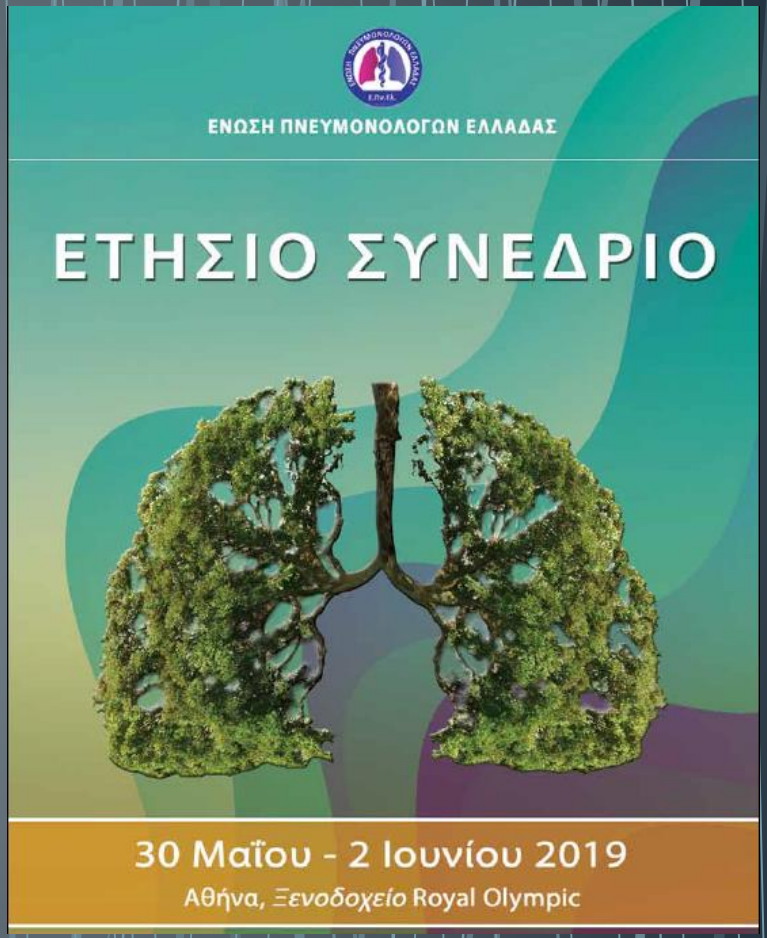
ΕΠΙΛΕΓΟΝΤΑΣ ΤΟ ΣΩΣΤΟ ΒΙΟΛΟΓΙΚΟ ΠΑΡΑΓΟΝΤΑ ΣΤΟ ΑΣΘΜΑ

ΠΕΤΡΟΣ ΜΠΑΚΑΚΟΣ
ΑΝΑΠΛΗΡΩΤΗΣ ΚΑΘΗΓΗΤΗΣ ΠΝΕΥΜΟΝΟΛΟΓΙΑΣ
Α' ΠΑΝ/ΚΗ ΠΝΕΥΜ/ΚΗ ΚΛΙΝΙΚΗ
Ν.Ν.Θ.Α «ΣΩΤΗΡΙΑ»



ΑΡΧΙΚΑ…

Τα βήματα αξιολόγησης του σοβαρού – μη ελεγχόμενου άσθματος

Step 1: Determining that the patient has asthma

- ***Λανθασμένη διάγνωση άσθματος αναφέρεται στη βιβλιογραφία σε ποσοστά 12–30%***

TABLE 6 Diseases which can masquerade as severe asthma

Adults

- Dysfunctional breathlessness/vocal cord dysfunction
- Chronic obstructive pulmonary disease
- Hyperventilation with panic attacks
- Bronchiolitis obliterans
- Congestive heart failure
- Adverse drug reaction (*e.g.* angiotensin-converting enzyme inhibitors)
- Bronchiectasis/cystic fibrosis
- Hypersensitivity pneumonitis
- Hypereosinophilic syndromes
- Pulmonary embolus
- Herpetic tracheobronchitis
- Endobronchial lesion/foreign body (*e.g.* amyloid, carcinoid, tracheal stricture)
- Allergic bronchopulmonary aspergillosis
- Acquired tracheobronchomalacia
- Churg–Strauss syndrome

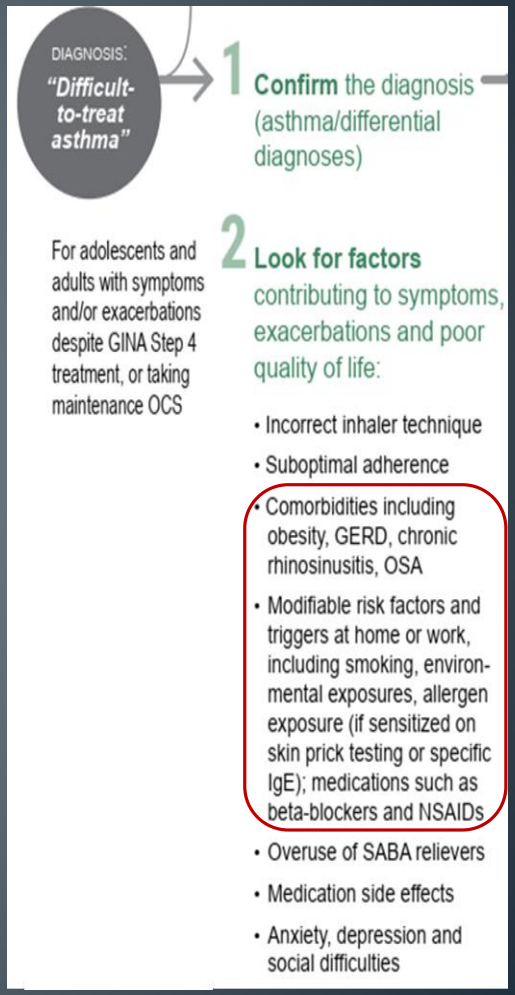
ΣΤΗ ΣΥΝΕΧΕΙΑ…

Step 2: assessing comorbidities and contributory factors

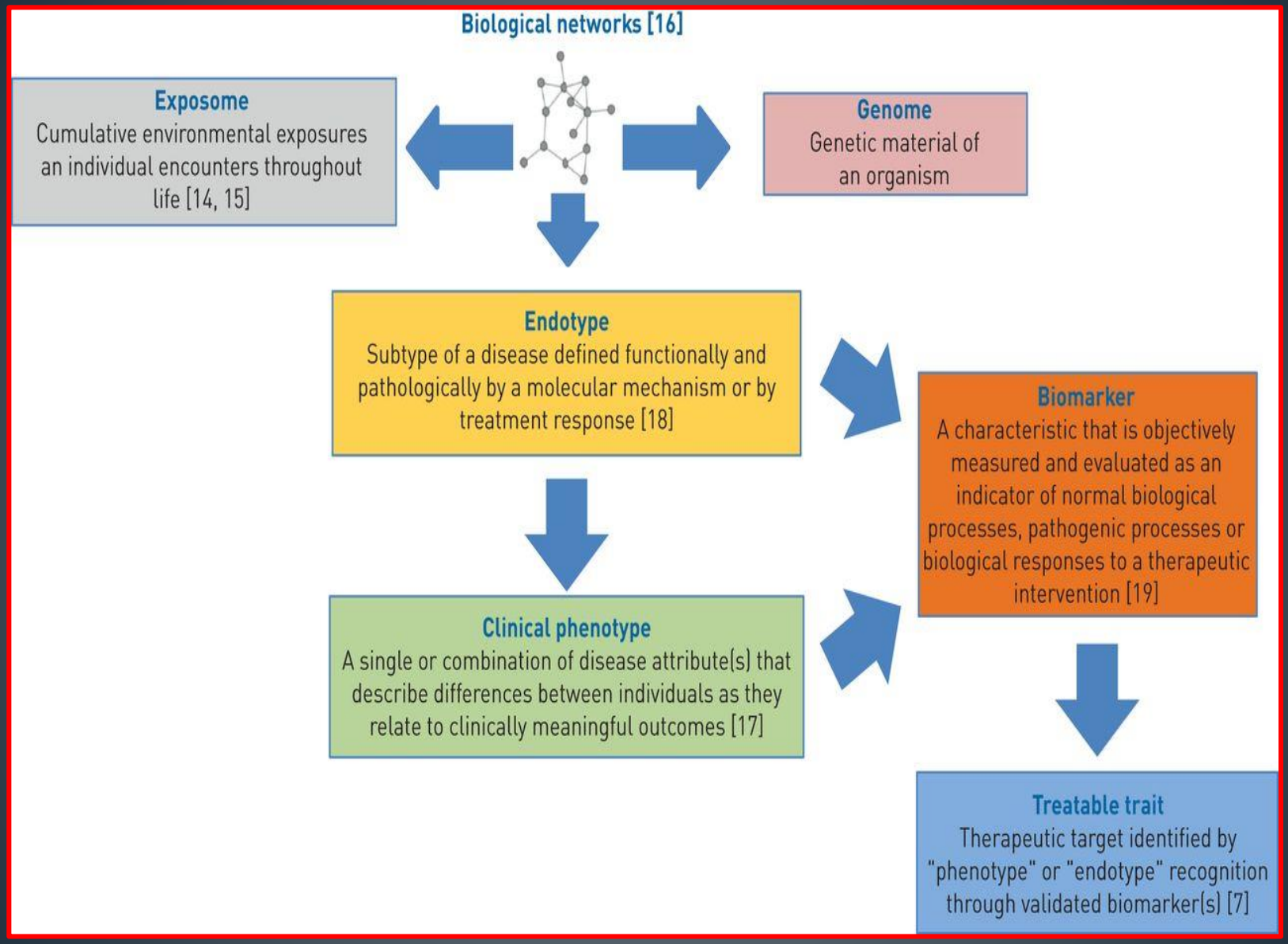
TASK FORCE REPORT
ERS/ATS GUIDELINES ON SEVERE ASTHMA

TABLE 7 Comorbidities and contributory factors

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



Chung KF. et al ERJ. 2014,
Diagnosis and Management of Difficult-to-treat and Severe Asthma in adolescent and adult patients GINA 2018

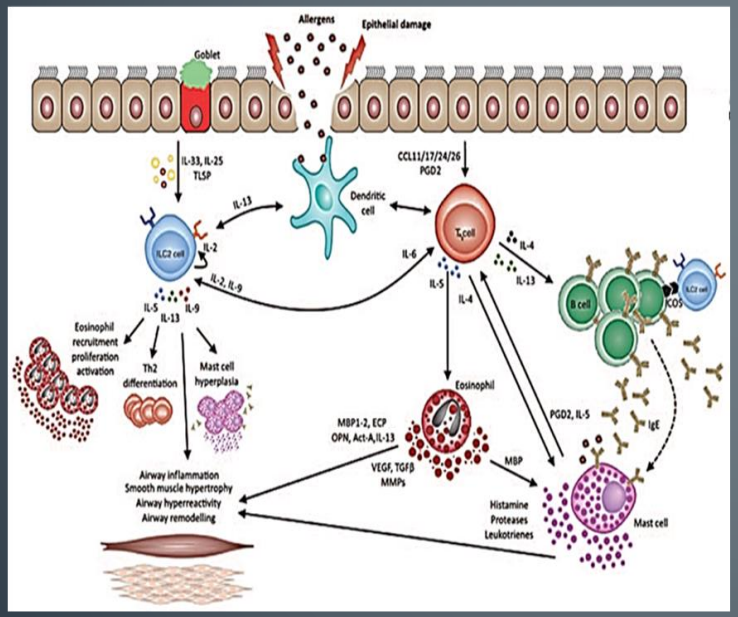


Agustí A et al. Eur Respir J 2017

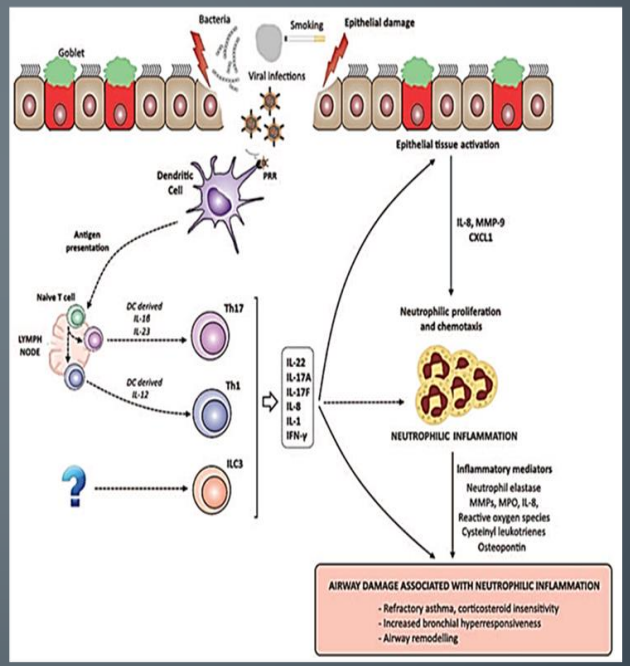
ΦΑΙΝΟΤΥΠΟΙ ΣΟΒΑΡΟΥ ΑΣΘΜΑΤΟΣ

ΕΔΩ ΞΕΚΙΝΑ Η ΣΤΟΧΕΥΜΕΝΗ ΘΕΡΑΠΕΙΑ

T2-HIGH ASTHMA

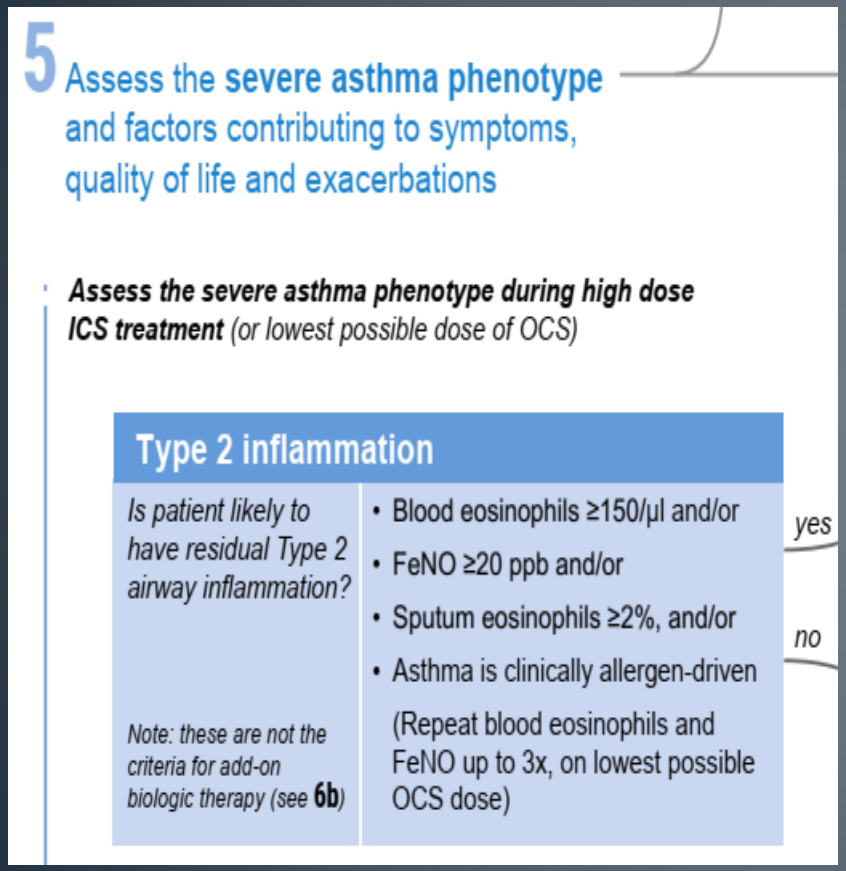


T2-LOW ASTHMA



Samitas K, Zervas E, Gaga M. Curr Opin Pulm Med 2017

Η ΑΞΙΑ ΤΗΣ ΑΠΟΚΑΛΥΨΗΣ ΤΟΥ ΦΑΙΝΟΤΥΠΟΥ ΚΑΙ ΕΝΔΟΤΥΠΟΥ ΤΗΣ ΝΟΣΟΥ



Investigate for comorbidities/differential diagnoses *and treat/refer as appropriate*

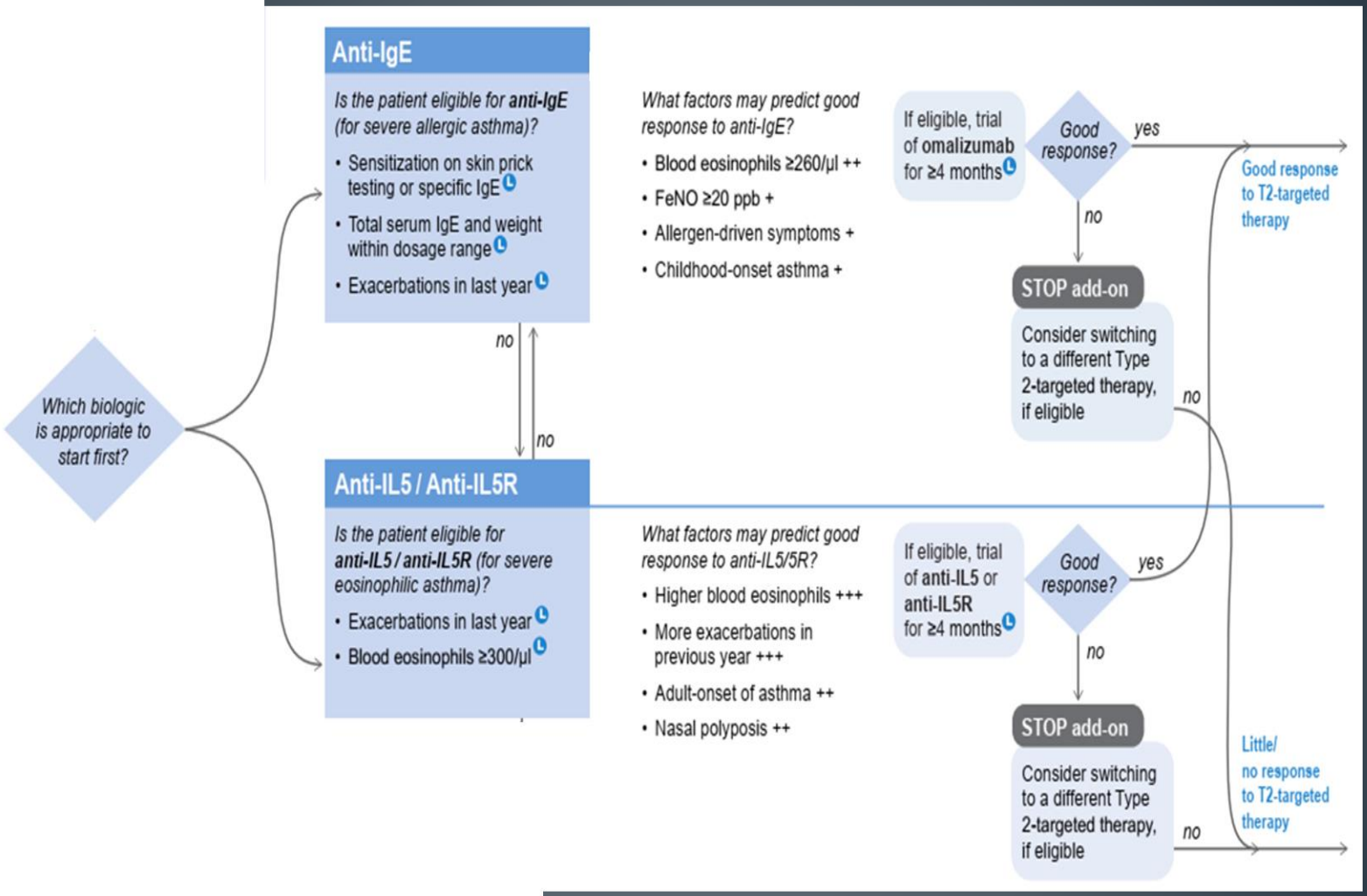
- Consider: CBC, CRP, IgG, IgA, IgM, IgE, fungal precipitins; CXR and/or HRCT chest; DLCO
- Skin prick testing or specific IgE for relevant allergens, if not already done
- Other directed testing (e.g. ANCA, CT sinuses, BNP, echocardiogram) based on clinical suspicion

Consider need for social/psychological support

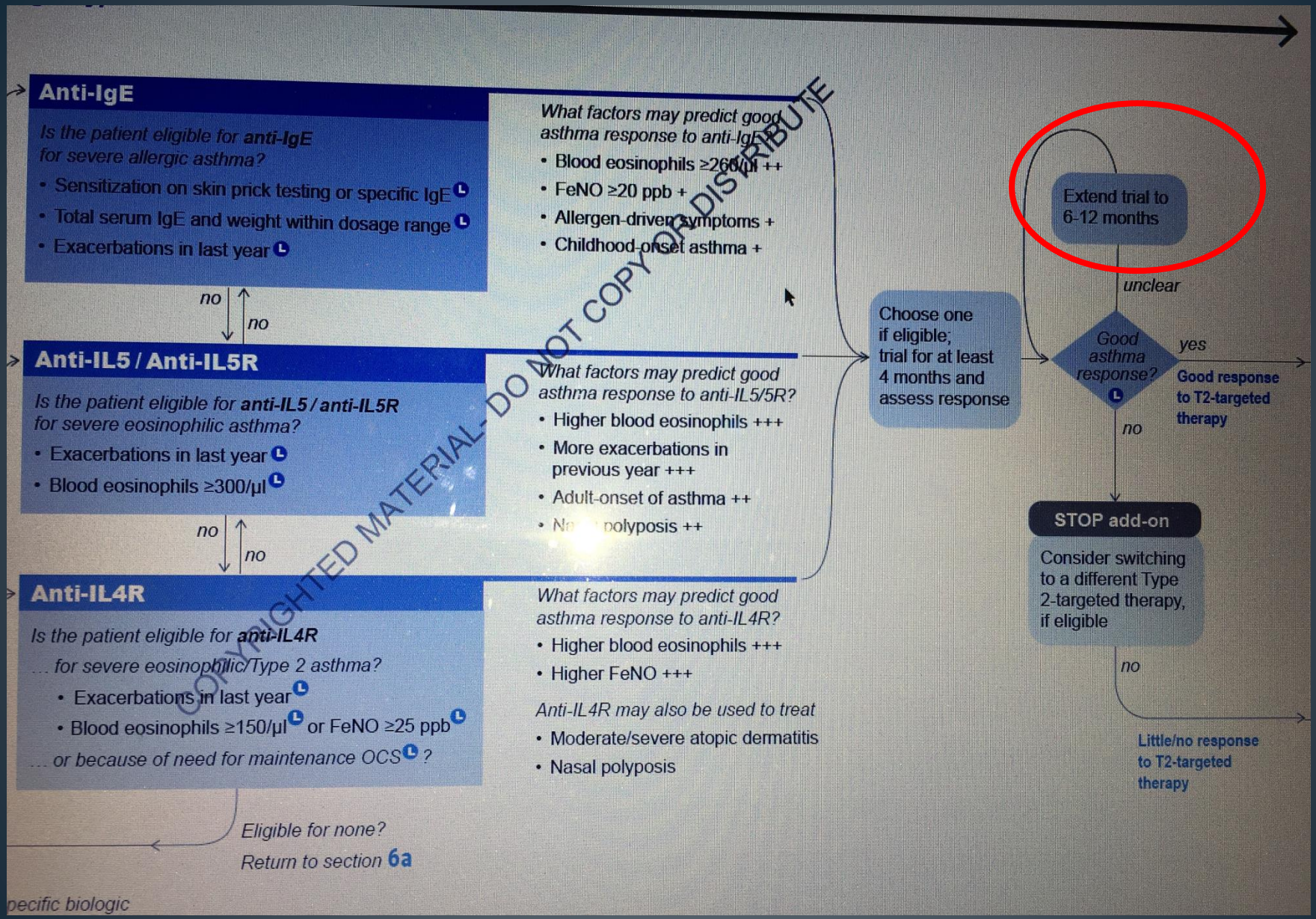
Involve multidisciplinary team care (if available)

Invite patient to enroll in registry (if available) or clinical trial (if appropriate)

Diagnosis and Management of Difficult-to-treat and Severe Asthma in adolescent and adult patients GINA 2018



Diagnosis and Management of Difficult-to-treat and Severe Asthma in adolescent and adult patients GINA 2018



Σοβαρό άσθμα – αλληλοεπικάλυψη αλλεργικού και ηωσινοφιλικού φαινοτύπου? Define predominant phenotype

A. Allergic predominant asthma	B. Eosinophilic predominant asthma
1. Early onset	1. Late onset
2. ***SPT/RAST (+) with clinically significant allergies****	2. SPT/RAST (-) or (+) with no clinically significant allergies
3. IgE > 100 IU/ml	3. IgE < 100 IU/ml
4. Allergic rhinitis	4. Nasal Polyps
5. High FeNO (30-50 ppb)	5. Very high FeNO > 50 ppb
6. Blood eosinophils < 300 cells/μl	6. ***Blood eosinophils > 300 cells/μl ****

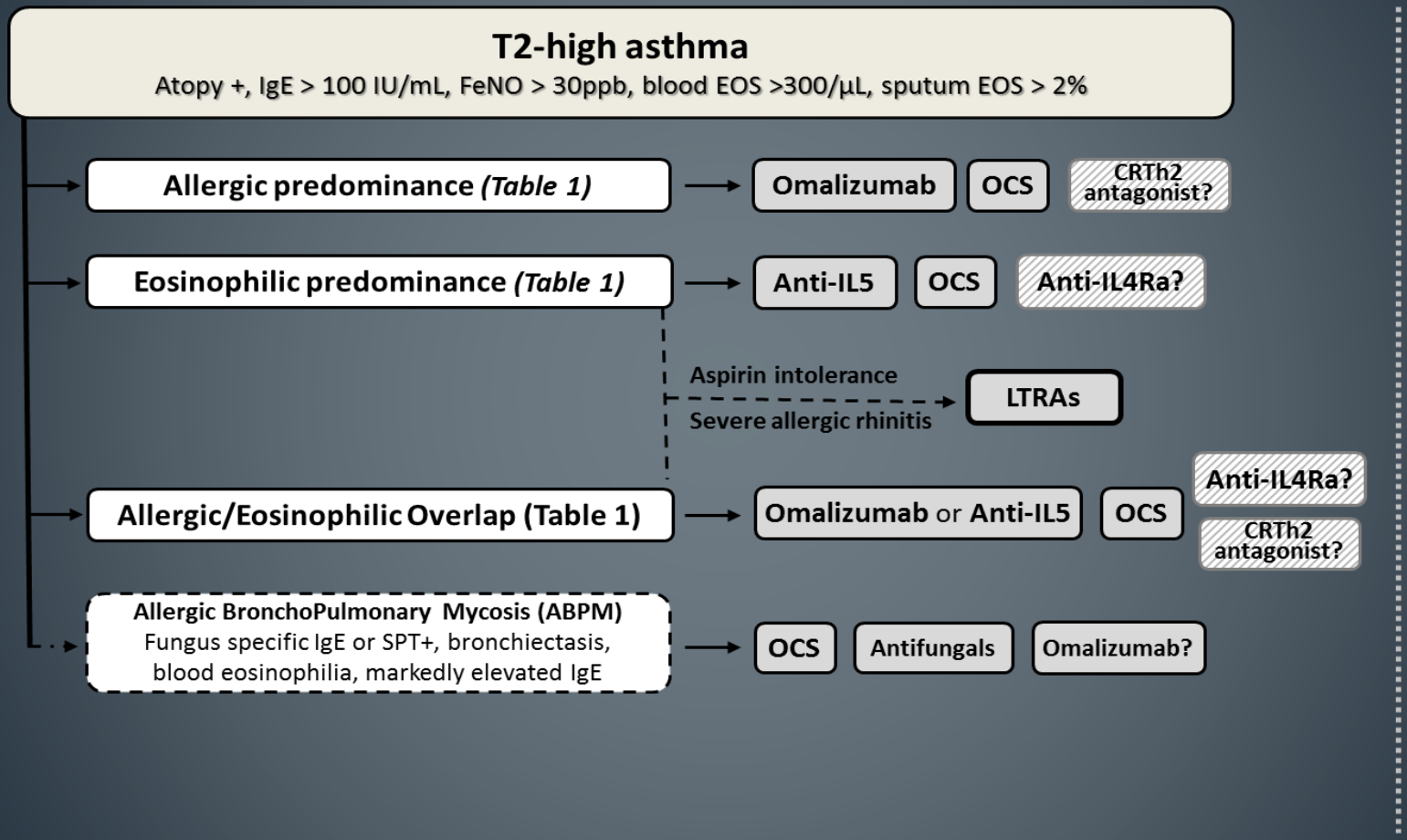
TABLE 2. Clinical features and biomarkers that can be used to differentiate between allergic and eosinophilic severe asthma. Check the number of relevant patient characteristics per column. If a patient has more features from column A or B it is more likely that he/she has allergic or eosinophilic predominant asthma, respectively. If the patient shares features from both columns, it is more likely that he/she suffers from eosinophilic/allergic overlap asthma.

Using the approach in everyday clinical practice, the ***vast majority of patients can be allocated in either allergic or eosinophilic predominant T2-high asthma***.

- In allergic predominant severe asthma, omalizumab is the treatment of choice, while
- in eosinophilic predominant asthma anti-IL-5 treatment (mepolizumab - benralizumab *s.c.* and reslizumab *i.v.* are the 3 currently approved representatives in this category) is the reasonable therapeutic approach

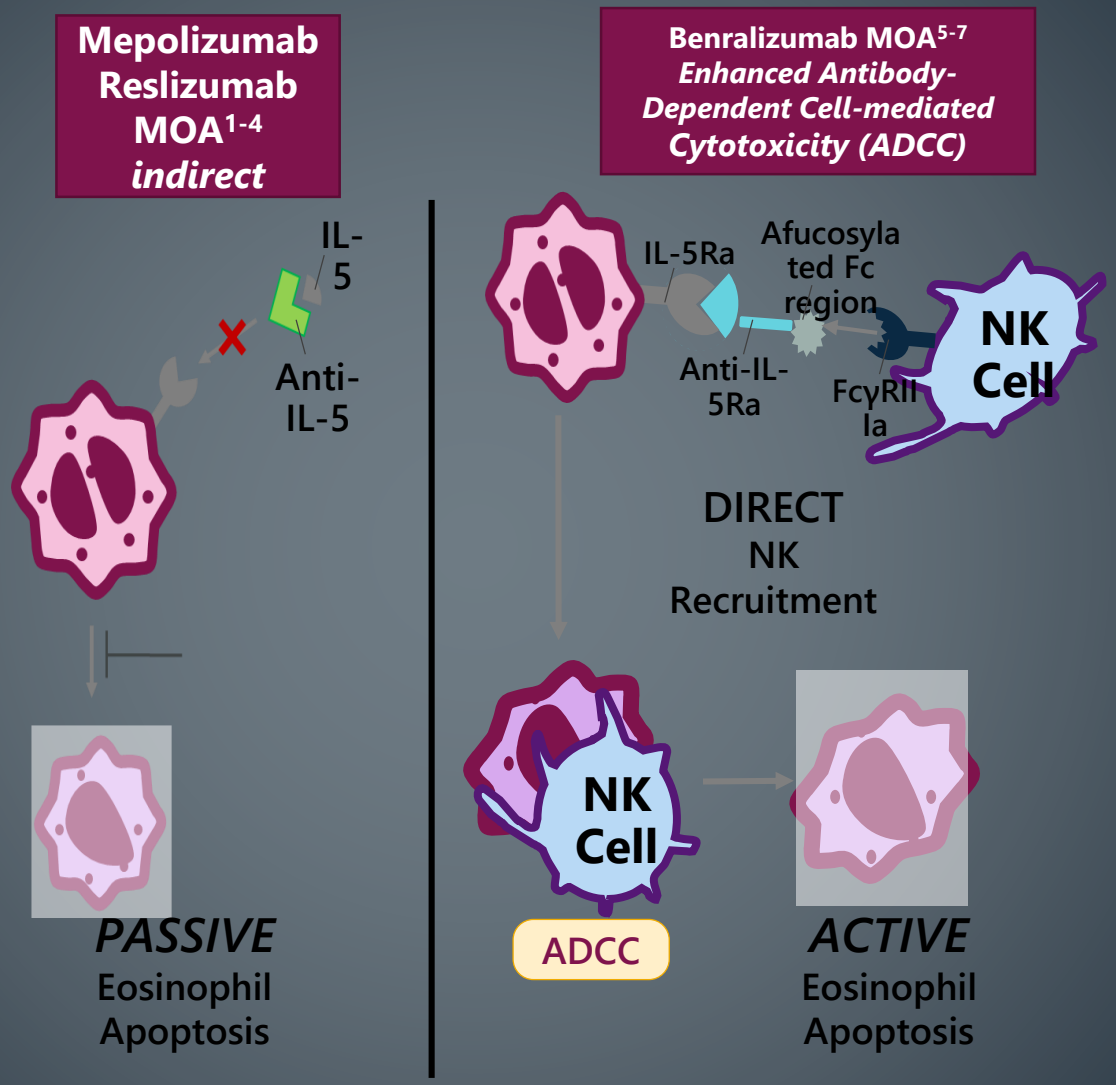
Zervas E. et al ERJ Open Res. 2018 Mar 6;4(1)

ΕΠΙΛΟΓΗ ΒΙΟΛΟΓΙΚΟΥ ΠΑΡΑΓΟΝΤΑ



Zervas E. et al ERJ Open Res. 2018 Mar 6;4(1)

Mechanism of Action: IL-5 Cytokine Targeted versus Eosinophil Targeted



IL-5 = interleukin 5; **IL-5Ra** = interleukin 5 receptor alpha; **MOA** = mechanism of action; **NK** = natural killer.

Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial

Ian D Pavord, Stephanie Korn, Peter Howarth, Eugene R Bleecker, Roland Buhl, Oliver N Keene, Hector Ortega, Pascal Chanez

- Πολυκεντρική, διπλά-τυφλή ελεγχόμενη με placebo μελέτη σε 81 κέντρα από 13 χώρες
- 621 ασθενείς
- Ιστορικό ≥ 2 παροξύνσεων το προηγούμενο έτος που απαίτησαν λήψη συστηματικών κορτικοστεροειδών
- Ηωσινοφιλική φλεγμονή: ηωσινόφιλα πτυέλων >3% OR FeNO>50ppb OR ηωσινόφιλα αίματος >300/μL OR επιδείνωση του ελέγχου του άσθματος μετά από ≤25% ελάττωση στην καθημερινή δόση συντήρησης των εισπνεόμενων ή από του στόματος κορτικοειδών
- Τυχαιοποίηση 1:1:1:1 (75, 150, 750mg IV, placebo)
- 13 εγχύσεις σε μεσοδιαστήματα 4 εβδομάδων

Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial

Ian D Pavord, Stephanie Korn, Peter Howarth, Eugene R Bleecker, Roland Buhl, Oliver N Keene, Hector Ortega, Pascal Chanez

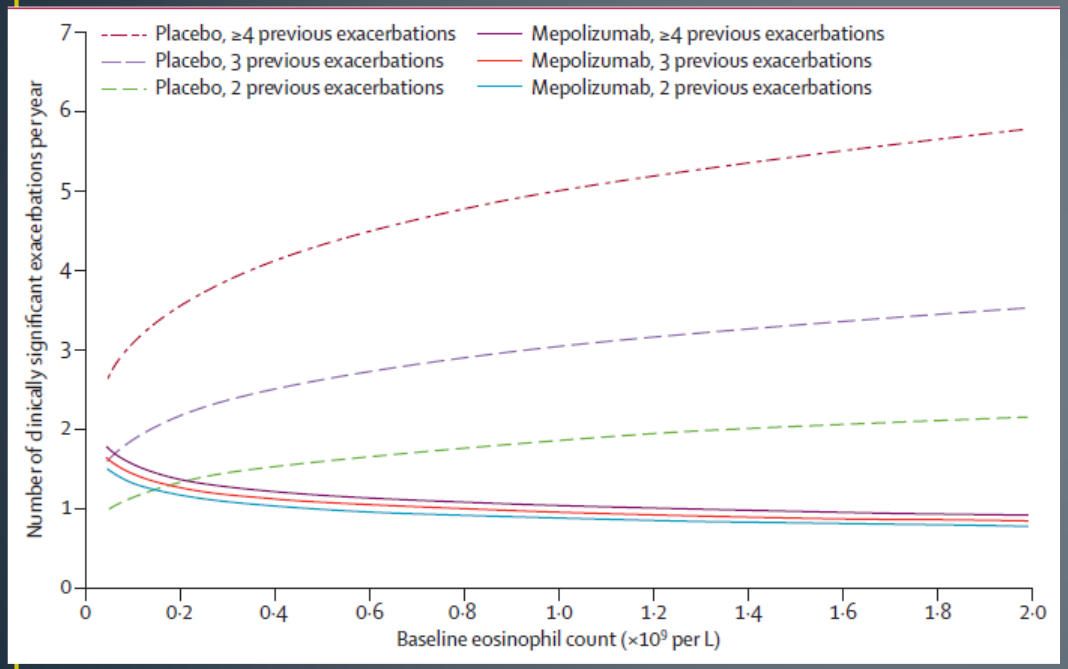
	Placebo group (n=155)	75 mg mepolizumab group (n=153)	250 mg mepolizumab group (n=152)	750 mg mepolizumab group (n=156)
Women	97 (63%)	104 (68%)	93 (61%)	93 (60%)
Age (years)	46·4 (11·3)	50·2 (10·8)	49·4 (11·6)	48·6 (11·1)
White ethnic origin	140 (90%)	139 (91%)	135 (89%)	140 (90%)
Body-mass index (kg/m²)	28·3 (6·1)	28·4 (6·0)	28·3 (5·9)	28·9 (5·8)
Former smoker	34 (22%)	31 (20%)	31 (20%)	37 (24%)
Duration of asthma (years)	17·9 (13·7)	19·0 (14·1)	20·4 (13·9)	19·1 (15·3)
Use of longacting β-agonists	150 (97%)	143 (93%)	145 (95%)	151 (97%)
Maintenance use of oral corticosteroids	45 (29%)	46 (30%)	50 (33%)	47 (30%)
Daily dose (mg)*	10 (10–20)	10 (10–20)	10 (8–20)	13 (10–20)
Nasal polyps†	16 (10%)	11 (7%)	22 (14%)	13 (8%)
Atopy‡	81 (52%)	78 (51%)	76 (50%)	76 (49%)
Prebronchodilator FEV_1 (mL)	1900 (653)	1810 (637)	1850 (672)	1950 (670)
Postbronchodilator FEV_1 (mL)	2290 (773)	2150 (695)	2220 (732)	2260 (784)
Percentage of predicted prebronchodilator FEV_1	59% (15)	60% (16)	59% (17)	61% (16)
Postbronchodilator FEV_1/FVC	67% (12)	68% (12)	66% (13)	68% (20)
Score on asthma control questionnaire	2·5 (1·1)	2·2 (1·1)	2·4 (1·1)	2·3 (1·2)
Score on asthma quality of life questionnaire	4·1 (1·2)	4·2 (1·2)	4·2 (1·2)	4·2 (1·2)
Blood eosinophil count (×10⁹/L)§¶	0·28 (1·01)	0·25 (0·95)	0·23 (1·20)	0·25 (0·93)
Sputum eosinophil count (%)§¶	6·8% (2·01); n=24	13·9% (1·47); n=18	8·1% (1·79); n=23	5·8% (2·15); n=21
FE_{NO} (ppb)§¶	33·7 (0·79)	29·2 (0·76)	31·4 (0·80)	31·6 (0·81)
Severe exacerbations in previous year	3·7 (3·8)	3·7 (3·1)	3·4 (2·4)	3·5 (2·8)
Exacerbations requiring admission in previous year	40 (26%)	35 (23%)	36 (24%)	39 (25%)

Data are n (%), mean (SD), or median (IQR), unless otherwise stated. *Prednisolone equivalent. †Self reported. ‡Positive atopic status was defined as a positive radioallergosorbent test for any of four specified aeroallergens. §Values below lower limit of quantification were replaced by half the lower limit of quantification. ¶Geometric mean on $\log_e$ scale.

Table 1: **Baseline characteristics of the intention-to-treat population**

Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial

Ian D Pavord, Stephanie Korn, Peter Howarth, Eugene R Bleecker, Roland Buhl, Oliver N Keene, Hector Ortega, Pascal Chanez



	Placebo group (n=155)	75 mg mepolizumab group (n=153)	250 mg mepolizumab group (n=152)	750 mg mepolizumab group (n=156)
Adverse events leading to withdrawal	6 (4%)	5 (3%)	8 (5%)	9 (6%)
Fatal adverse events	0	0	2 (1%)	1 (<1%)
Any on-treatment serious adverse events*	25 (16%)	20 (13%)	24 (16%)	19 (12%)
Respiratory, thoracic, and mediastinal disorders	17 (11%)	11 (7%)	16 (11%)	10 (6%)
Infections	5 (3%)	7 (5%)	3 (2%)	5 (3%)
Cardiac disorders	1 (<1%)	2 (1%)	1 (<1%)	4 (3%)
Injury, poisoning, and procedural complications	2 (1%)	1 (<1%)	2 (1%)	1 (<1%)
Gastrointestinal disorders	1 (<1%)	0	2 (1%)	1 (<1%)
Nervous system disorders	3 (2%)	0	0	1 (<1%)
Renal and urinary disorders	2 (1%)	0	2 (1%)	0
Vascular disorders	0	2 (1%)	1 (<1%)	1 (<1%)

*Patients can have more than one event; events shown are those reported in four or more patients across all groups.

Table 3: Adverse events

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

	DREAM (n=616)		MENSA (n=569)		Combined* (n=1185)	
	Placebo (n=155)	Mepolizumab (n=461)	Placebo (n=189)	Mepolizumab (n=380)	Placebo (n=344)	Mepolizumab (n=841)
≥150 cells per µL						
n (%)	121 (78%)	346 (75%)	157 (83%)	296 (78%)	278 (81%)	642 (76%)
Exacerbation rate per year	2·47	1·13	1·65	0·78	1·94	0·92
Rate ratio vs placebo (95% CI)	..	0·46 (0·35–0·60)	..	0·47 (0·35–0·63)	..	0·48 (0·39–0·58)
≥300 cells per µL						
n (%)	86 (55%)	216 (47%)	106 (56%)	202 (53%)	192 (56%)	418 (50%)
Exacerbation rate per year	2·66	1·11	1·98	0·78	2·19	0·89
Rate ratio vs placebo (95% CI)	..	0·42 (0·31–0·56)	..	0·39 (0·28–0·55)	..	0·41 (0·33–0·51)
≥400 cells per µL						
n (%)	64 (41%)	149 (32%)	87 (46%)	161 (42%)	151 (44%)	310 (37%)
Exacerbation rate per year	3·12	1·03	2·06	0·66	2·36	0·81
Rate ratio vs placebo (95% CI)	..	0·32 (0·23–0·46)	..	0·32 (0·22–0·46)	..	0·34 (0·27–0·44)
≥500 cells per µL						
n (%)	50 (32%)	114 (25%)	66 (35%)	124 (33%)	116 (34%)	238 (28%)
Exacerbation rate per year	3·34	0·92	2·11	0·58	2·49	0·75
Rate ratio vs placebo (95% CI)	..	0·27 (0·19–0·39)	..	0·27 (0·18–0·41)	..	0·30 (0·23–0·40)

Lancet Respir Med 2016; 4: 549–56

Προβλεπτικοί δείκτες απάντησης στο benralizumab σε ασθενείς με σοβαρό άσθμα: pooled analysis των SIROCCO και CALIMA

	Placebo	Benralizumab Q4W	Benralizumab Q8W
Annual exacerbation rate			
<150 cells per µL			
Number of patients analysed	122	101	105
Rate estimate (95% CI)	1·26 (0·98 to 1·61)	0·97 (0·72 to 1·30)	0·91 (0·67 to 1·22)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·29 (−0·71 to 0·13)	−0·35 (−0·76 to 0·06)
Rate ratio *vs* placebo (95% CI)	..	0·77 (0·52 to 1·13)	0·72 (0·49 to 1·06)
p value *vs* placebo	..	0·18	0·10
150–299 cells per µL			
Number of patients analysed	137	136	147
Rate estimate (95% CI)	1·22 (0·96 to 1·54)	0·78 (0·60 to 1·02)	0·94 (0·73 to 1·21)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·43 (−0·79 to −0·08)	−0·27 (−0·65 to 0·10)
Rate ratio *vs* placebo (95% CI)	..	0·64 (0·45 to 0·92)	0·77 (0·55 to 1·09)
p value *vs* placebo	..	0·0152	0·15
300–449 cells per µL			
Number of patients analysed	205	216	201
Rate estimate (95% CI)	1·03 (0·85 to 1·26)	0·62 (0·50 to 0·78)	0·72 (0·57 to 0·90)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·41 (−0·66 to −0·17)	−0·32 (−0·58 to −0·05)
Rate ratio *vs* placebo (95% CI)	..	0·60 (0·44 to 0·81)	0·69 (0·51 to 0·94)
p value *vs* placebo	..	0·0008	0·0178
≥450 cells per µL			
Number of patients analysed	306	295	298
Rate estimate (95% CI)	1·16 (1·00 to 1·36)	0·69 (0·58 to 0·83)	0·58 (0·48 to 0·70)
Absolute difference estimate *vs* placebo (95% CI)	..	−0·47 (−0·69 to −0·25)	−0·59 (−0·80 to −0·37)
Rate ratio *vs* placebo (95% CI)	..	0·59 (0·47 to 0·75)	0·50 (0·39 to 0·64)
p value *vs* placebo	..	<0·0001	<0·0001

The NEW ENGLAND JOURNAL of MEDICINE

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Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma

Elisabeth H. Bel, M.D., Ph.D., Sally E. Wenzel, M.D., Philip J. Thompson, M.D., Charlene M. Prazma, Ph.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., Hector G. Ortega, M.D., Sc.D., and Ian D. Pavord, D.M., for the SIRIUS Investigators*

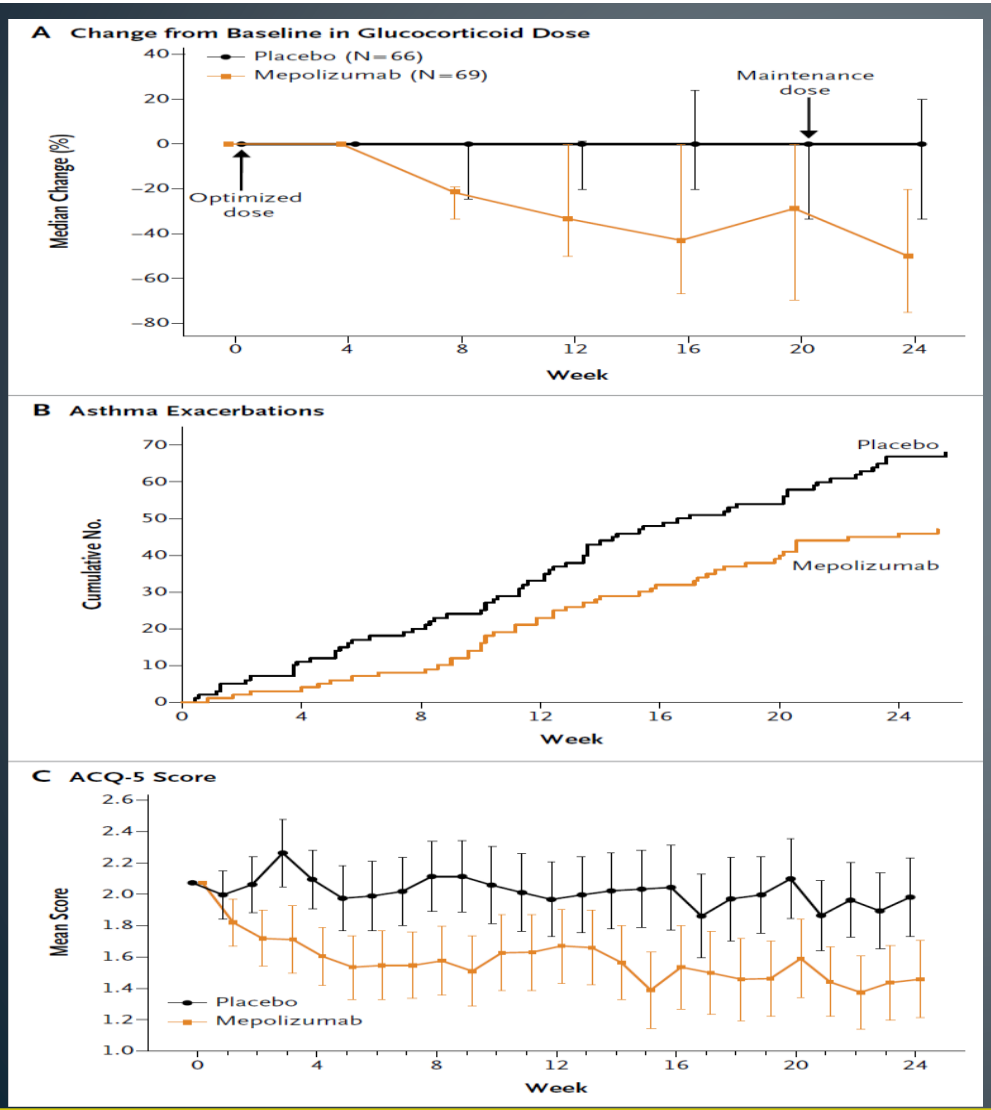
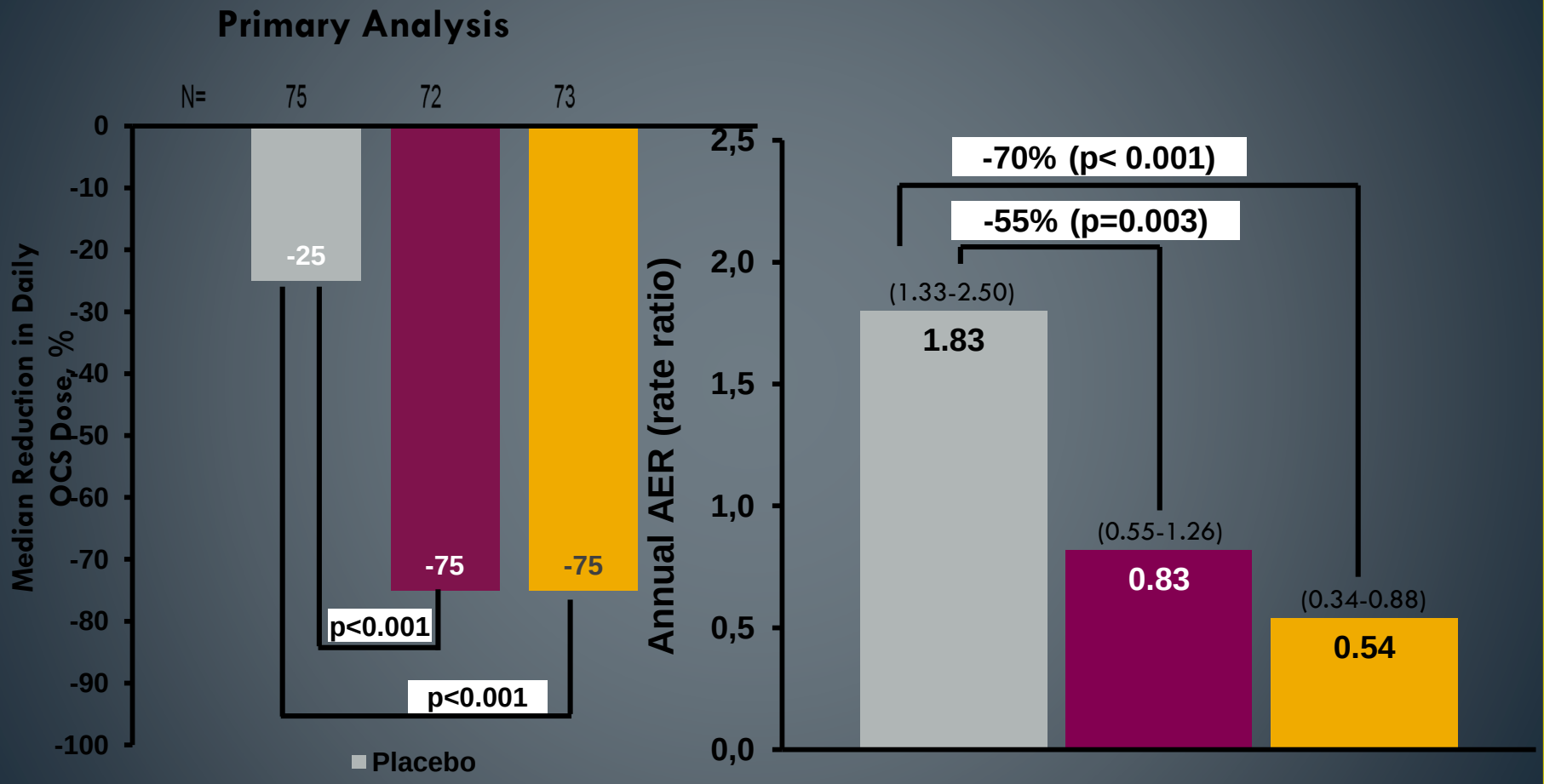


Table 1. Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Placebo (N=66)	Mepolizumab (N=69)
Mean age (range) — yr	50 (28–70)	50 (16–74)
Female sex — no. (%)	30 (45)	44 (64)
Body-mass index†	29.5±6.0	27.8±5.9
Former smoker — no. (%)	25 (38)	28 (41)
Duration of asthma — yr	20.1±14.4	17.4±11.8
Median daily oral glucocorticoid dose — mg‡		
At screening	15.0	12.5
During optimization phase	12.5	10.0
Duration of oral glucocorticoid use ≥5 yr — no. (%)	31 (47)	34 (49)
FEV_1 before bronchodilation		
Mean — liters	2.00±0.82	1.90±0.66
Percent of predicted value	57.8±18.5	59.6±17.0
FEV_1:FVC ratio before bronchodilation — %§	61±11.7	63±12.4
Percent reversibility of FEV_1	24.8±18.1	27.3±17.4
ACQ-5 score¶	2.0±1.2	2.2±1.3
SGRQ score‖	45±18	50±18
Geometric mean IgE on $\log_e$ scale — U/ml	114±1	117±1
Geometric mean blood eosinophil count on $\log_e$ scale — cells/μl**	230±1001	250±1245
Severe exacerbations in previous year — no./patient	2.9±2.8	3.3±3.4
Exacerbations in the previous year requiring hospitalization — no. (%)	9 (14)	14 (20)
History of asthma-related intubation — no. (%)	3 (5)	2 (3)

ZONDA: Το Benralizumab μειώνει σημαντικά την δόση των OCS την εβδομάδα 28 και τις παροξύνσεις παράλληλα με τη μείωση των OCS



Nair P et al. *N Engl J Med*. 2017;376:2448-2458.

ΣΩΣΤΗ ΕΠΙΛΟΓΗ ΑΣΘΕΝΩΝ

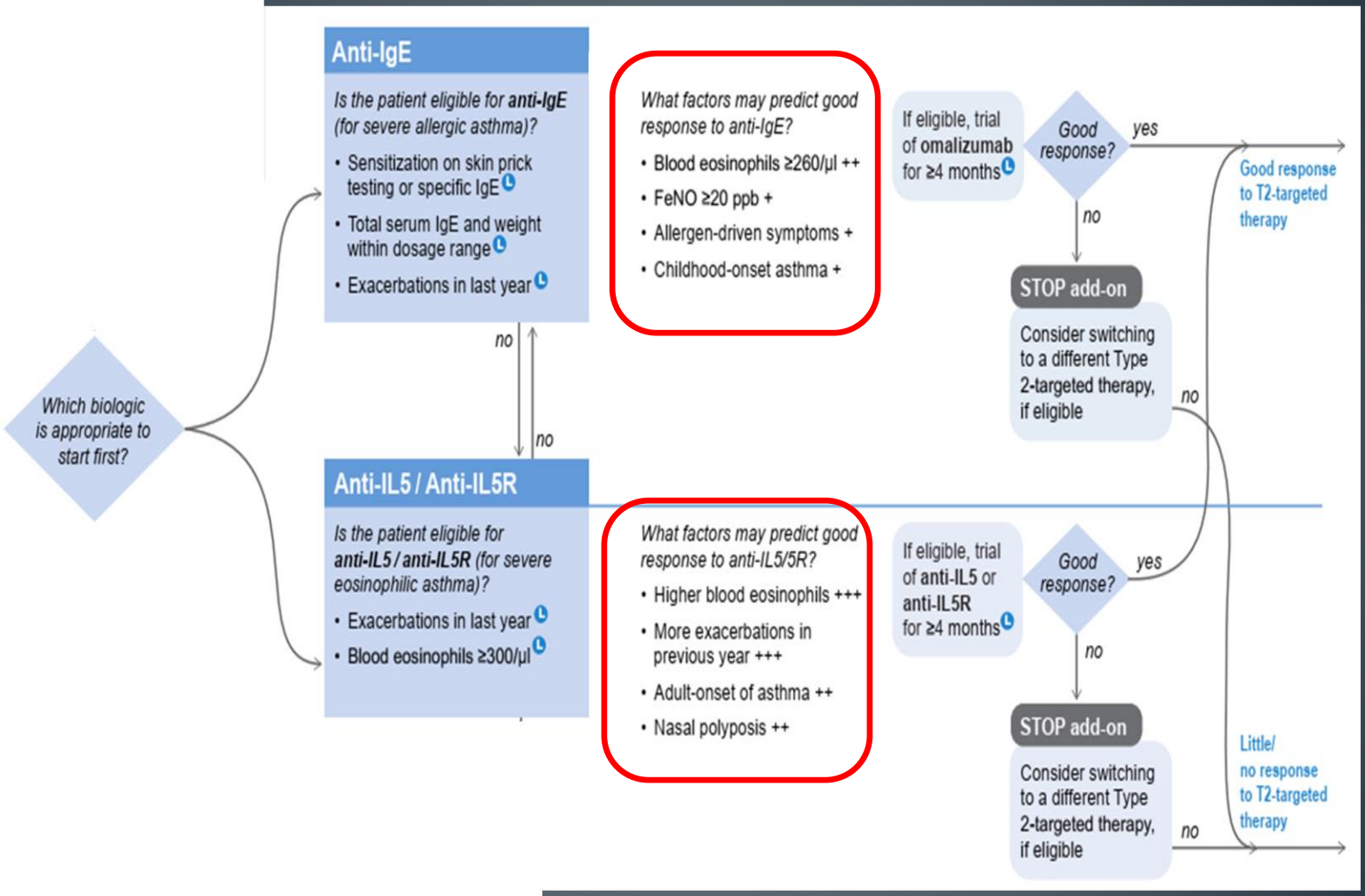
- Σοβαρό άσθμα με

  - > 2 παροξύνσεις που απαιτούν λήψη συστηματικών κορτικοειδών Ή

  - καθημερινή λήψη συστηματικών κορτικοειδών

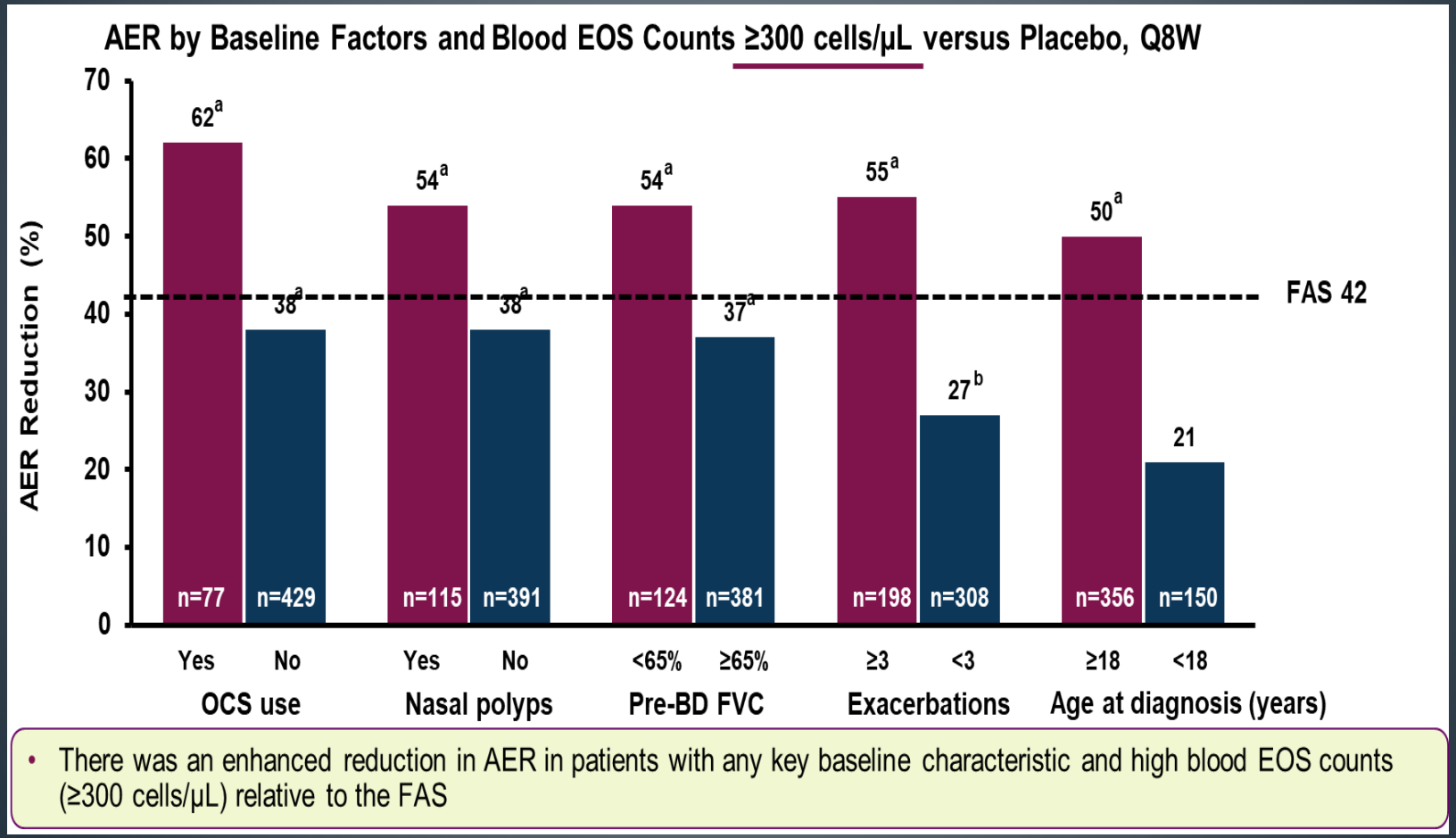
ΚΑΙ

  - εμμένουσα ηωσινοφιλική φλεγμονή (ως δείκτης τα αυξημένα ηωσινόφιλα περιφερικού αίματος)



Diagnosis and Management of Difficult-to-treat and Severe Asthma in adolescent and adult patients GINA 2018

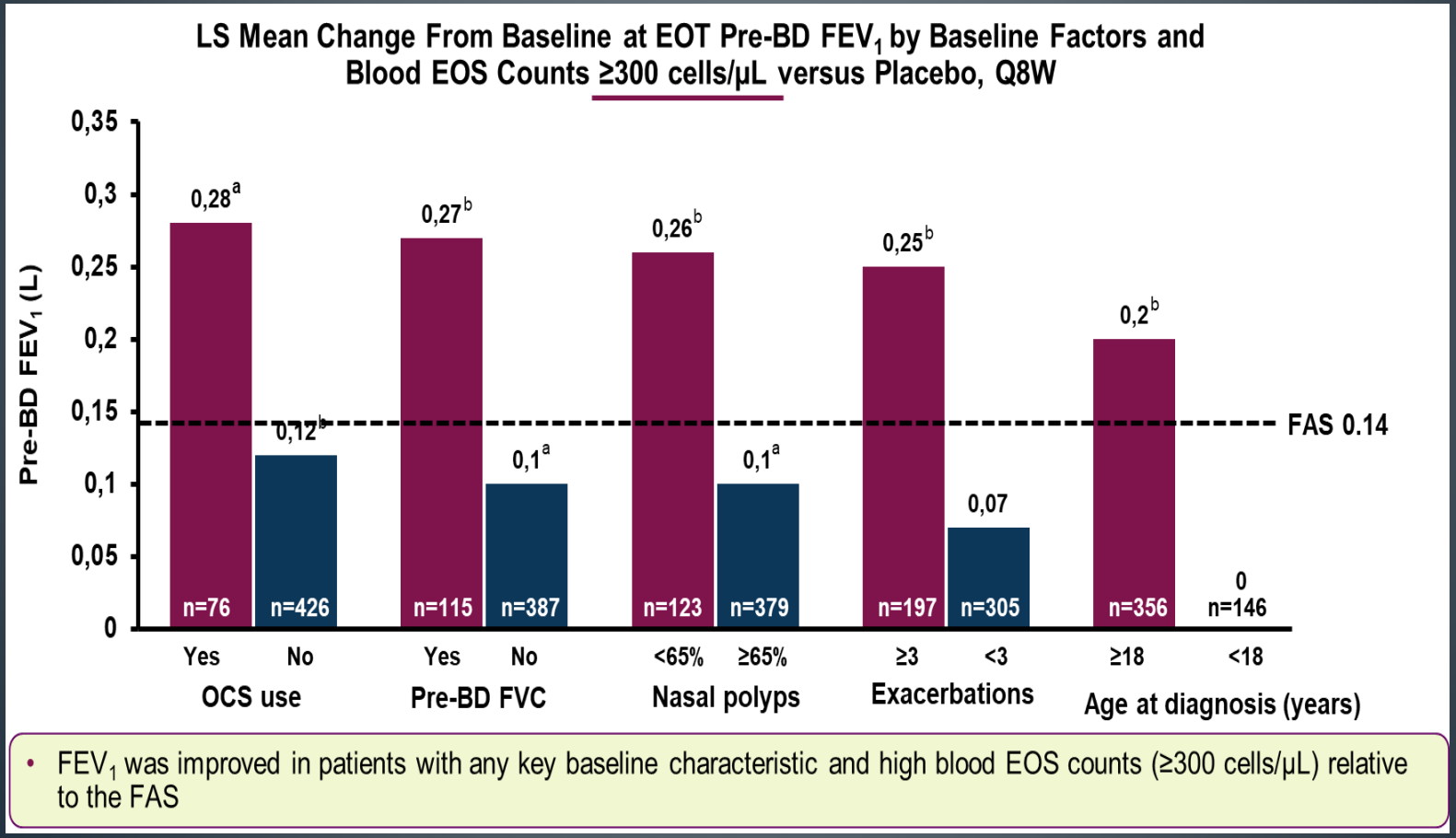
Μείωση παροξύνσεων σε σχέση με βασικά χαρακτηριστικά της νόσου και αριθμό EOS αίματος (Pooled SIROCCO and CALIMA; ≥300 EOS)



- There was an enhanced reduction in AER in patients with any key baseline characteristic and high blood EOS counts (≥300 cells/μL) relative to the FAS

Bleecker ER, Wechsler ME, Mark FitzGerald J, et al. Eur Respir J 2018; Oct 18;52(4)

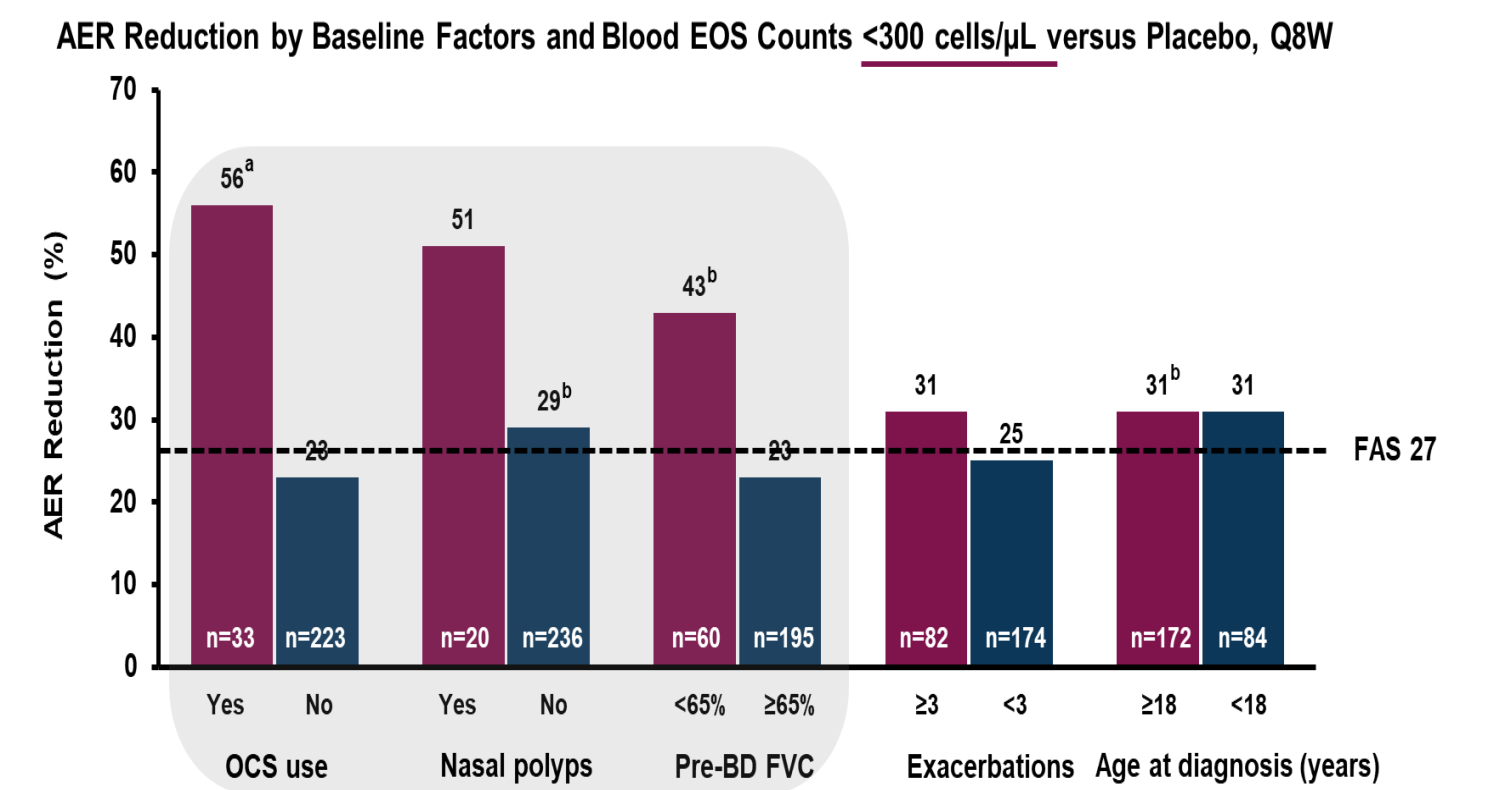
Βελτίωση FEV_1 σε σχέση με βασικά χαρακτηριστικά της νόσου και αριθμό EOS αίματος (Pooled SIROCCO and CALIMA; ≥300 EOS)



- FEV_1 was improved in patients with any key baseline characteristic and high blood EOS counts (≥300 cells/µL) relative to the FAS

Bleecker ER, Wechsler ME, Mark FitzGerald J, et al. Eur Respir J 2018; Oct 18;52(4)

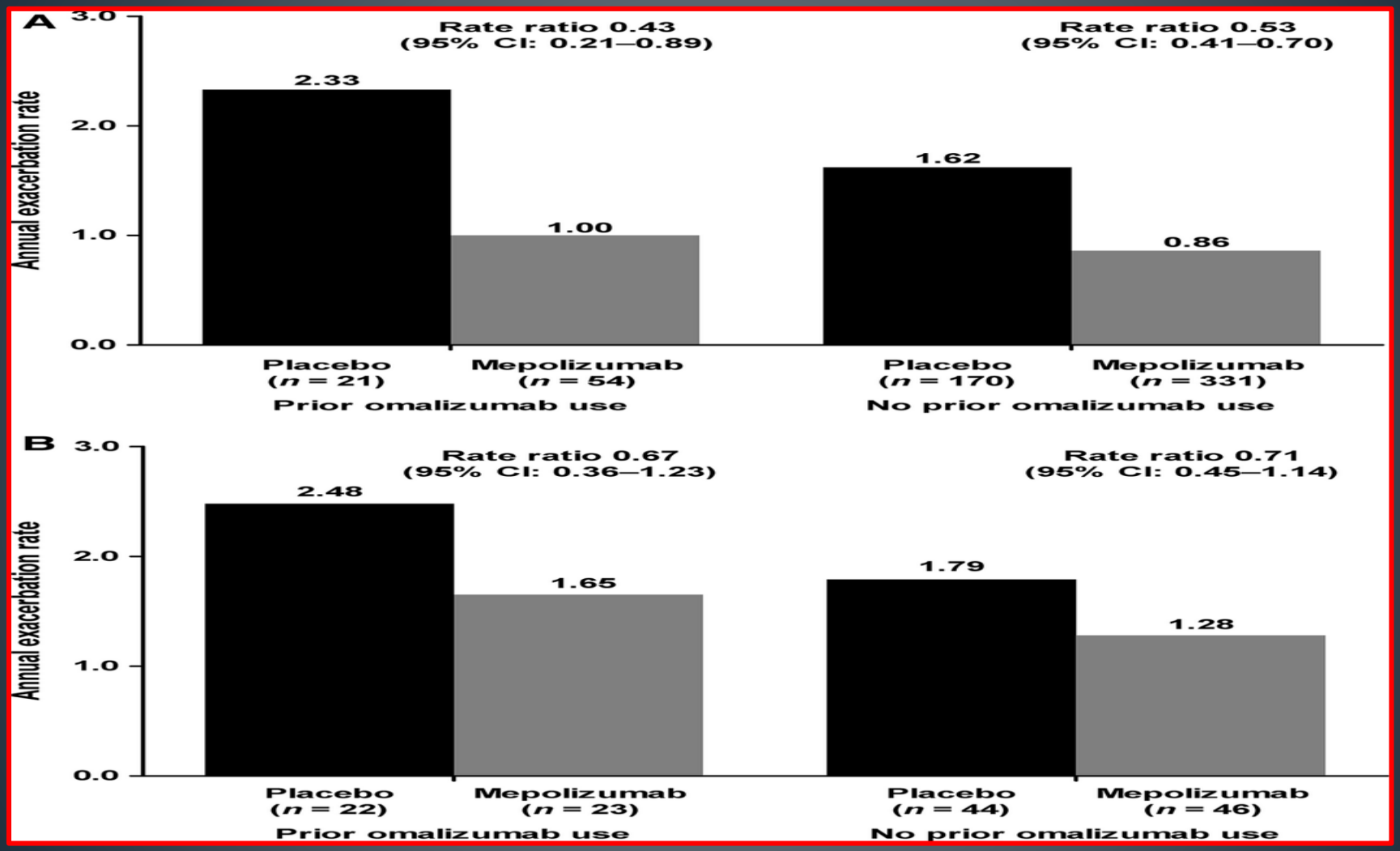
Μείωση παροξύνσεων σε σχέση με βασικά χαρακτηριστικά της νόσου και αριθμό EOS αίματος (Pooled SIROCCO and CALIMA; <300 EOS)



- In patients with <300 cells/ μL, **current OCS use, nasal polyps and pre-BD FVC <65% had the greatest impact** on AER reductions

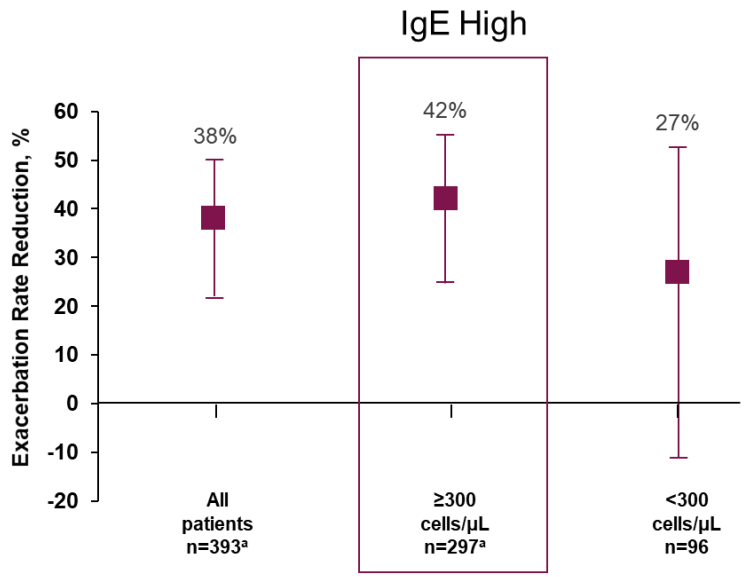
Bleecker ER, Wechsler ME, Mark FitzGerald J, et al. Eur Respir J 2018; Oct 18;52(4)

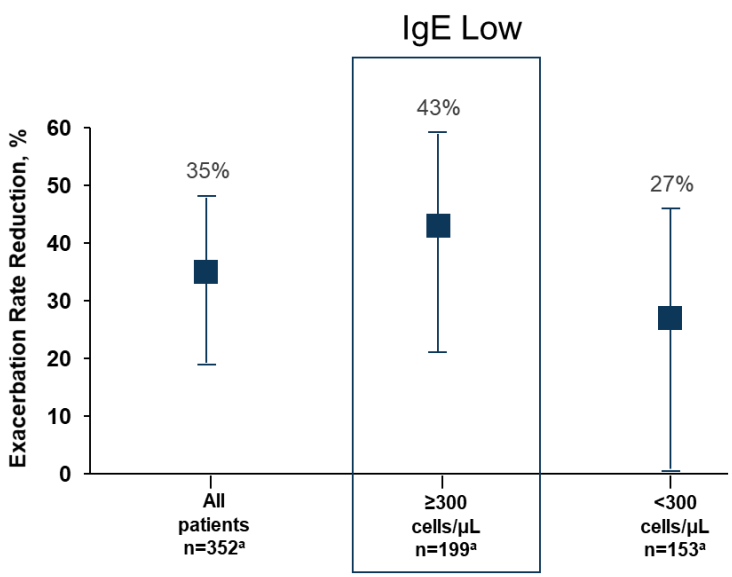
Mepolizumab σε ασθματικούς που είχαν λάβει Omalizumab



Magnan A et al Allergy 2016

Benralizumab: *Μείωση παροξύνσεων* ανεξαρτήτως τιμής IgE ορού





- The annual exacerbation rate ratio with benralizumab was 0.58 (95% CI, 0.45 to 0.75; p<0.0001) relative to placebo in patients who had high IgE concentrations and blood EOS counts ≥300 cells/µL
- There were greater reductions in AAER with benralizumab in patients with baseline blood EOS counts ≥300 cells/µL vs. <300 cells/µL

Chipps BE et al, Ann Allergy Asthma Immunol. 2018;120:504-511

Pre-screening/ Run-in phase: **Continue omalizumab** plus all maintenance therapy (0–6 weeks)

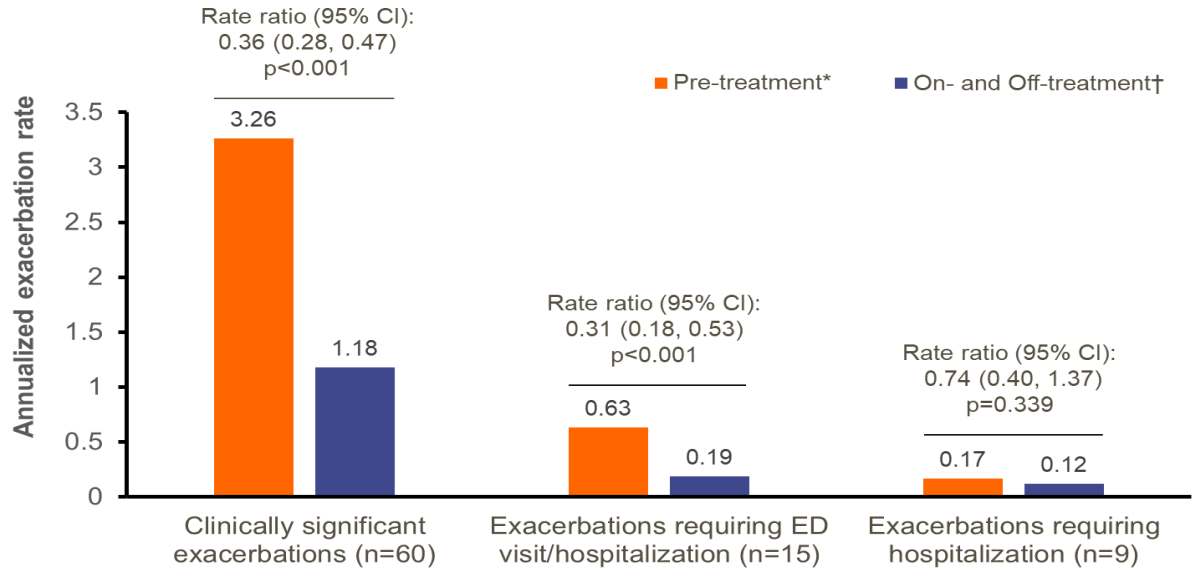
Treatment phase: **Mepolizumab 100 mg SC every 4 weeks,** plus all maintenance therapy except omalizumab (28 weeks)

Follow-up (4 weeks)

W0 (baseline)	W4	W8	W12	W16	W20	W24	W28

Patients discontinue omalizumab and switch to mepolizumab

Figure 2. Pre-treatment and On- and Off-treatment annualized exacerbation rates (ITT population)



*Pre-treatment refers to the 12 months prior to screening; †On- and Off-treatment refers to the time between first dose and study conclusion, regardless of treatment discontinuation; n numbers represent the number of exacerbations recorded On- and Off-Treatment. CI, confidence interval.

ΣΥΜΠΕΡΑΣΜΑΤΑ

- ΣΟΒΑΡΟ ΑΣΘΜΑ: Precision medicine– endotypes – clinical phenotypes – treatable traits
- Οι βιολογικές θεραπείες απευθύνονται σε μικρές υποομάδες ασθενών με σοβαρό ανθιστάμενο στη θεραπεία άσθμα
- Η επιλογή του σωστού βιολογικού παράγοντα είναι επιτακτική ανάγκη για τη βελτίωση του ασθενούς και τη δημόσια υγεία
- Όσο περισσότερες διαθέσιμες βιολογικές θεραπείες έχουμε, τόσο πιο απαραίτητη θα είναι η εξονυχιστική φαινοτύπιση του ασθματικού για την καλύτερη δυνατή επιλογή
- Είναι σημαντικό να κατανοήσουμε τους υποκείμενους μηχανισμούς

ΕΥΧΑΡΙΣΤΩ