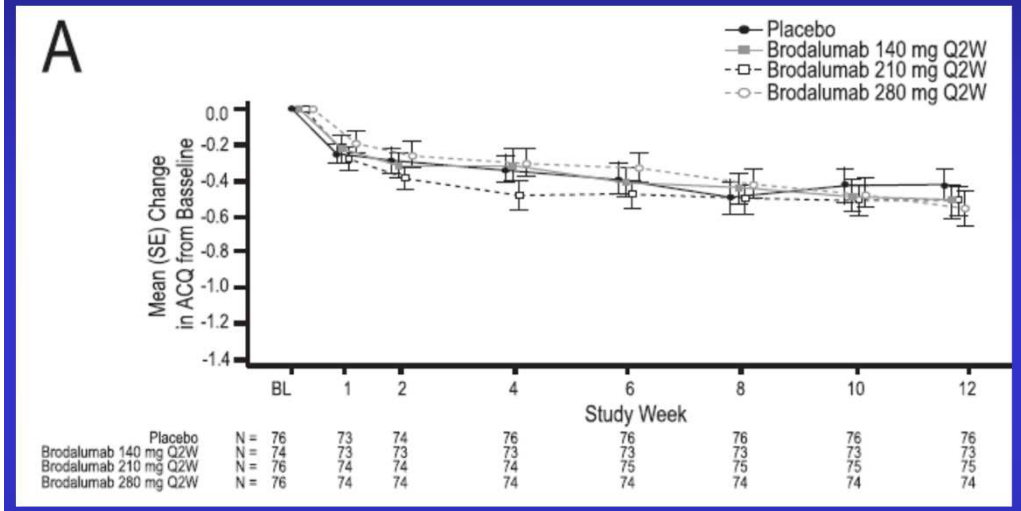


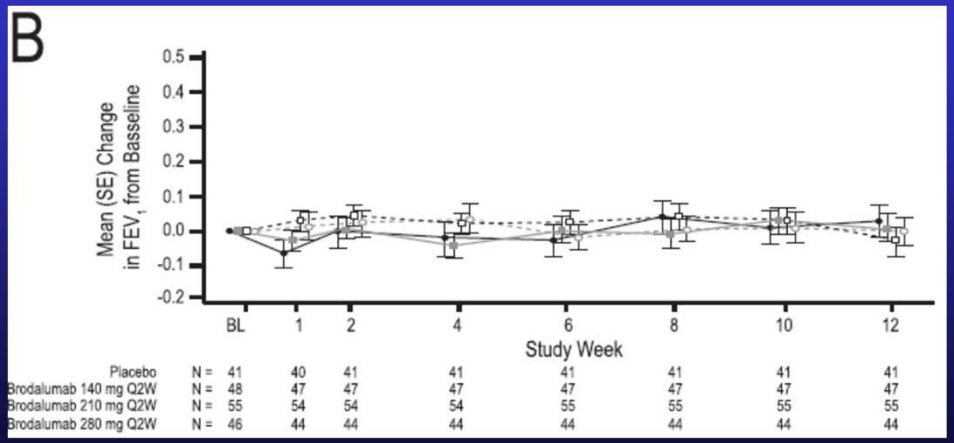


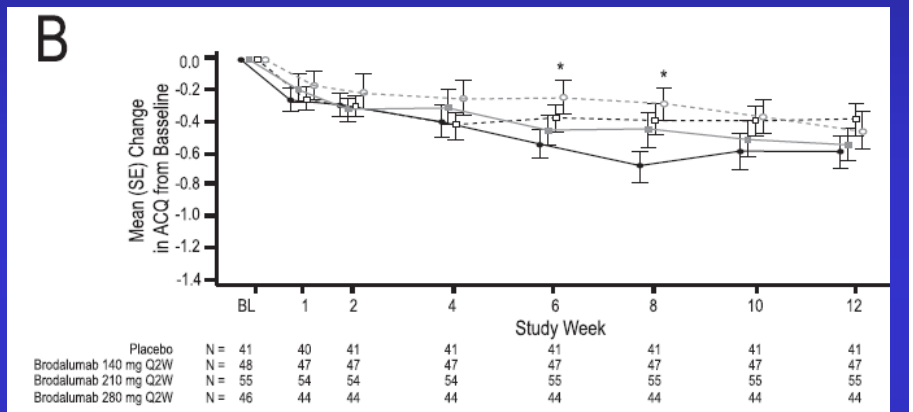
Randomized, Double-Blind, Placebo-controlled Study of Brodalumab, a Human Anti–IL-17 Receptor Monoclonal Antibody, in Moderate to Severe Asthma

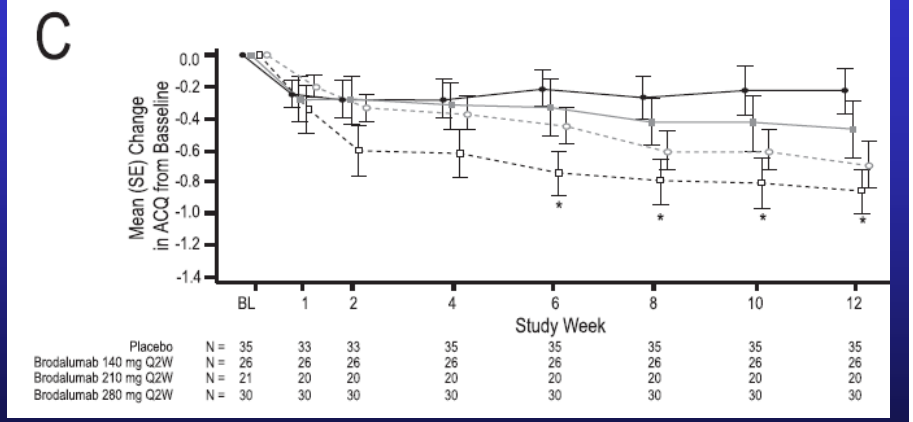
William W. Busse[1], Stephen Holgate[2], Edward Kerwin[3], Yun Chon[4], JingYuan Feng[4], Joseph Lin[4], and Shao-Lee Lin[4]

AJRCCM 2013

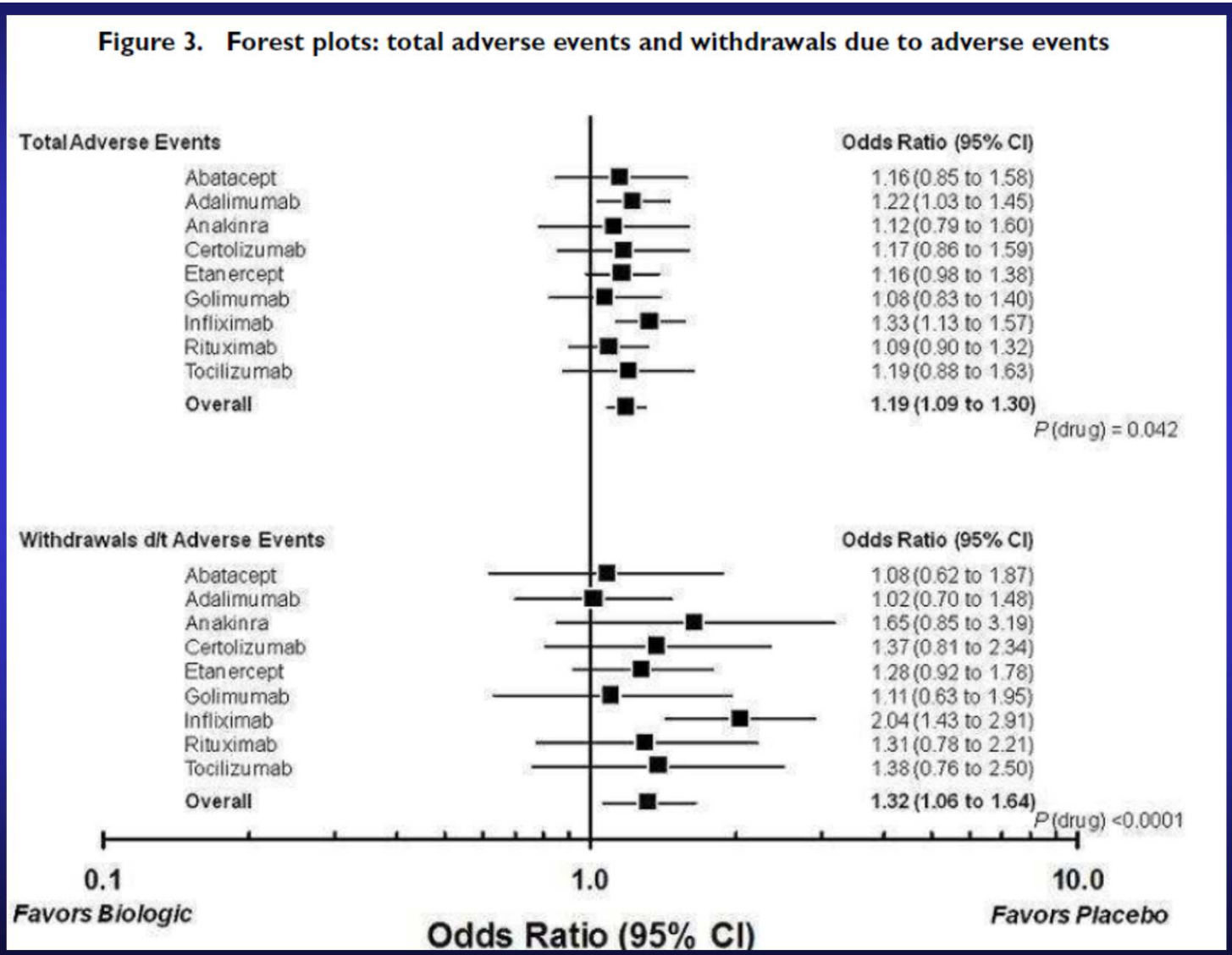








Adverse effects of biologics: a network meta-analysis and Cochrane overview (Review)



Cochrane 2011

TREATMENT	COMMON AEs	SPECIAL OR SEVERE AEs
Anti-IgE (Omalizumab, Xolair ™)	Nasopharyngitis, headache, induration at injection site (<10%)	Anaphylaxis-like reactions (~ 0.09%) Churg-Strauss S. (exceptional case reports)
Anti IL-5 (Mepolizumab, Nucala ™)	Nasopharyngitis, headache, upper respiratory infection (10-25% of pats. Injection site reaction (<10% of PTS)	Anti-mepolizumab Ab detection (5%). 1 case of anaphylaxis with s.c. administration
Anti IL-5 (Reslizumab)	Similar occurrence in placebo and active groups	2 cases of anaphylaxis (0.05%) with i.v. administration
Anti IL-4/IL-13 (Dupilumab)	Pharyngitis, headache (8-13%). Injection site reaction (30%)	1 case of angioedema. 4/52 (7%) hyper eos in the active group
Anti IL-13 (Lebrikizumab)	Injection site reactions (~ 10%). Similar rate of AEs in active and placebo groups, mostly mild.	1 case of Lofgren syndrome and 1 case of low platelet probably treatment-related
Anti IL-13 (Tralokinumab)	asthma, headache and nasopharyngitis more frequent in active (6-13%)	Urinary tract infection (4%) Increased eos (2-6%)

The safety of Mabs for the tretment of asthma.
Passalacqua G et al, EXP OPIN DRUG SAF 2016

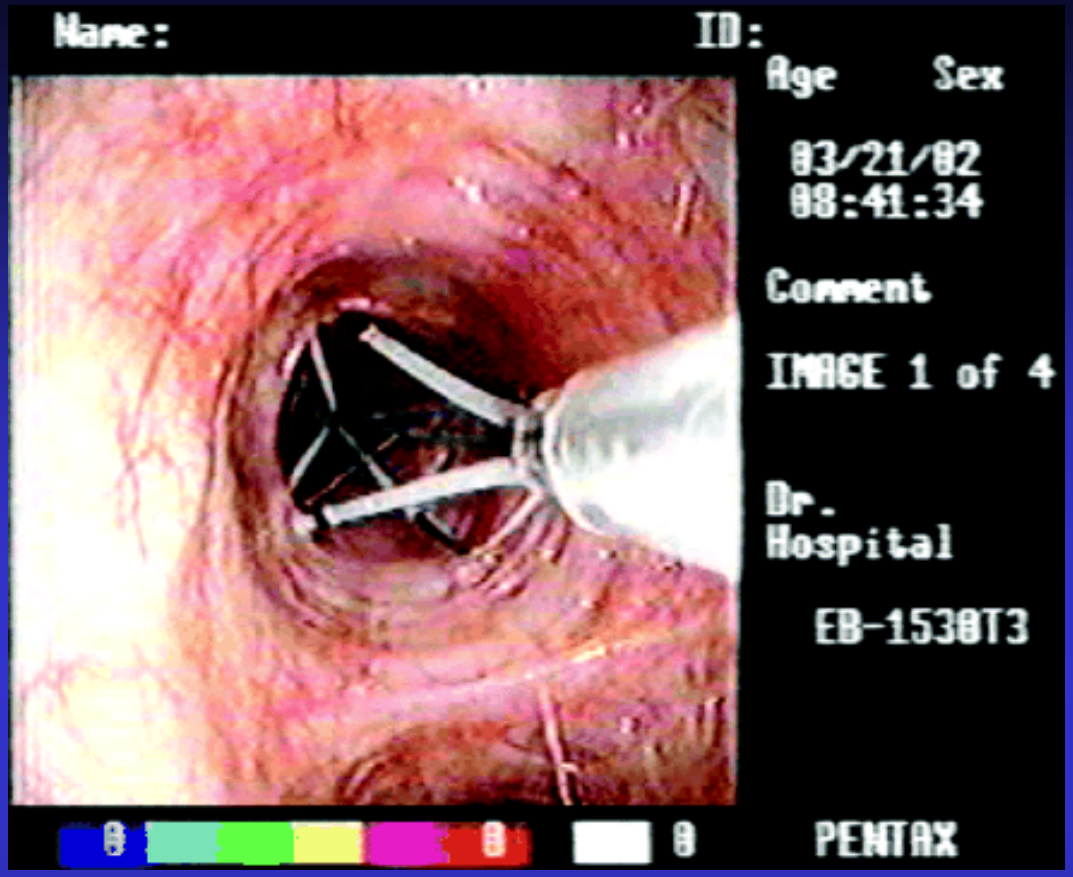
CONCLUSION

Mabs are a versatile and promising approach for severe asthma

They are not totally devoid of side effects

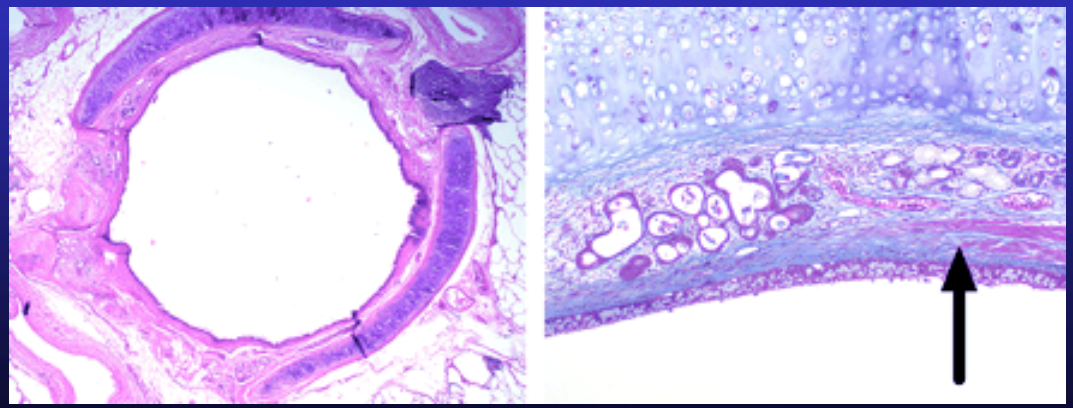
Mediators and cytokines ofte overlap in action, therefore the selective blockage of one of them could result to be clinically irrelevant

Biological agents, together with AIT remain a reasonable paradigm of personalized medicine



Termoplastica Bronchiale (bronchial thermoplasty)

Ablazione del muscolo liscio dei bronchi segmentari e subsegmentari, mediante applicazione endoscopica di radiofrequenza a 460 kHz



REVIEW Open Access

Therapeutic interventions in severe asthma

Giorgio Walter Canonica[1*], Gianenrico Senna[2], Patrick D. Mitchell[3], Paul M. O'Byrne[3], Giovanni Passalacqua[1] and Gilda Varricchi[4]

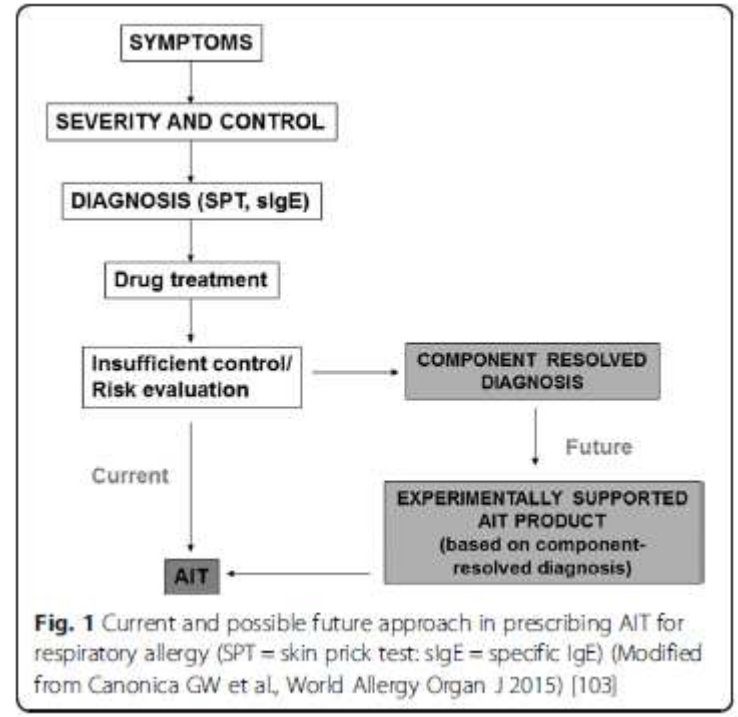
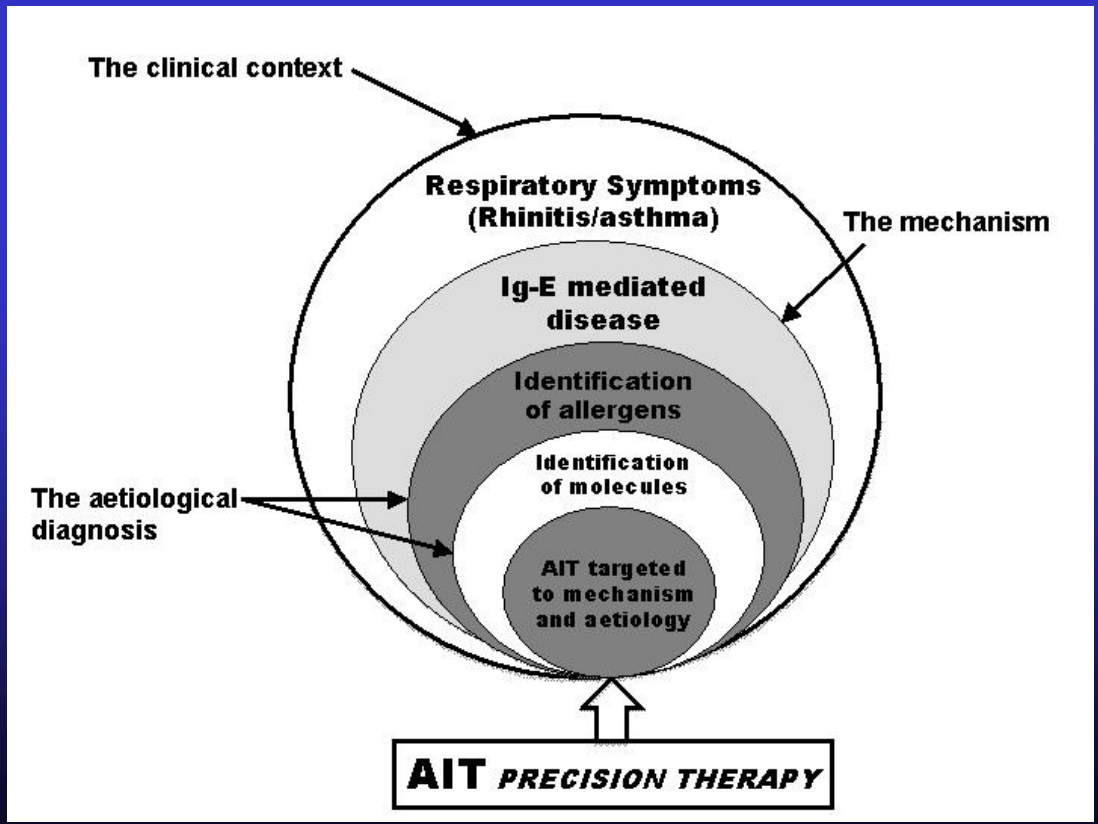


Fig. 1 Current and possible future approach in prescribing AIT for respiratory allergy (SPT = skin prick test; sIgE = specific IgE) (Modified from Canonica GW et al., World Allergy Organ J 2015) [103]

Passalacqua G, Canonica GW. WAO J 2015



The path to personalized medicine in asthma

Diego Bagnasco, Matteo Ferrando, Stefano Bernardi, Giovanni Passalacqua & Giorgio Walter Canonica

Bagnasco et al.,Exp.Rev.Resp.Med.2016

Future scenario in Allergy & Asthma treatment

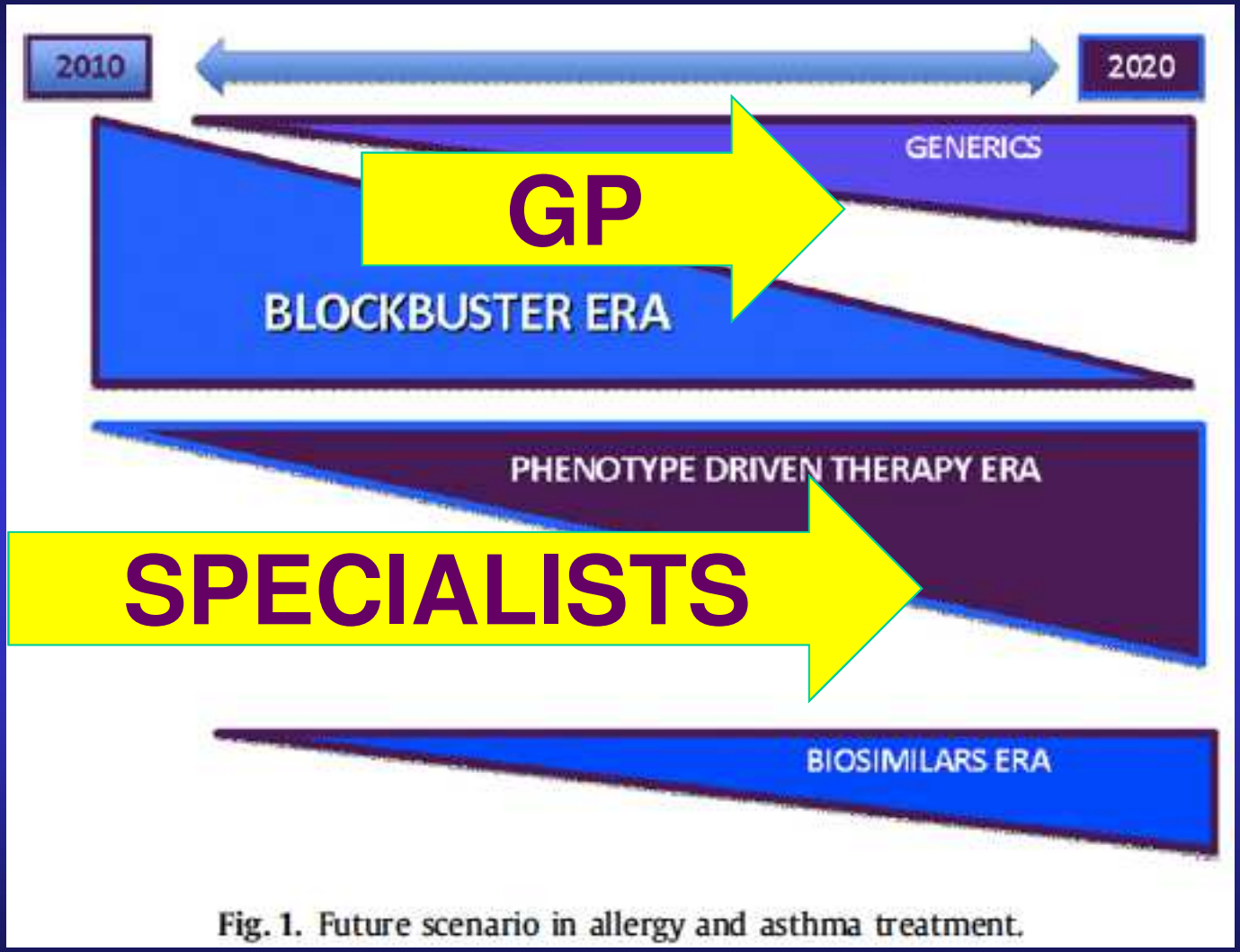


Fig. 1. Future scenario in allergy and asthma treatment.

Braido, Holgate, Canonica. Pulm.Pharm.Ther. 2012

OPEN PROBLEMS:

The definition of “severe asthma”

Predictive biomarkers?

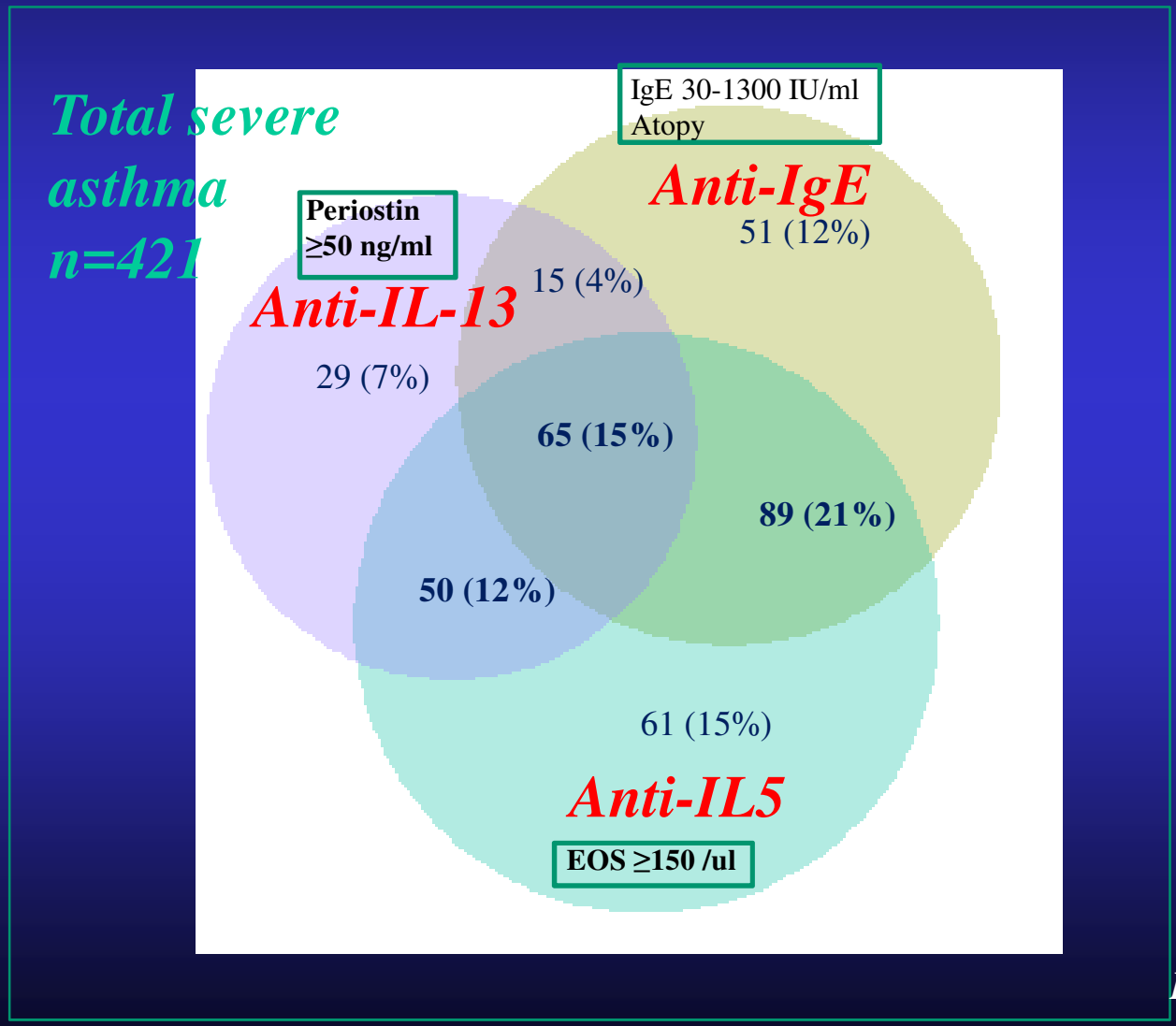
Unequivocal definition of hypereosinophilia

Cost/benefit? Safety?

Effectiveness in real life?

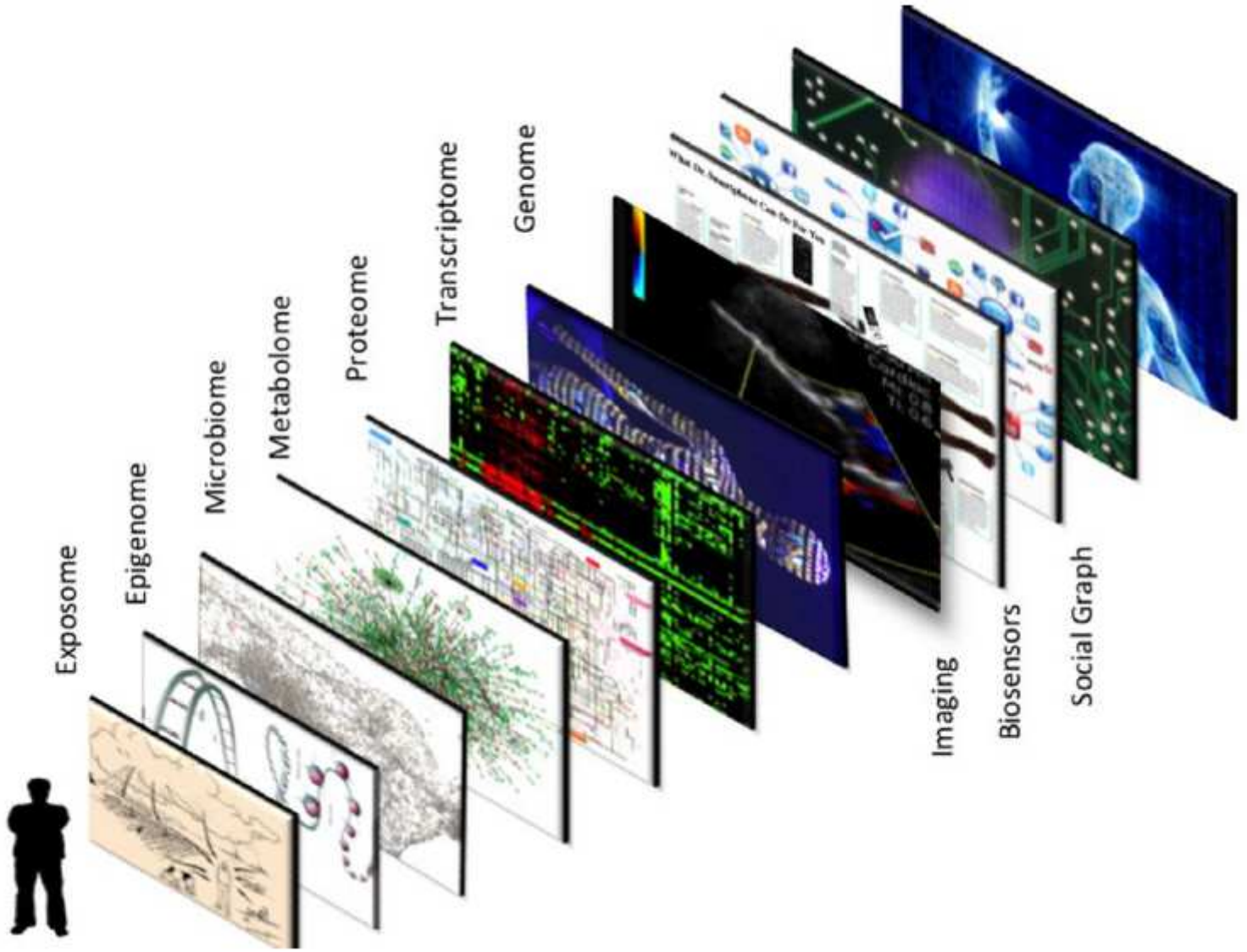
Potential anti-Th2 treatment approaches in severe asthma

Assuming anti-IL5, anti-IgE and anti-IL13 available



Stelios Pavlidis

Data from UBIOPRED



INDIVIDUALIZED MEDICINE From Pre-Womb to Tomb

Eric J. Topol, MD

Cell, 2014

GRAZIE !!!!

passalacqua@unige.it