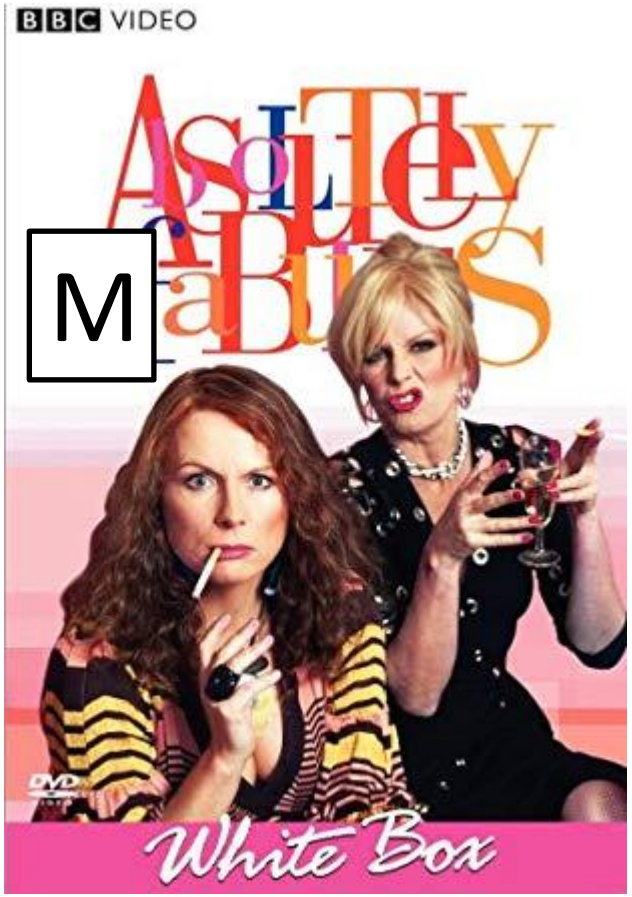
Biologics

Dr Paddy Dennison

Biologics



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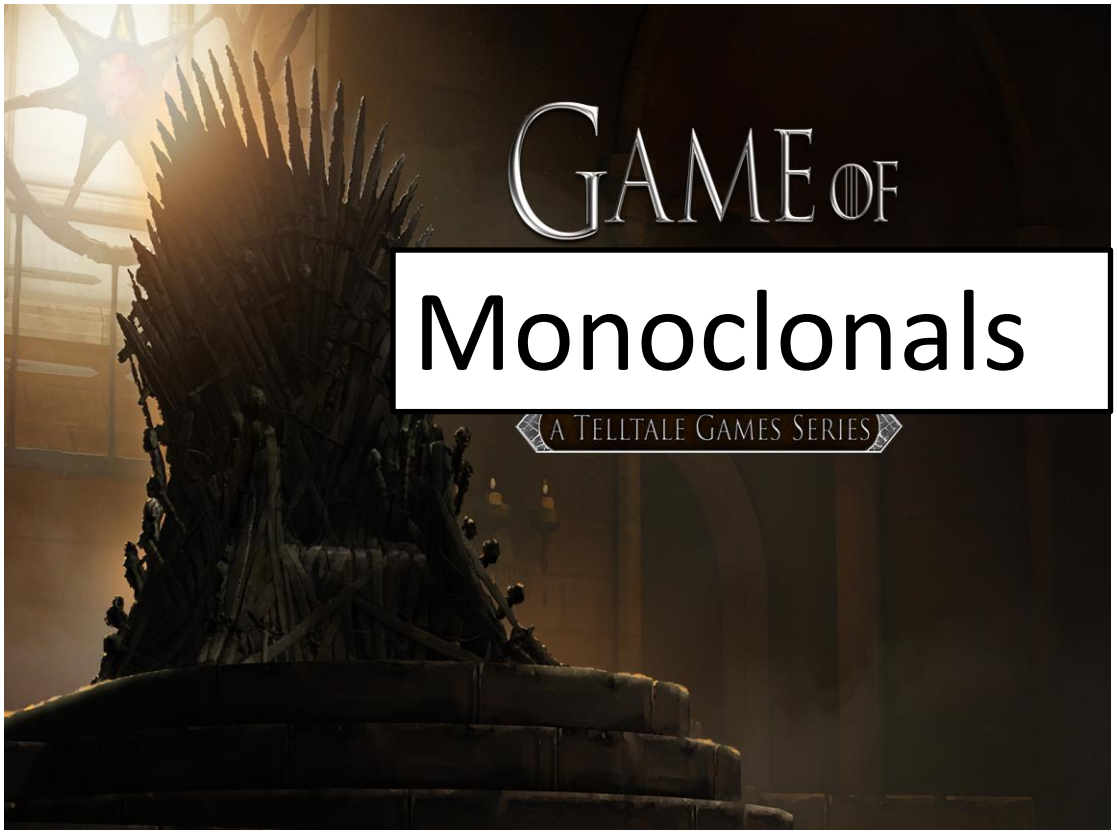
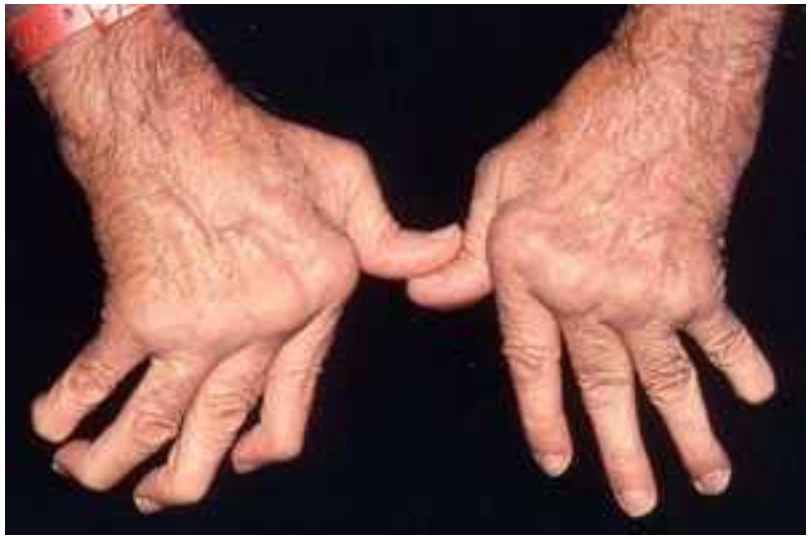


- Is it worth the hype?
- Who gets/is going to get killed off along the way/resurrected?
- When's the next series/what's the next big thing

Summary

- Increasing use of monoclonals, targeting select populations of severe asthmatics
- Already target atopic
- IL-5/eosinophilic targeting now here, ~50% reduction, mainly in exacerbation/OCS dose, less impressive on lung function/questionnaires
  - Think of them in anyone having 3-4 exacerbations/year, with eosinophils > 0.3-0.4, ONCE ALL THE BASICS HAVE BEEN DONE
- IL-4/13 about to arrive
- Varied criteria, this and the treatments to come will make this a complex but interesting area.

Imagine you were a rheumatologist in the 1990's



Drug	Target	Route/Freq
Etanercept	TNF-alpha	S/c, weekly
Infliximab	TNF-alpha	Iv, monthly
Adalimumab	TNF-alpha	s/c, fortnightly
Golimumab	TNF-alpha	s/c, monthly
Certolizumab	TNF-alpha	s/c, monthly
Abatacept	APC/T cell interaction	Iv or s/c, variable
Rituximab	B cells/CD20	Iv, monthly
Toclizumab	B cell activation	Iv monthly

- Not replaced DMARD's/MTX, but 2-3.5% fail to respond
- Some are self-administered at home
- Changing criteria over time
- Biosimilars already approved

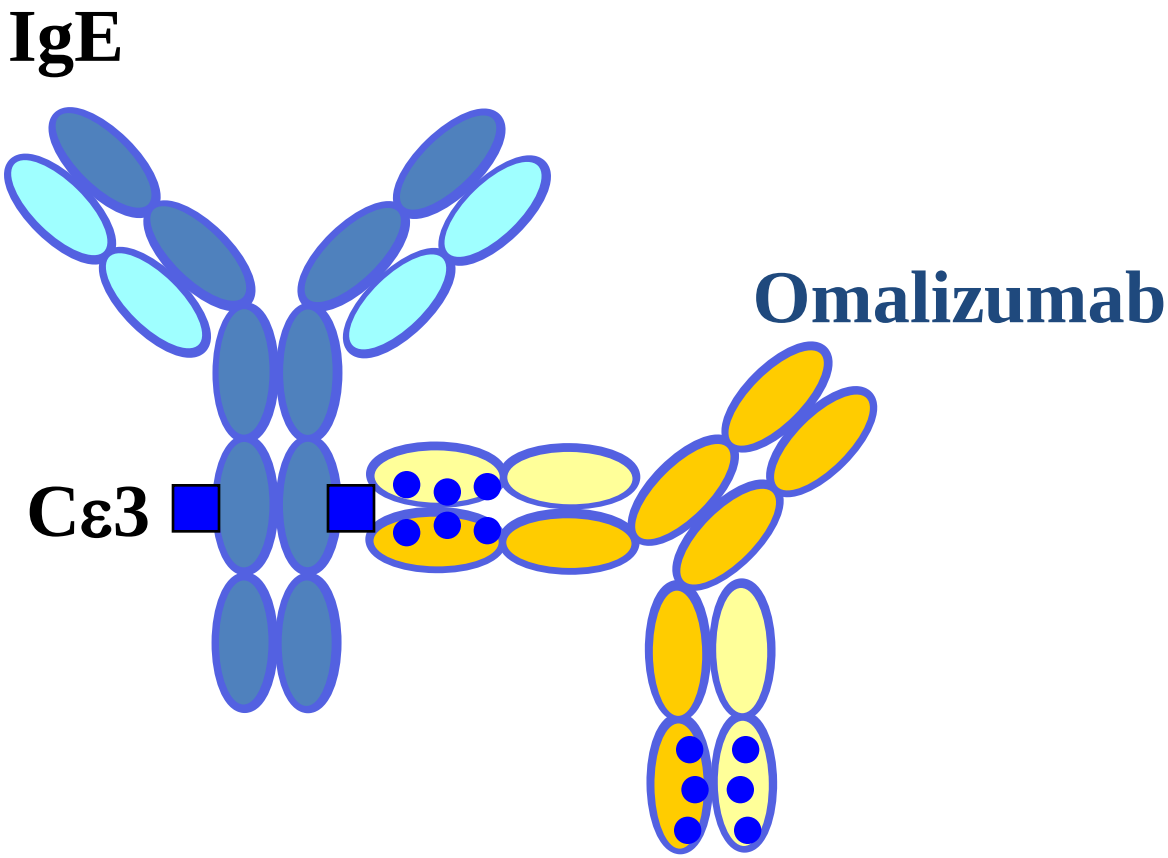
Before all that

- Check the basics
  - Adherence/compliance
  - Technique
  - Treat comorbidities
- Accurate phenotyping
  - Atopic vs non-atopic
  - Th2-high vs Th2-low
- What are you trying to achieve?
  - Less exacerbations, better lung function, etc.
- What the patient wants/is willing to have

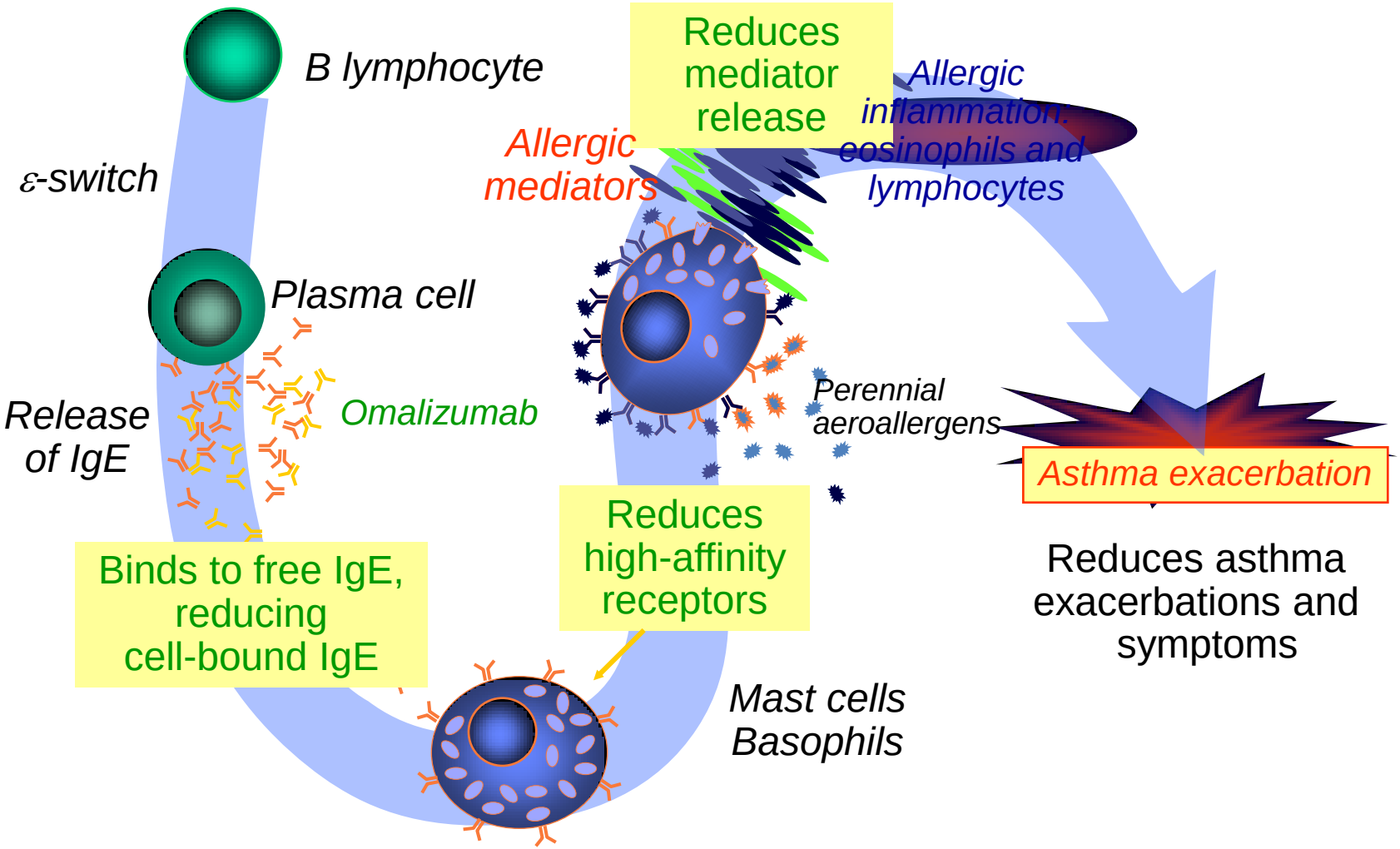
What monoclonals are there?

- Anti-IgE
  - Omalizumab (Xolair), (?biosimilars to come)
- 'Anti-eosinophilic'
  - Anti-Il5: Mepolizumab(Nucala), Reslizumab (Cinquaero).
  - Anti-IL5Ralpha: Benralizumab (Fasenra)
  - Anti-IL4/13: Dupilumab (Dupixent)
- Anti-thymic stromal lymphopoietin (TSLP)
  - Tezepeulumab

- Omalizumab (Xolair®)
  - Licensed ~ 2003 - first novel therapy in 30 years.



Omalizumab mechanism of action in IgE-mediated asthma



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plus a long-acting inhaled beta2-agonist.

Baseline IgE (IU/ml)	Body weight (kg)									
	≥20–25	>25–30	>30–40	>40–50	>50–60	>60–70	>70–80	>80–90	>90–125	>125–150
≥30–100	75	75	75	150	150	150	150	150	300	300
>100–200	150	150	150	300	300	300	300	300	450	600
>200–300	150	150	225	300	300	450	450	450	600	
>300–400	225	225	300	450	450	450	600	600		
>400–500	225	300	450	450	600	600				
>500–600	300	300	450	600	600					
>600–700	300		450	600						
>700–800										
>800–900										
>900–1,000										
>1,000-1,100										

ADMINISTRATION EVERY 2 WEEKS
SEE TABLE 3

Revised NICE Guidelines

- Omalizumab is recommended as an option for treating severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimised standard therapy in people aged 6 years and older

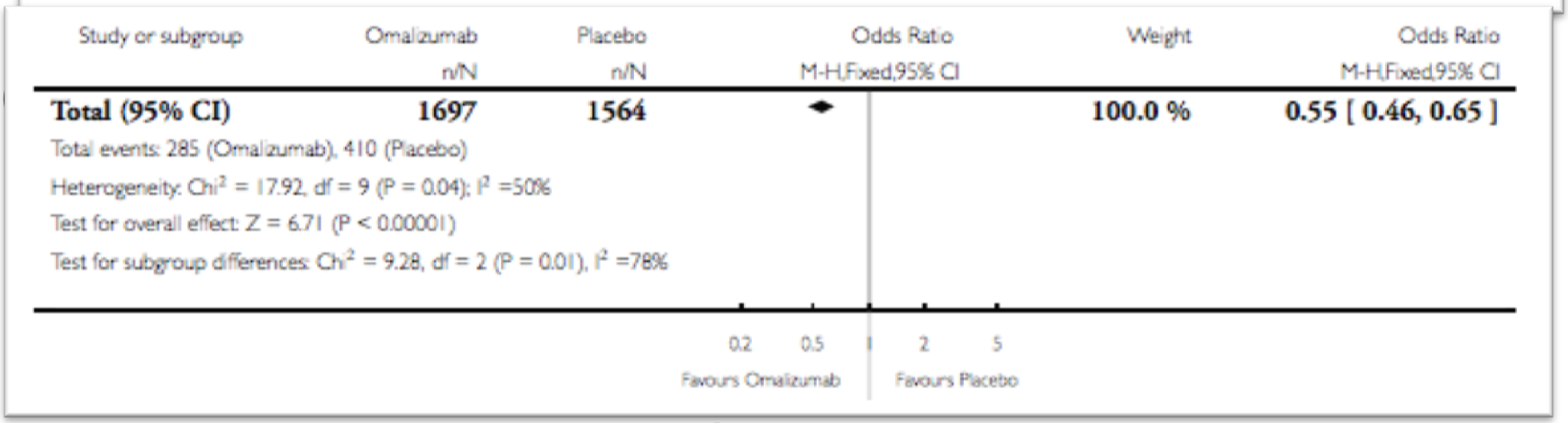
- Who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year)

Effects of omalizumab

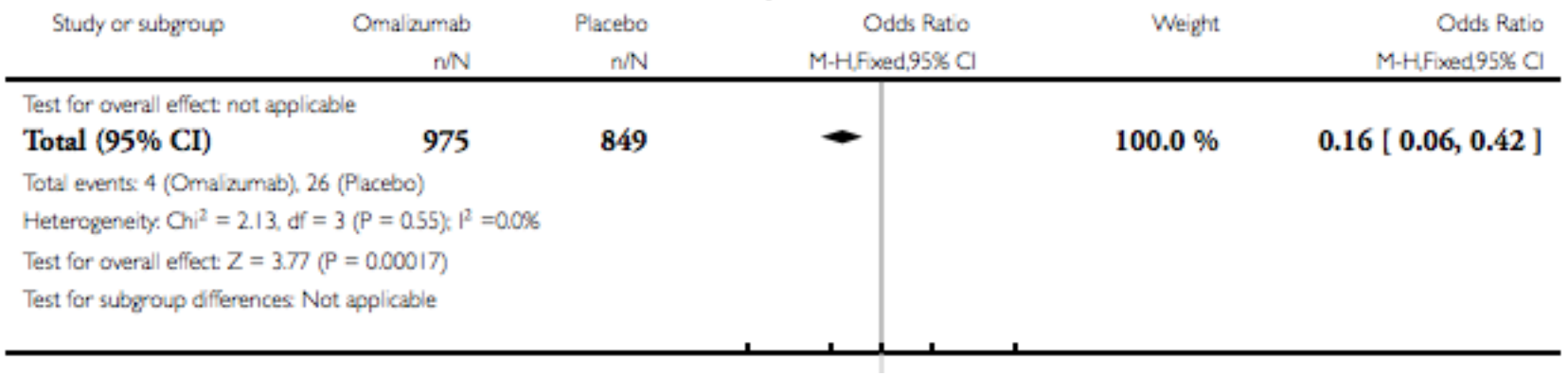
- Pathological
  - Reduced free IgE
  - Downregulated $F_{CE}RI$ expression
  - Reduction in sputum/tissue eosinophilia.
  - Attenuation of early and late phase responses to allergen challenge.

Effects of omalizumab

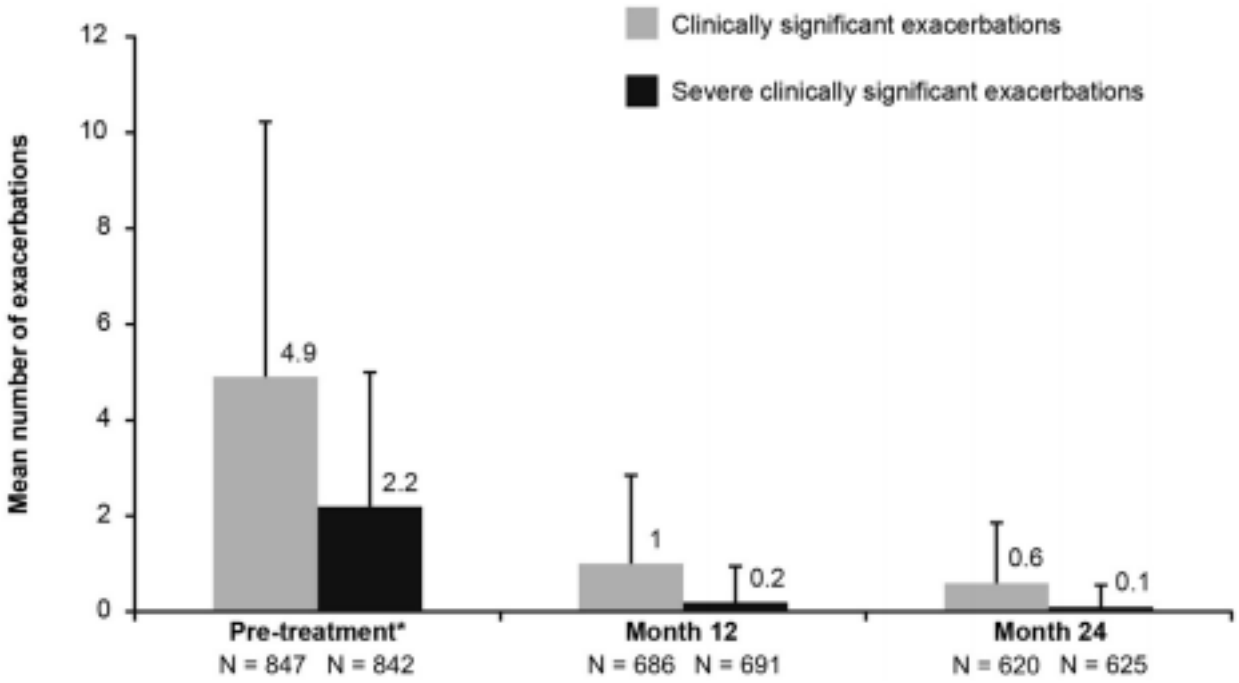
- **Analysis 1.1. Comparison 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 1 Number of participants with at least one exacerbation (ICS and OCS users).**



Analysis 1.3. Comparison 1 Subcutaneous omalizumab + steroid versus placebo + steroid (stable steroid), Outcome 3 Hospitalisations.



Effects of omalizumab



The eXpeRience registry: The 'real-world' effectiveness of omalizumab in allergic asthma

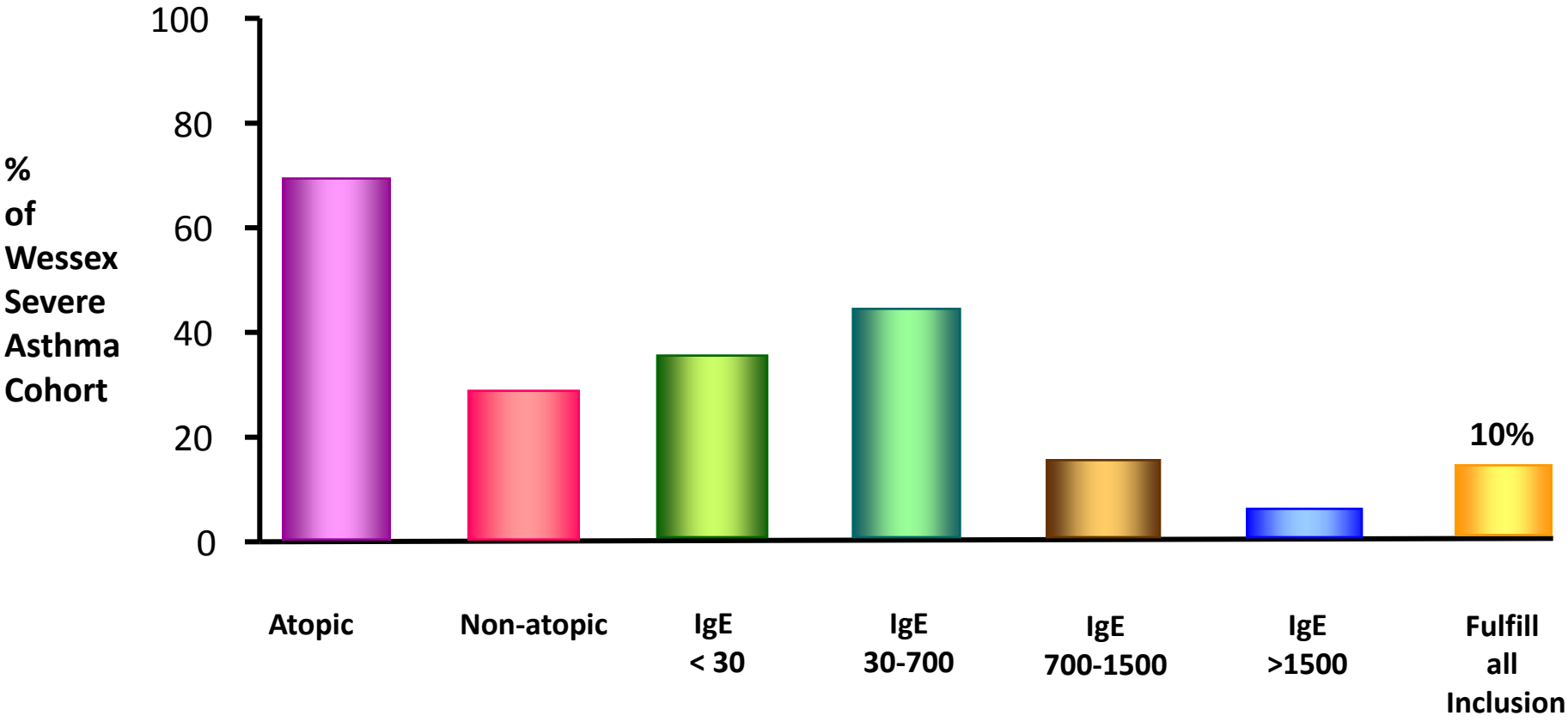
G.-J. Braunstahl [a,*], C.-W. Chen [b], R. Maykut [c], P. Georgiou [d], G. Peachey [d], J. Bruce [c]

Effects of omalizumab

	Patients receiving continuous OCS at baseline (n=90)	Patients not receiving continuous OCS at baseline (n=46)
OCS use over 1 year pre-omalizumab, g	6.8±4.34	3.0±2.44
OCS reduction† (%)	36	26
Patients reducing/stopping OCS‡, n (%)	59 (65.6)	28 (60.9)
Responders#, n (%)	71 (78.9)	41 (89.1)
Change in exacerbations† (%)	-54.6***	-49.3***
Change in hospitalizations† (%)	-60.6***	-61.9***
Change in A&E visits† (%)	-68.1***	-73.6***
Change in % predicted FEV_1 at week 16†, (%)	+8.7±15.08**	+14.7±26.15

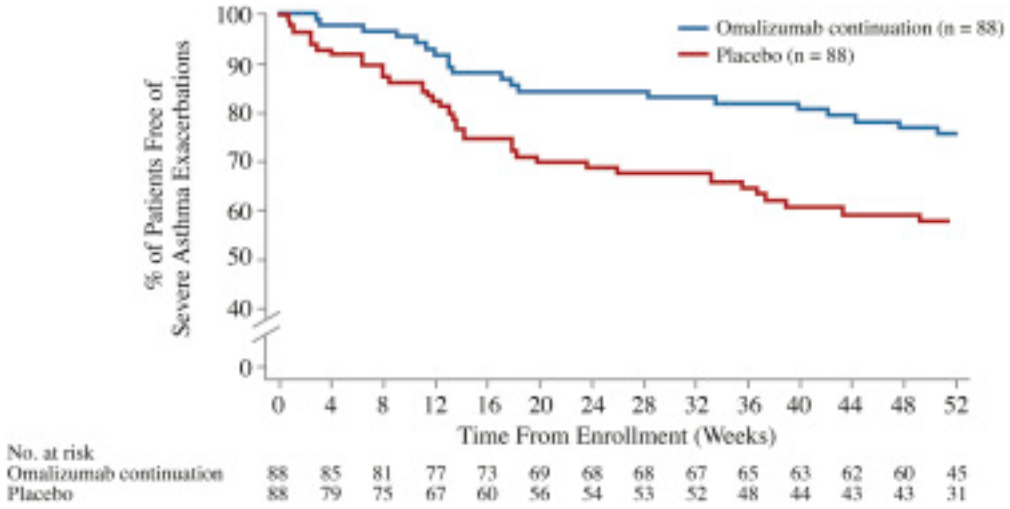
The APEX study: A retrospective review of responses of severe allergic asthma patients to omalizumab on continuous or non-continuous oral corticosteroids in UK clinical practice

IgE distribution:Wessex Severe Asthma Cohort

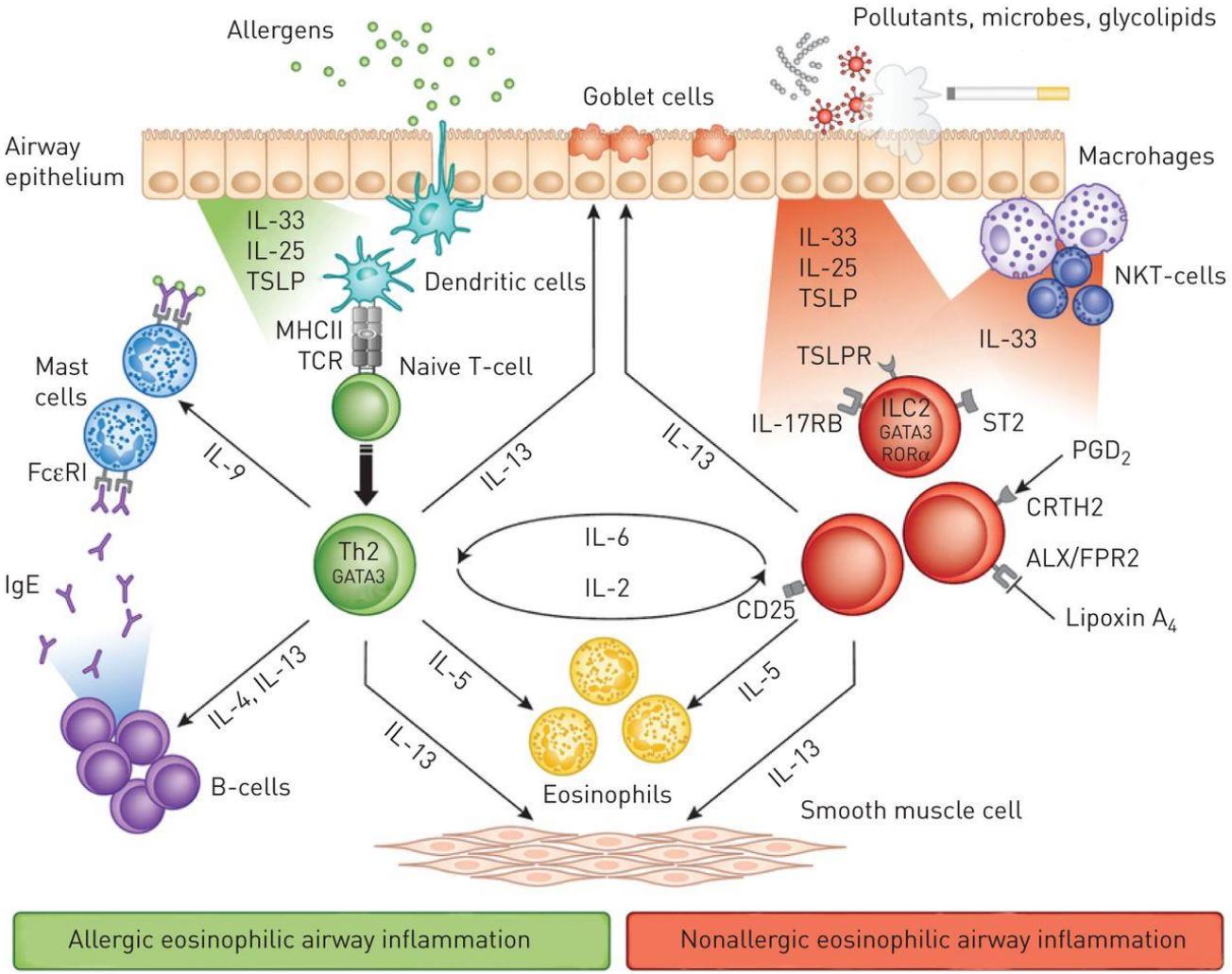


Effects of omalizumab

- Does it work for everyone?
  - 80% response rate in trials even in carefully selected patients
  - ?atopic disease needed:
- Cost implications
  - Duration of treatment still unknown



Two different pathways lead to eosinophilic airway inflammation in asthma.



Jantina C. de Groot et al. ERJ Open Res 2015;1:00024-2015

Critical role of eosinophils in asthma

- Definition
  - Elevated levels of eosinophils in bronchial biopsies or sputum despite chronic and correct use of adequate doses of ICS

  = 5% of all adult asthma patients
- Increased eosinophil count associated with:
  1. Increased asthma severity
  2. Increased risk of subsequent exacerbations
  3. Increased asthma mortality (7.4x greater)

Bousket et al., 1990; Tran et al., 2014; Zeiger et al., 2014; Ulrik and Frederiksen, 1995)

Clinical profile of (late-onset) eosinophilic asthma patients

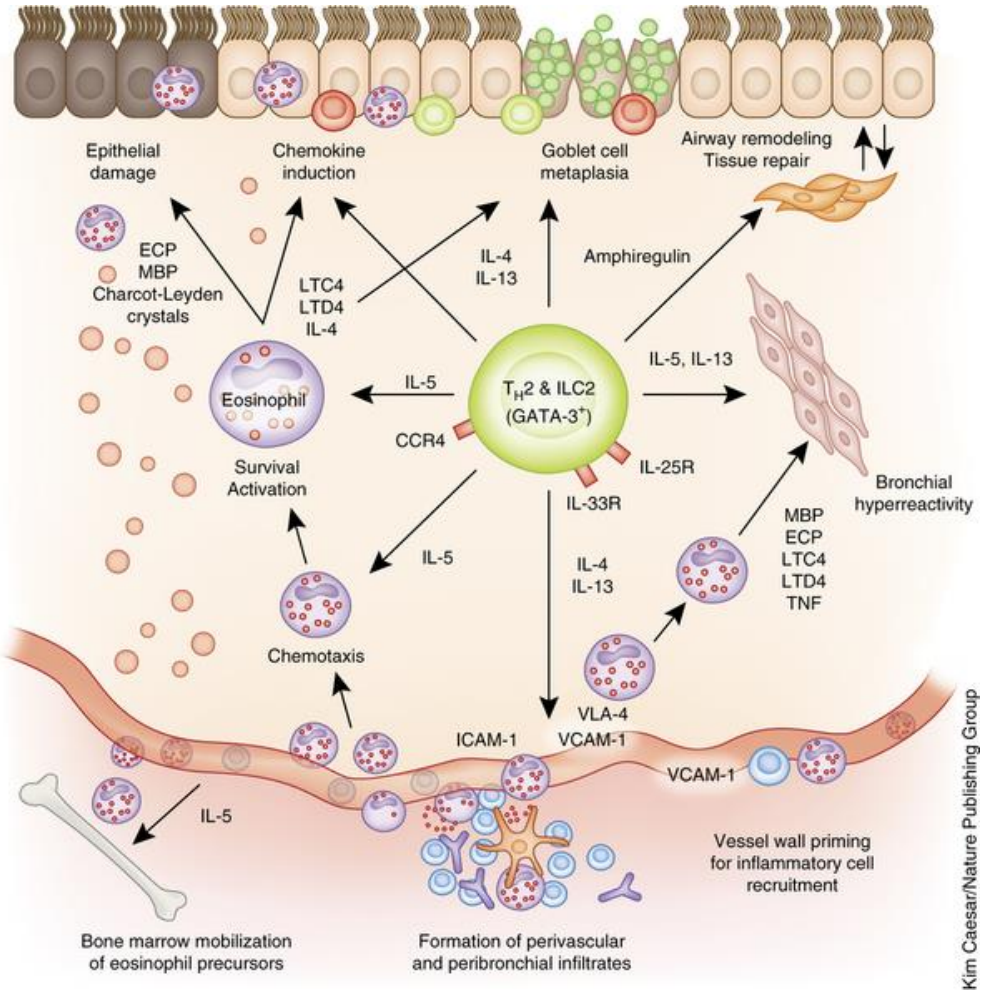
Adult onset of asthma
Equal distribution between sexes
Few or no allergies to common allergens
Elevated eosinophils in peripheral blood
At risk of severe exacerbations
Normal or moderately elevated IgE level
Low FEV1 and often persistent airflow limitation
Air trapping and dynamic hyperinflation
Chronic rhinosinusitis with nasal polyposis
Aspirin sensitivity
Good response to systemic corticosteroids

Groot et al., ERJ Open Res 2015

Mepolizumab

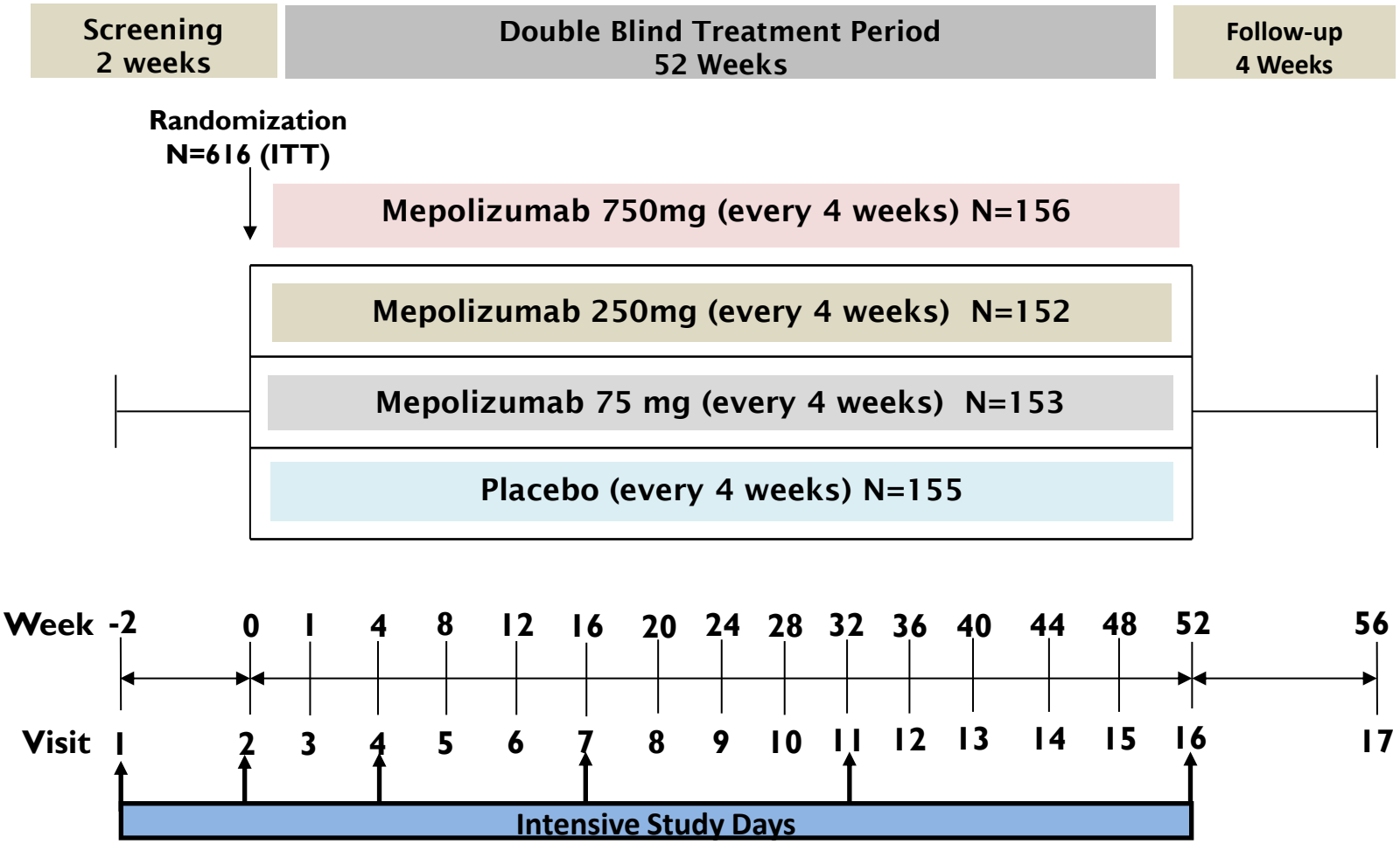
Humanised Monoclonal antibody anti IL-5

Mepolizumab for severe eosinophilic asth (DREAM): a multicentre, double-blind, placebo-controlled trial
Pavord et al, Lancet 2012



DREAM Study Design

(**D**ose **R**anging **E**fficacy **A**nd safety with **M**epolizumab)



Pavord I, et al. Lancet 2012;380:651-59.

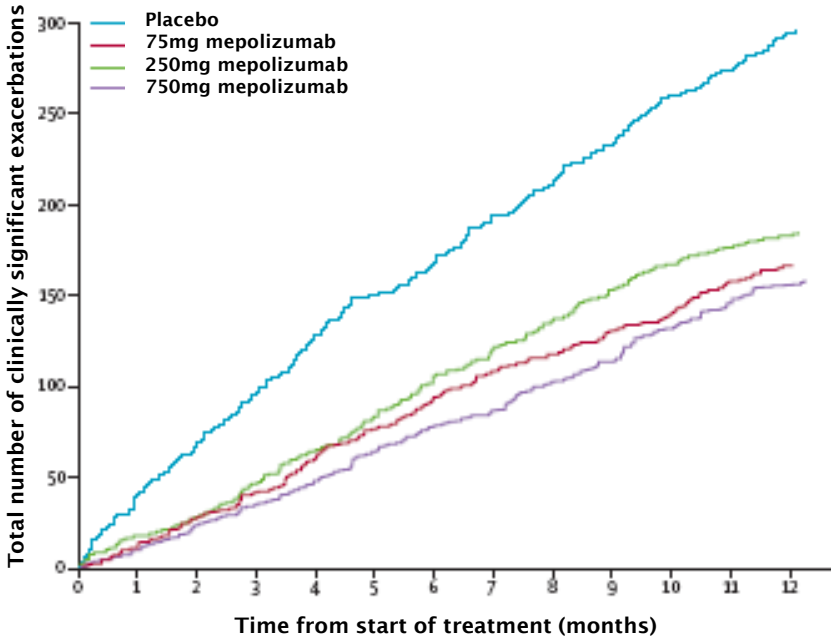
Key Inclusion Criteria

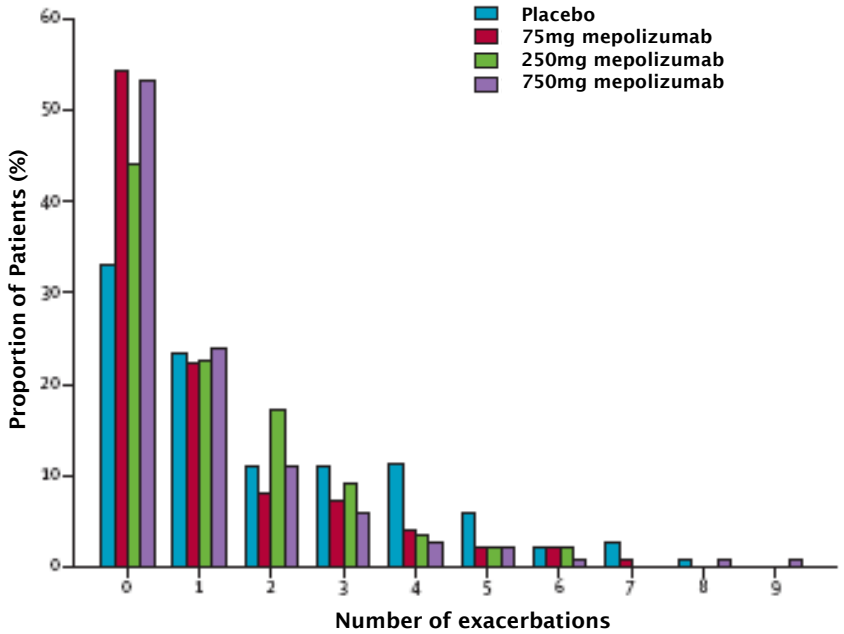
- Clinical features of severe refractory asthma for ≥12 months
- Requirement for regular treatment with high dose ICS (i.e., ≥880μg/day FP or equivalent), with or without maintenance OCS, and controller therapy (e.g., LABA, LTRA) in the prior 12 months
- FEV_1 <80% predicted
- Subjects with airway inflammation which was likely to be eosinophilic in nature as indicated by one of the following characteristics in the previous year:
  - elevated peripheral blood eosinophil level of ≥300/μL
  - sputum eosinophils ≥3%
  - eNO ≥50 ppb
  - Prompt deterioration of asthma control following a ≤25% reduction in regular maintenance dose of ICS or OCS
- Confirmed history of ≥2 asthma exacerbations requiring treatment with oral or systemic corticosteroids in the prior12 months

Pavord I, et al. Lancet 2012;380:651-59.

Exacerbations

Cumulative Number Over Time and Distribution





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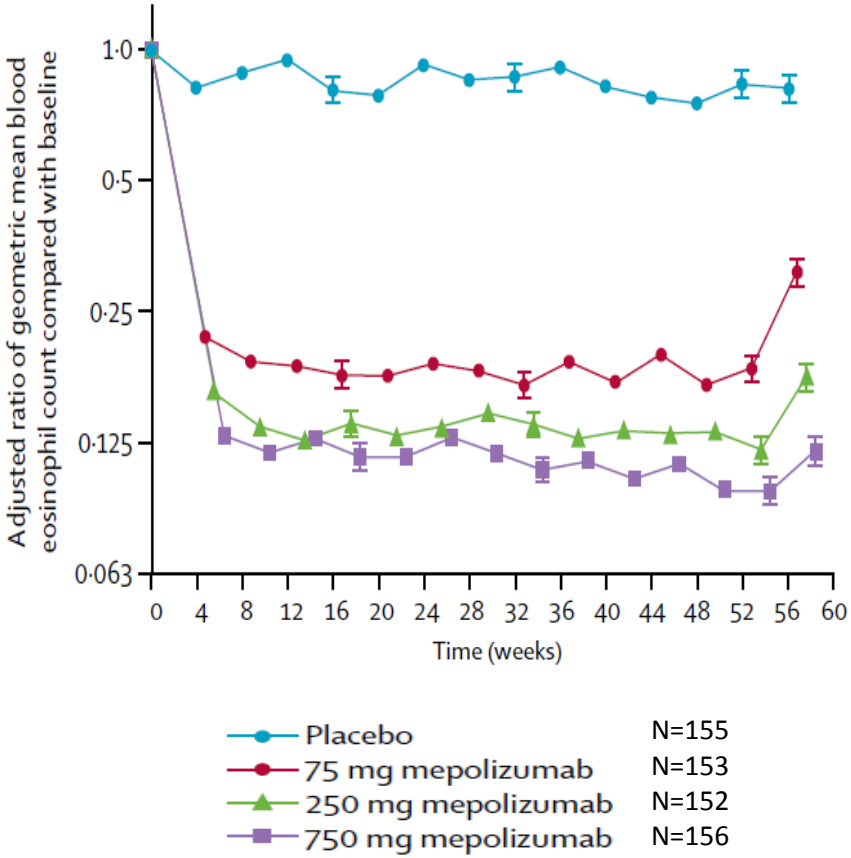
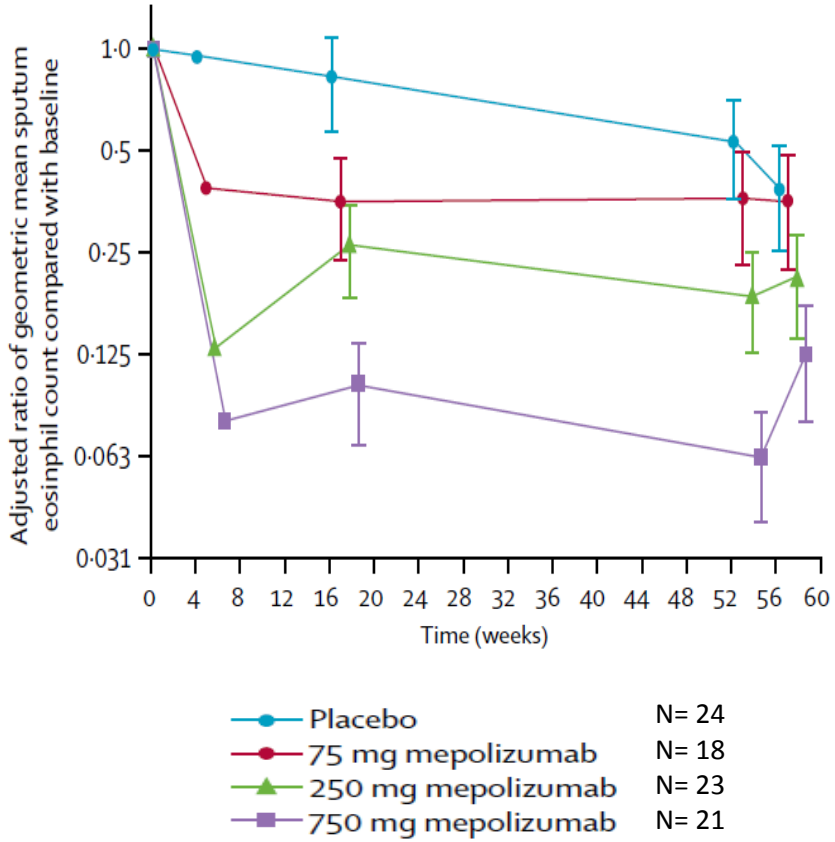
Change in Eosinophils

Blood

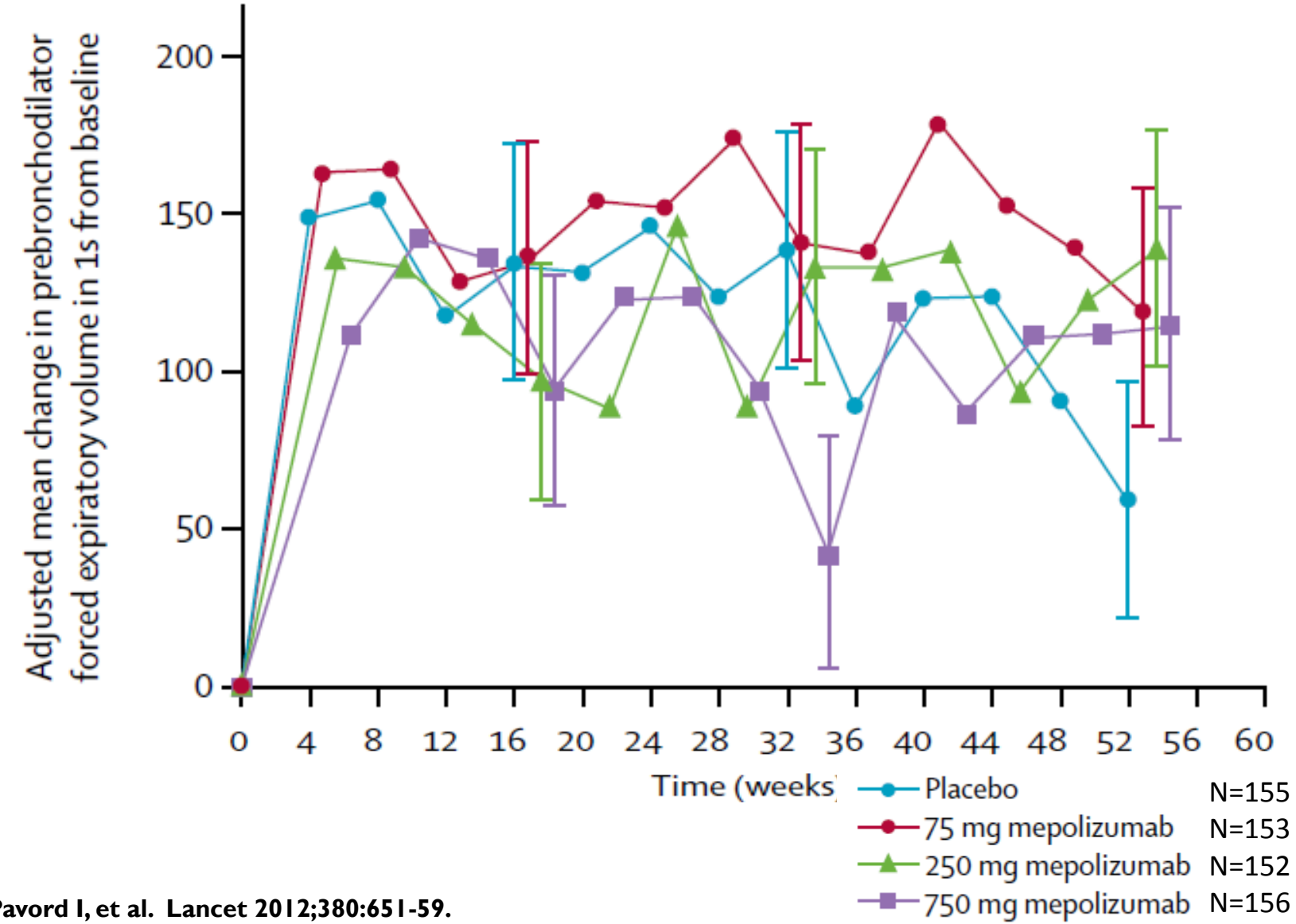


Sputum



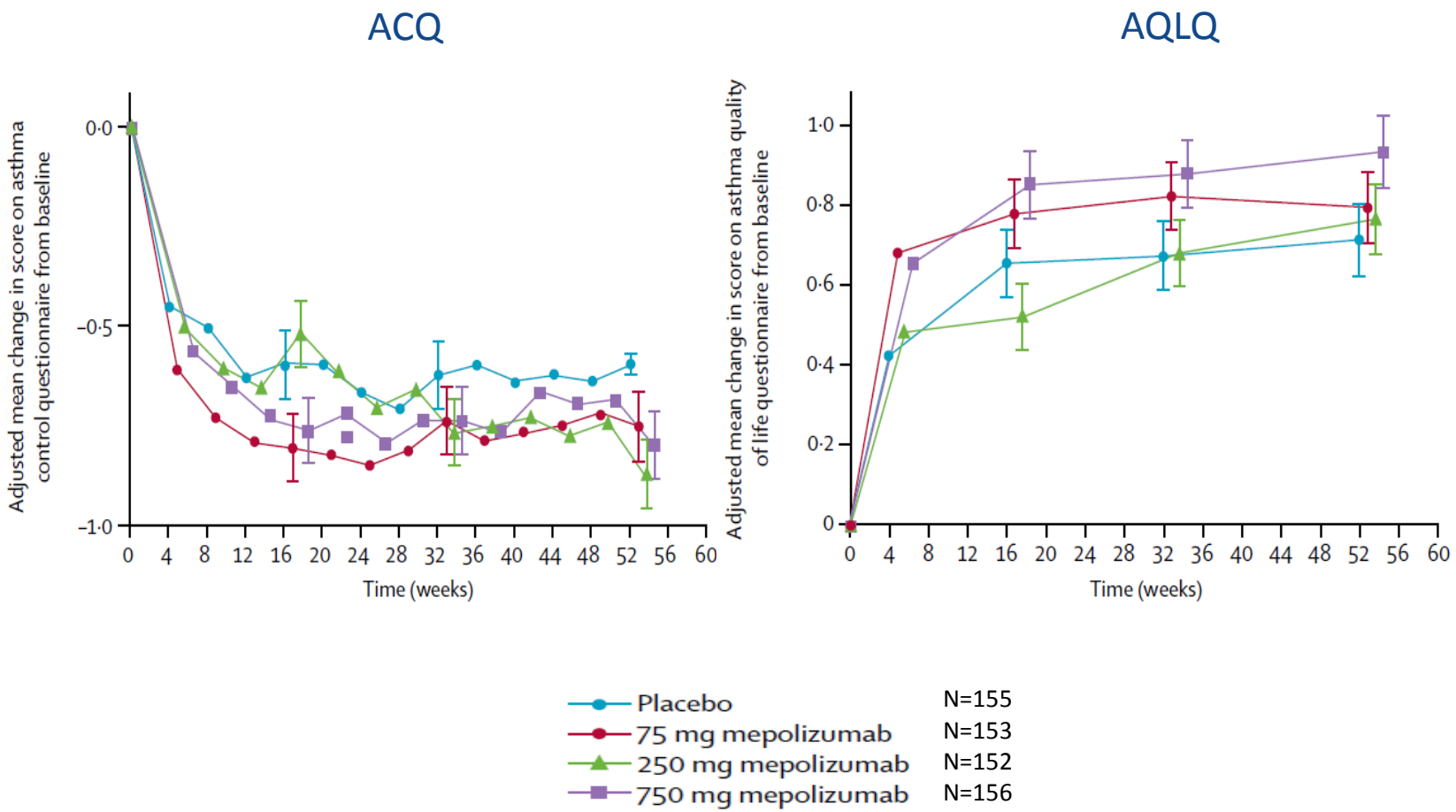
Pavord I, et al. Lancet 2012;380:651-59.

Change in FEV_1



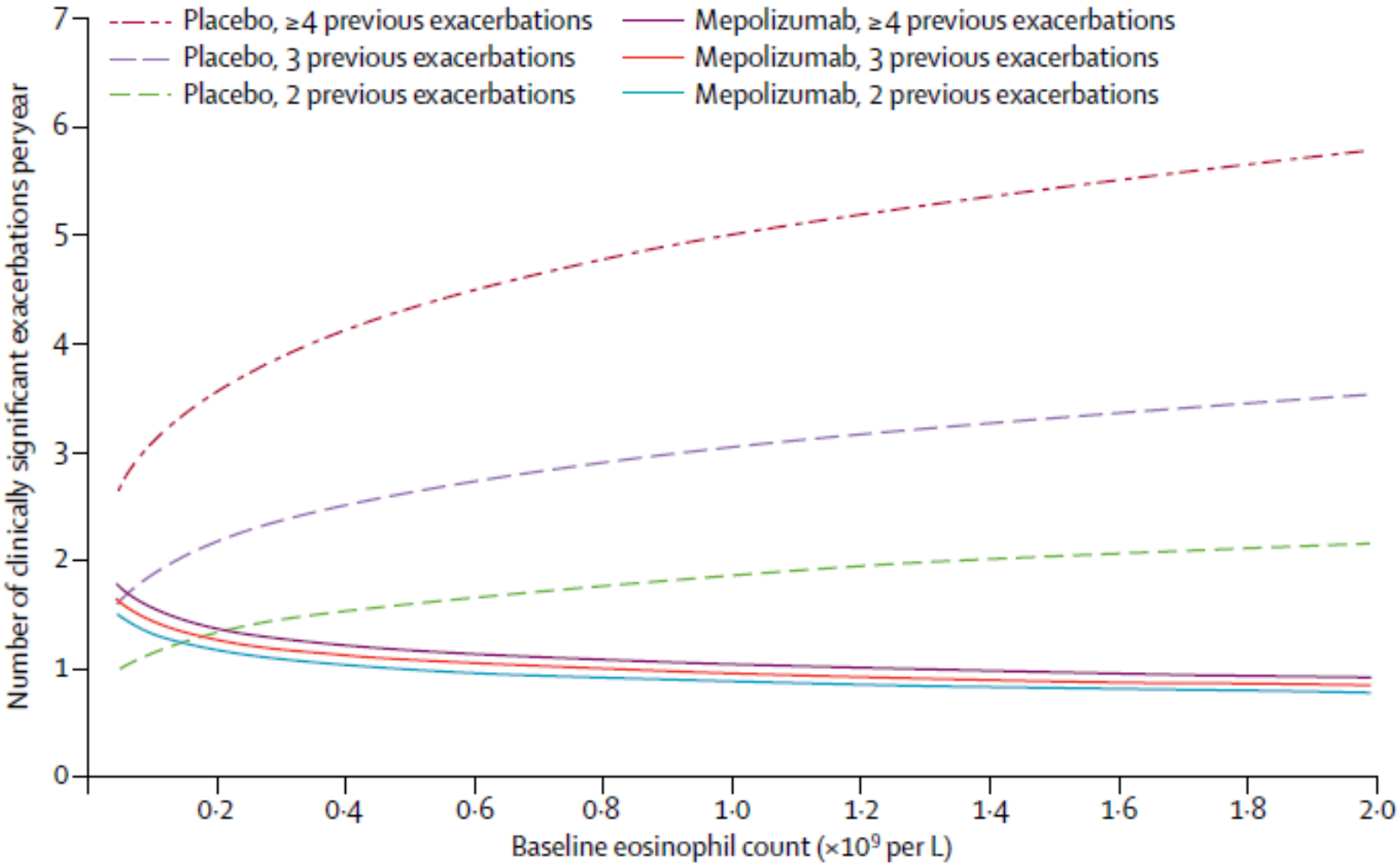
Pavord I, et al. Lancet 2012;380:651-59.

Change in ACQ and AQLQ Score



Pavord I, et al. Lancet 2012;380:651-59.

Predictive Modelling of Rate of Exacerbations



Done on the basis of blood eosinophil count at baseline, history of exacerbations and treatment with mepolizumab or placebo

Pavord I, et al. Lancet 2012;380:651-59.

MENSA: **Me**polizumab as adjunctive therapy in patie**n**ts with **s**evere **a**sthma

Criteria

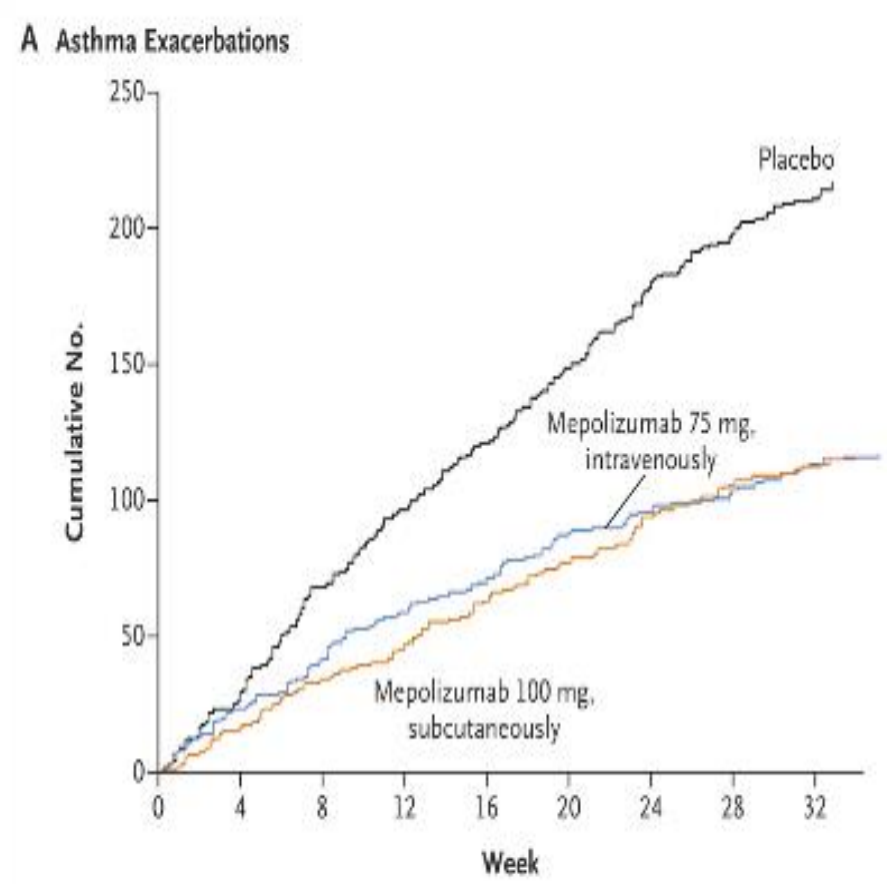
- Age 12-82
- FEV_1 <80%
- Reversability/BHR
- 2 exacerbations in previous year
- High dose ICS and LABA
- Eo >0.15 at screening or >0.3 in previous year

Intervention

- Placebo
- 75mg intravenous
- 100mg subcut

Ortega et al NEJM 2014

MENSA: **Me**polizumab as adjunctive therapy in patie**n**ts with **s**evere **a**sthma



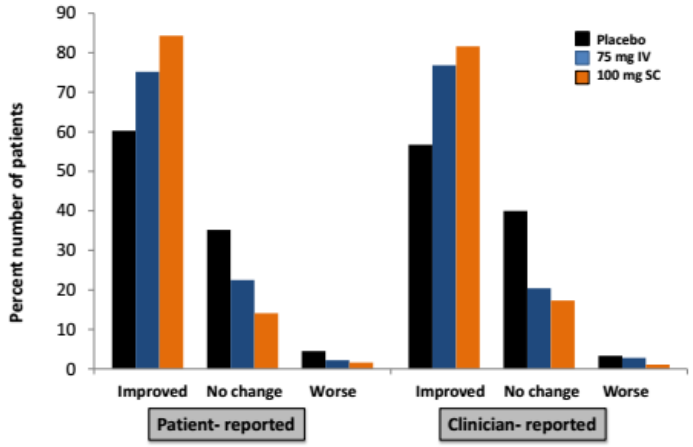
Exacerbations resulting in ED visit or hospitalisation:

- Subcutaneous-mepo group: 6%
- Placebo group: 13%

Ortega et al NEJM 2014

MENSA: **Me**polizumab as adjunctive therapy in patie**n**ts with **s**evere **a**sthma

Figure S5. Patient and clinician-rated overall evaluation of response to therapy at Week 32

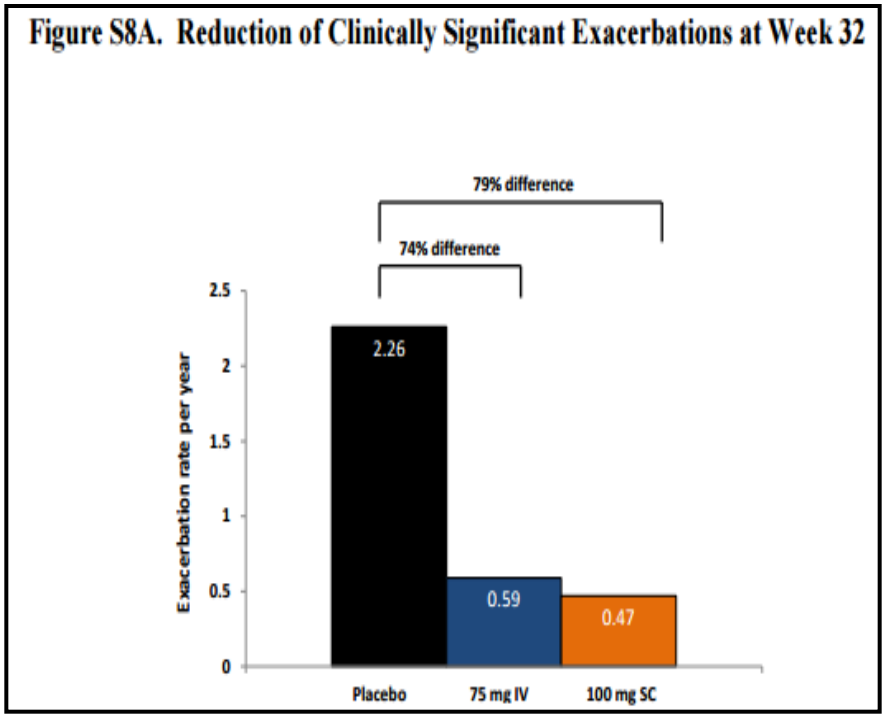


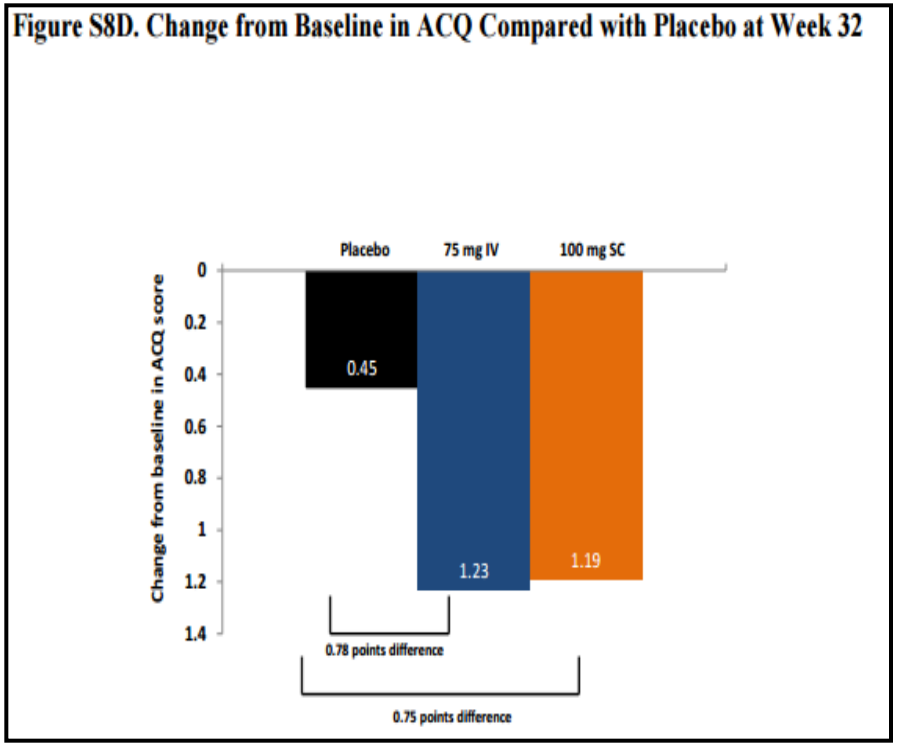
Note: The "improvement" category represents (significantly, moderately and mildly) and the "worse" category represents (significantly, moderately and mildly).

Ortega et al
NEJM 2014

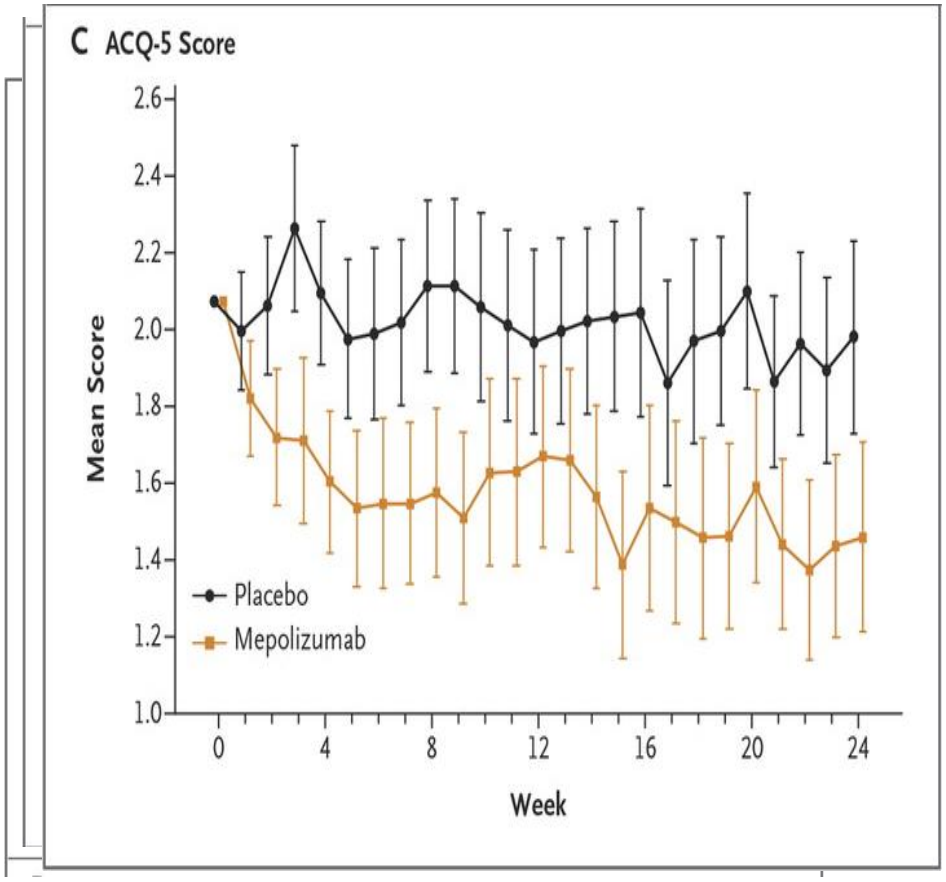
Eosinophil > 0.5 x 10^9/L

Wessex Asthma Network





Steroid reduction: SIRIUS



Bel et al.,
NEJM 2014

Wessex Asthma Network

Table S5. Dose of Prednisone from initiation to the end of the study

Time Period	Placebo		Mepolizumab 100 mg	
	Mean Daily Prednisone mg dose (SD)	Median Daily Prednisone mg dose (range)	Mean Daily Prednisone mg dose (SD)	Median Daily Prednisone mg dose (range)
Screening	15.2 (6.7)	15 (5-35)	15.1 (9.3)	12.5 (5-35)
Baseline	13.2 (6.3)	12.5 (5-35)	12.4 (7.2)	10.0 (5-35)
Baseline-wk 4	14.5 (7.6)	12.5 (5-40)	12.7 (7.3)	10.0 (5-35)
Weeks 4-8	12.5 (7.6)	10.0 (2.5-36)	10.0 (7.1)	8.5 (2.5-30)
Weeks 8-12	11.3 (7.9)	10.0 (1-45)	9.6 (9.0)	5.7 (1-53)
Weeks 12-16	11.5 (7.9)	10.0 (0-34)	10.2 (9.9)	5.4 (0-36)
Weeks 16-20	10.6 (7.4)	10.0 (0-30)	8.6 (8.8)	5.0 (0-38)
Weeks 20-24	10.5 (7.8)	10.0 (0-30)	8.6 (11.9)	3.1 (0-67)

Total cessation of oral steroids:

- Mepolizumab group 14%
- Placebo group 5%

Mepolizumab

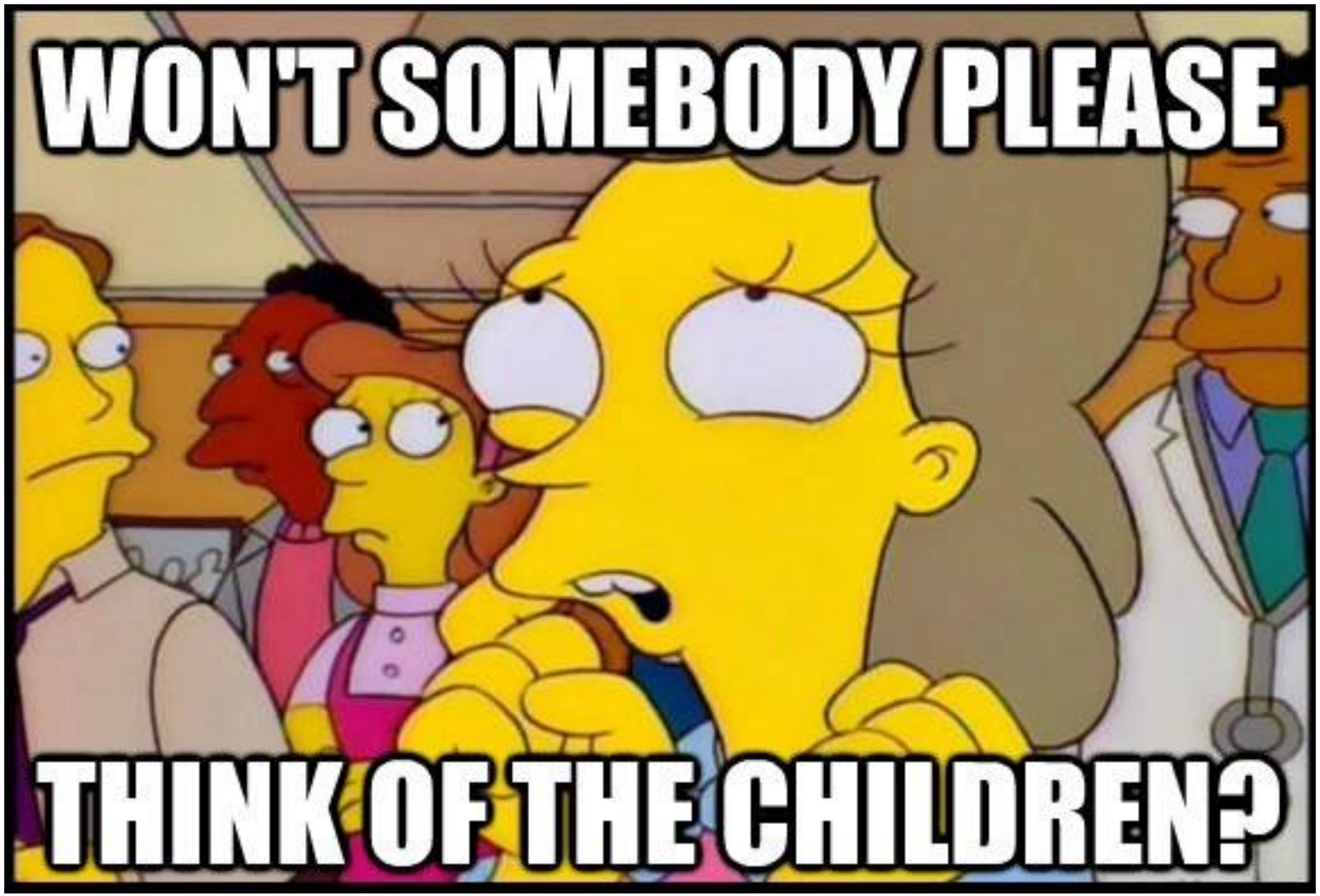
- Reduction in exacerbation rate over one year compared with standard of care.(~50%)
- Reduction in oral corticosteroid usage (~50%)
- Can expect ~80% response rate

Mepolizumab

- NICE approval Jan 2017
  - >18 years old
  - Optimised on standard therapy
  - Eosinophil count >0.3 in last 12 months
  - >4 exacerbations in last 12 months, or continuous OCS equivalent to 5mg/day for 3 months

- 1 year treatment, only in specialist centres, looking for reduction in exacerbations >50%
- Real-world data being collected
- ≥4.5 years of data re: longterm use

Mepolizumab



Mepolizumab - paediatrics

- European Commission has granted the biologic marketing authorisation as an add-on treatment for severe refractory eosinophilic asthma in patients aged six up to 17 years.
- Not yet NICE approved.
- Initial trial data only included 28 patients <17 yrs old
- Trials in progress…

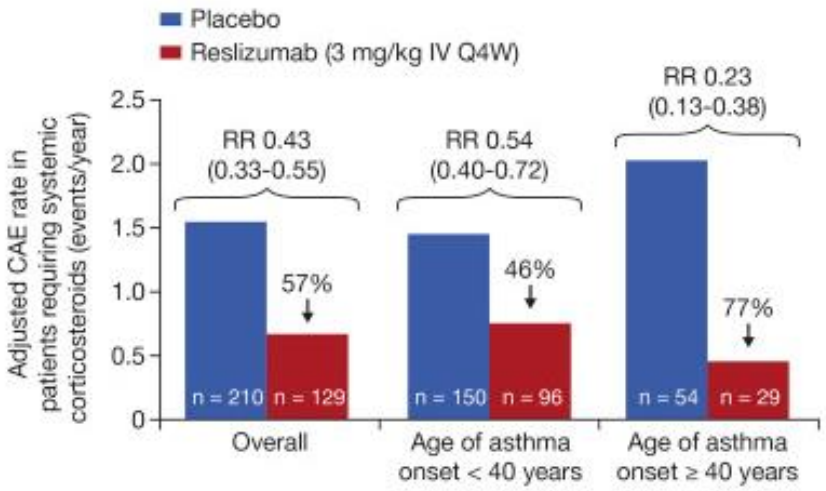
Other IL-5 treatments

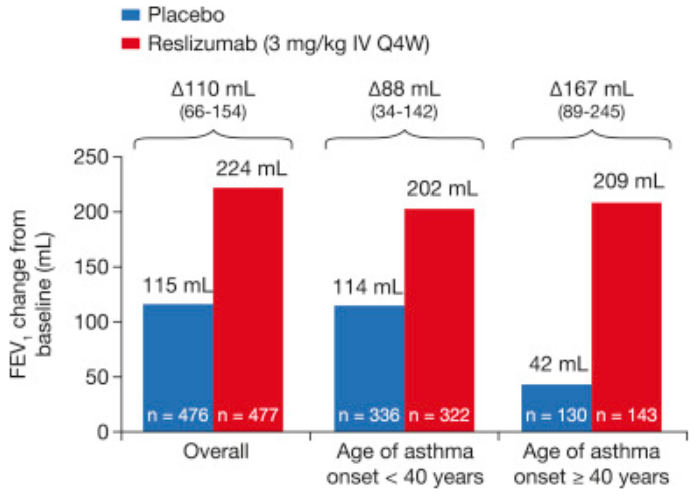
- Reslizumab (Cinquaero) (TEVA)
- Iv treatment every 4 weeks
- Weight-based (but no upper limit)
- NICE decision 20/7/2017, indicated in adults if inadequately controlled and:
  - Eosinophils >0.4 ‘has been recorded’*
  - >3 or more exacerbations requiring systemic OCS*

- *Differing trial data

Reslizumab - evidence

- Less trial evidence
- 2 duplicate trials, 931 patients
  - Castro et al, Lancet Respir J 2015
  - Medium-High dose ICS, >1 exacerbations last 12 months, eosinophils >0.4





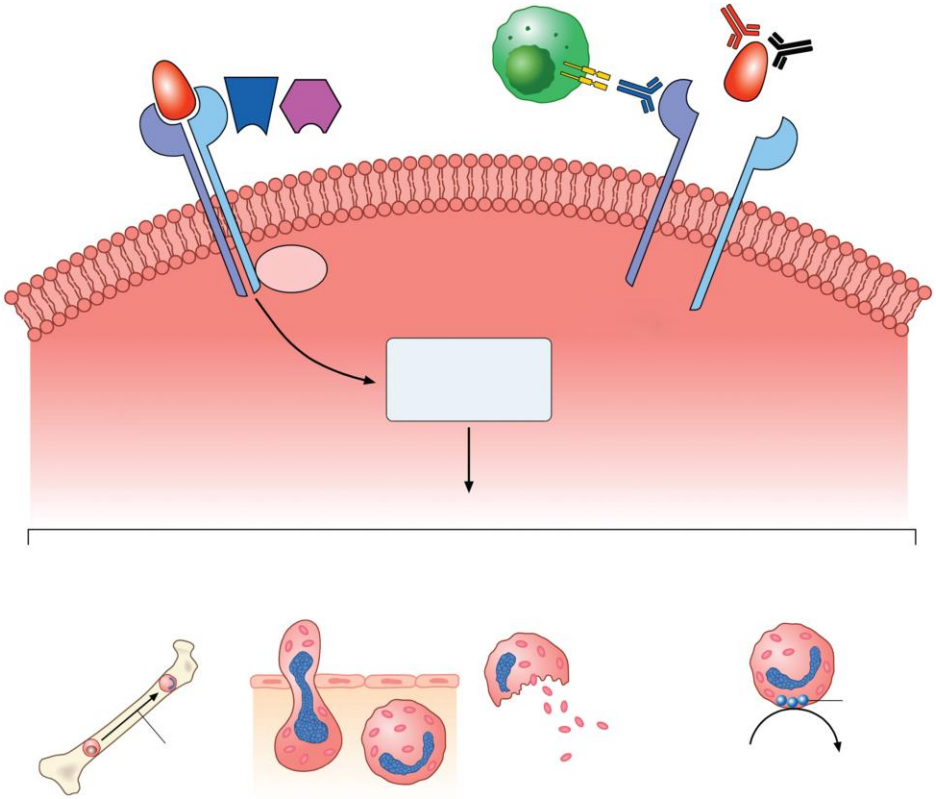
  - Less impressive changes in ACQ/AQLQ (vs placebo)

Reslizumab - evidence

- Steroid sparing trial in progress…
- Subcutaneous form trial in progress…
- No paediatric license, one small pharmacokinetic study

Benralizumab (Fasenra)

- Anti-IL5Rα target
- Stops IL-5 binding, but also induces apoptosis of eosinophils (via NK cells)
- Subcutaneous injection, 30mg given 4 weekly for 3 months, then 8 weekly thereafter

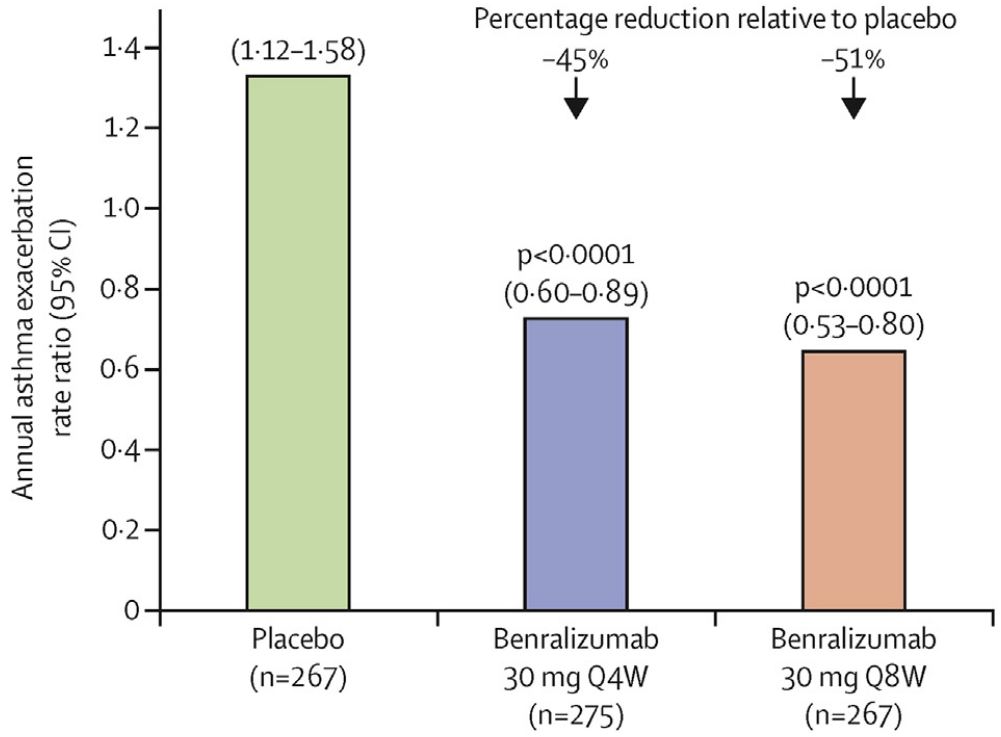


Benralizumab

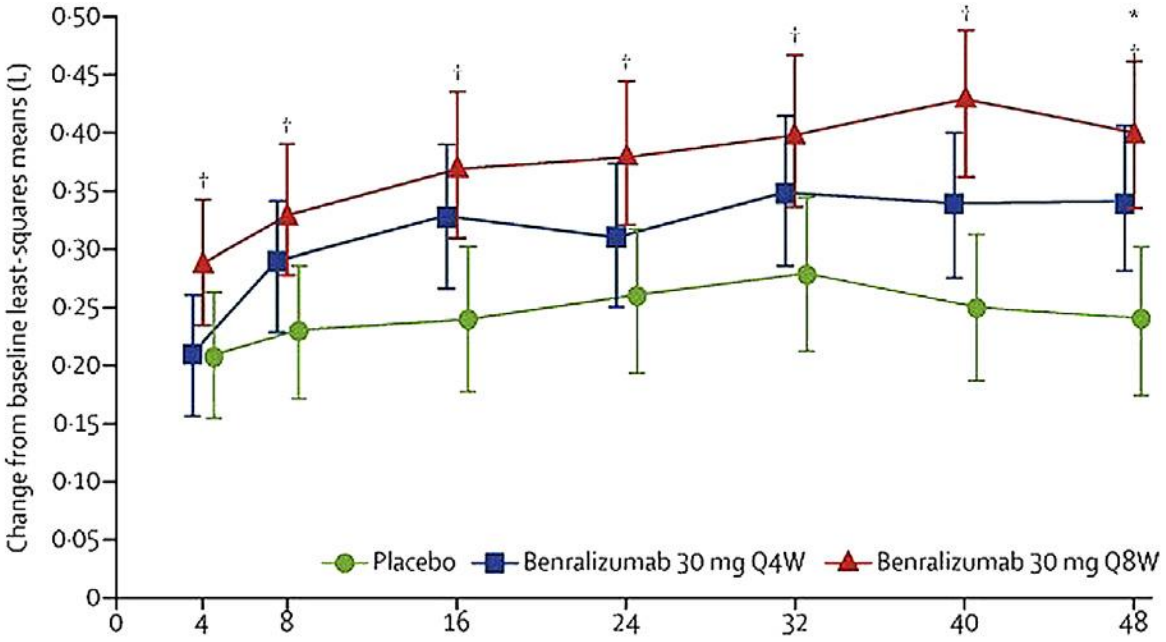
- Subcutaneous injection, 30mg given 4 weekly for 3 months, then 8 weekly thereafter
- 2 large Phase 3 trials (SIROCCO, CALIMA) – high dose ICS + LABA, (+/-OCS), 2 or more exacerbations

Benralizumab

- 2 large Phase 3 trials (SIROCCO, CALIMA) – high dose ICS + LABA, (+/-OCS), 2 or more exacerbations



Benralizumab- change in FEV1



Number at risk								
Benralizumab Q4W	275	261	259	251	253	243	245	236
Benralizumab Q8W	267	251	258	250	251	240	236	235
Placebo	267	249	253	246	247	238	232	233

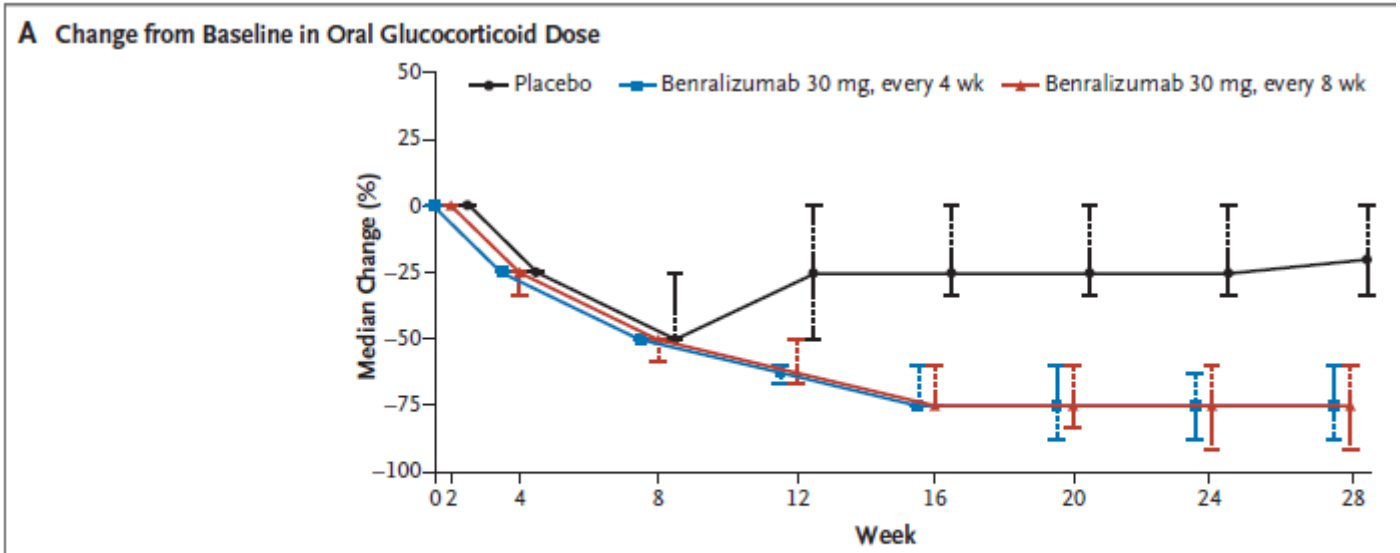
Trial (duration)	Annual exacerbation rate	FEV_1 change from baseline (L)
SIROCCO (48 weeks)		
Placebo	1.33 (267 patients)	0.239 (233 patients)
Benralizumab (every 4 weeks)	0.73 (275 patients)	0.345 (236 patients)
Benralizumab (every 8 weeks)	0.65 (267 patients)	0.398 (235 patients)
CALIMA (56 weeks)		
Placebo	0.93 (248 patients)	0.215 (244 patients)
Benralizumab (every 4 weeks)	0.60 (241 patients)	0.340 (238 patients)
Benralizumab (every 8 weeks)	0.66 (239 patients)	0.330 (238 patients)

Subcutaneous injections of benralizumab 30 mg were added to patients' usual therapy of high-dose inhaled corticosteroids plus long-acting beta agonists.

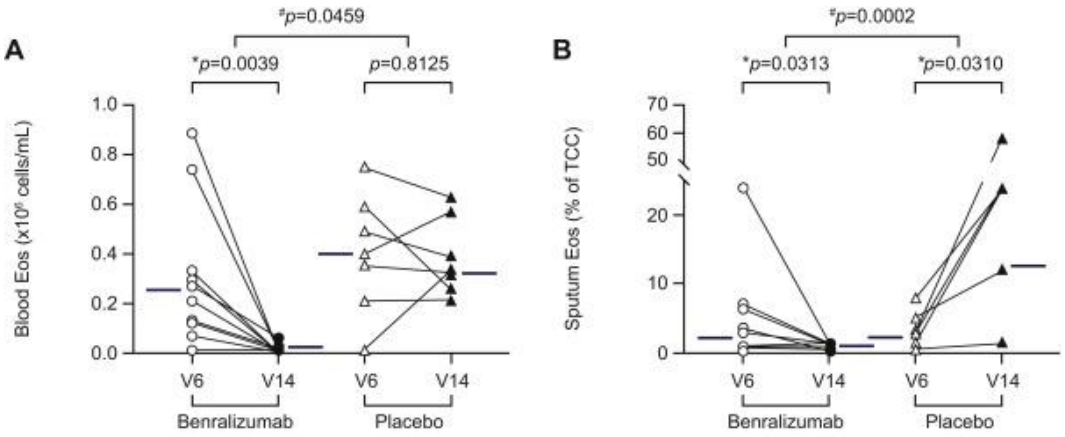
Participants in the analysis had blood eosinophil counts of at least 300 cells/microlitre ($\geq 0.3 \times 10^9$/L) at baseline. (The normal reference range for blood eosinophils is around $0–0.6 \times 10^9$/L.)

Benralizumab – steroid sparing

- ZONDA trial
  - 28 week study, severe asthmatics on OCS
  - 75% reduction in OCS in treatment arm (25% reduction in placebo arm, 52-56% reduced to 0mg
  - 55-70% reduction in exacerbation rate



- Reduces blood and sputum eosinophilia



Sehmi et al, JACI 2018

Benralizumab – NICE TA (published 6/3/19)

- Benralizumab, as an add-on therapy, is recommended as an option for treating severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose inhaled corticosteroids and long-acting beta-agonists, only if:
  - the person has agreed to and followed the optimised standard treatment plan and
  - the blood eosinophil count has been recorded as 300 cells per microlitre or more and the person has had 4 or more exacerbations needing systemic corticosteroids in the previous 12 months, or has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months (that is, the person is eligible for mepolizumab) or
  - the blood eosinophil count has been recorded as 400 cells per microlitre or more with 3 or more exacerbations needing systemic corticosteroids in the past 12 months (that is, the person is eligible for reslizumab).

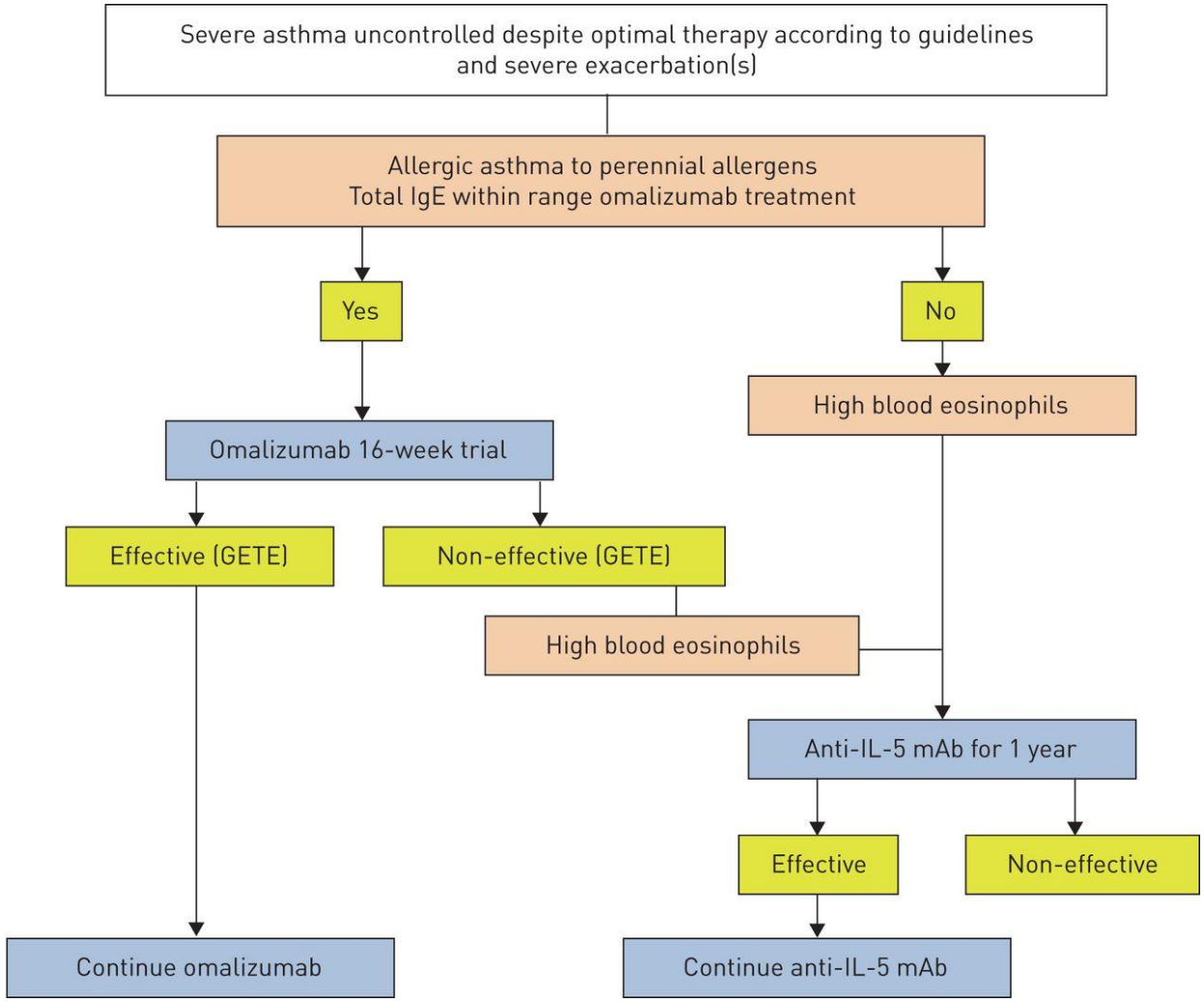
    Benralizumab is recommended only if the company provides it according to the commercial arrangement.
- If benralizumab, mepolizumab or reslizumab are equally suitable, start treatment with the least expensive option (taking into account drug and administration costs).

Which do I choose?

Which do I choose?

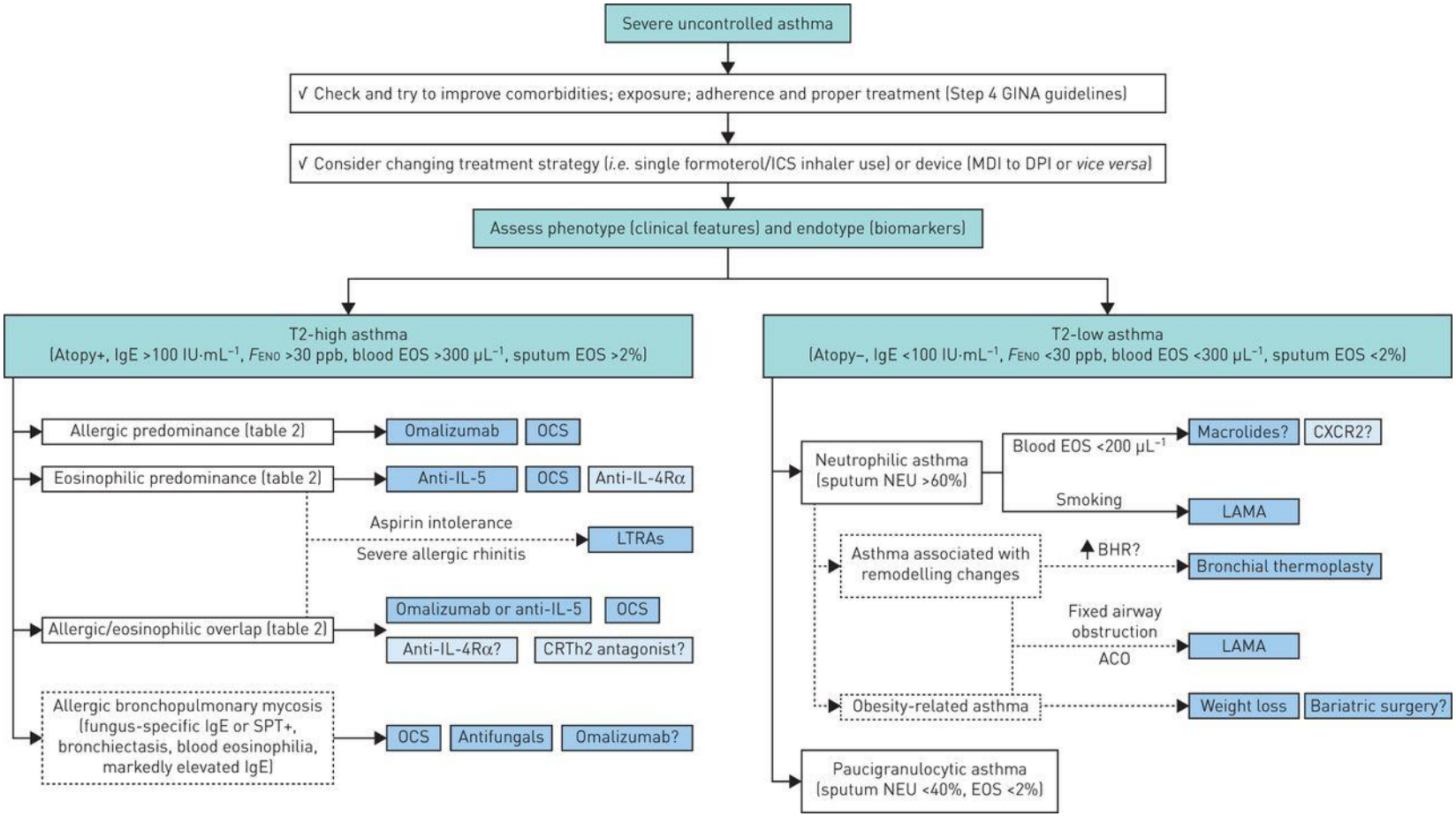
- Easy things – age, weight, NICE criteria
- ?Go with what you know
- ?Go with the practicalities/patient choice
  - Waiting lists
  - Self-injection coming
  - Homecare coming
  - Nursing support
- ?Phenotype even better

Care pathways for biologics in asthma.



Jean Bousquet et al. Eur Respir J 2017;50:1701782

A stepwise therapeutic approach in severe uncontrolled asthmatic subjects.



Eleftherios Zervas et al. ERJ Open Res 2018;4:00125-2017

TABLE 2

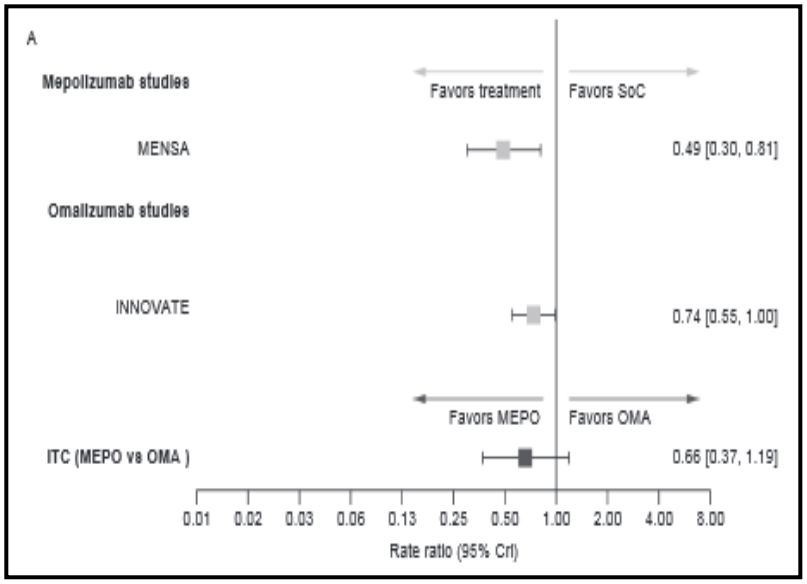
Clinical features and biomarkers that can be used to differentiate between allergic and eosinophilic T2-high severe asthma

	A: allergic-predominant asthma	B: eosinophilic-predominant asthma
1	Early onset	Late onset
2	SPT/RAST+ with clinically significant allergies#	SPT/RAST– or + with no clinically significant allergies
3	IgE >100 IU·mL^{-1}	IgE <100 IU·mL^{-1}
4	Allergic rhinitis	Nasal polyps
5	High F_{ENO} (30–50 ppb)	Very high F_{ENO} (>50 ppb)
6	Blood eosinophils <300 cells·µL^{-1}	Blood eosinophils >300 cells·µL^{-1}#

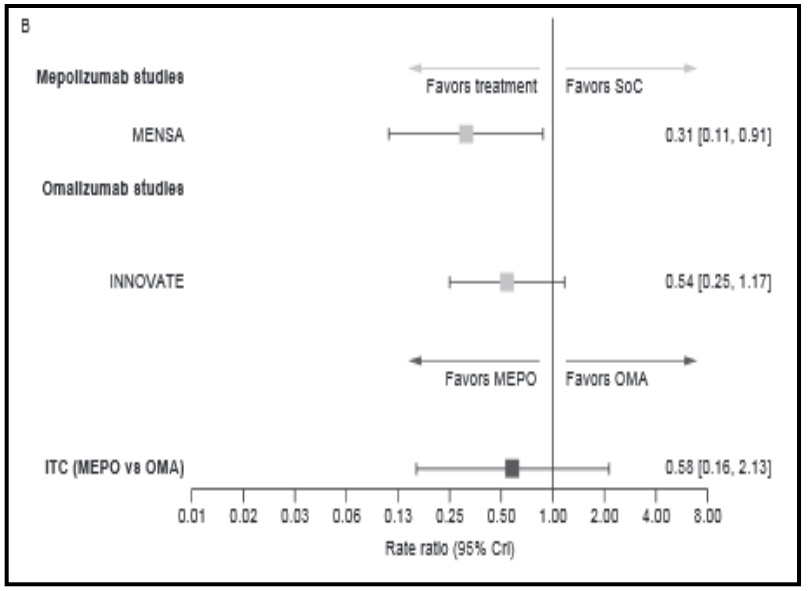
SPT: skin prick test; RAST: radioallergosorbent test; F_{ENO}: exhaled nitric oxide fraction. Check the number of relevant patient characteristics per column. If a patient has more features from column A or B it is more likely that he/she has allergic- or eosinophilic-predominant asthma, respectively. If the patient shares features from both columns, it is more likely that he/she suffers from eosinophilic/allergic overlap asthma. #: obligatory characteristics for allergic and/or eosinophilic asthma.

Which do I choose?

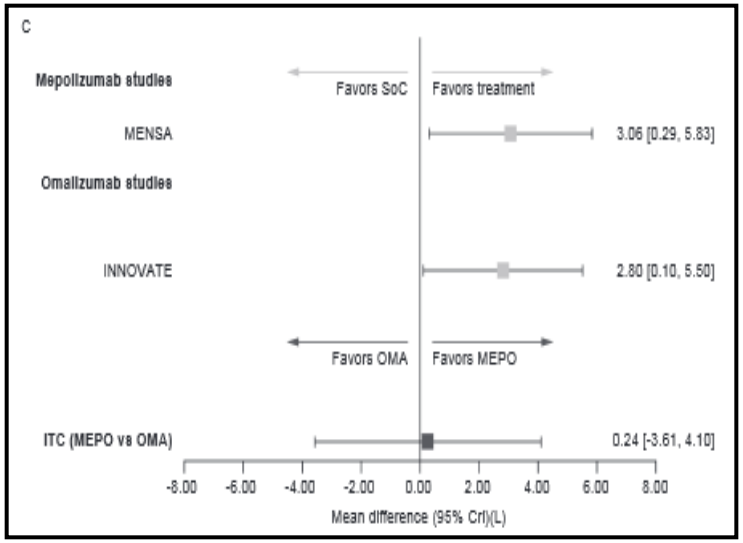
- Listen to drug-rep spin
  - Length of trial
  - ?Do we need some ‘good’ eosinophils
  - ?Does omalizumab have an antiviral effect
- No head to head, trials are subtly different



Exacerbations



Exacerbations requiring hospitalisation



Change in %pred FEV1

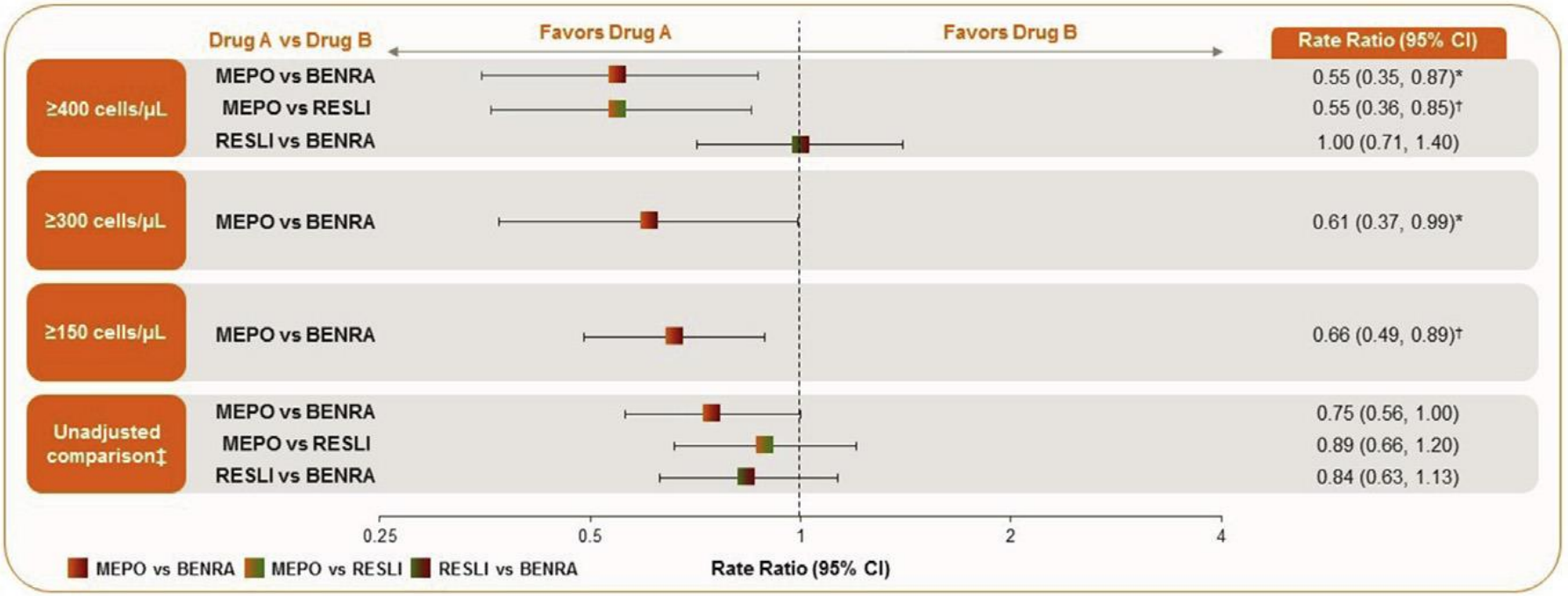
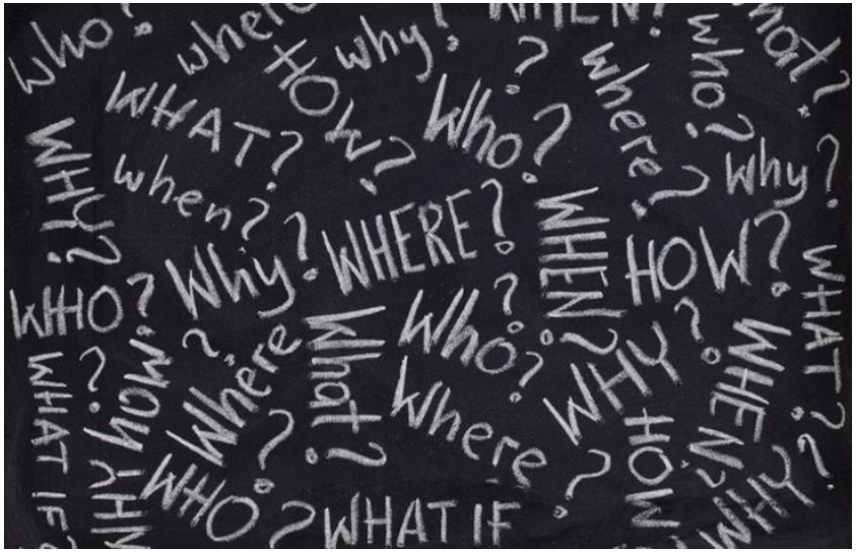
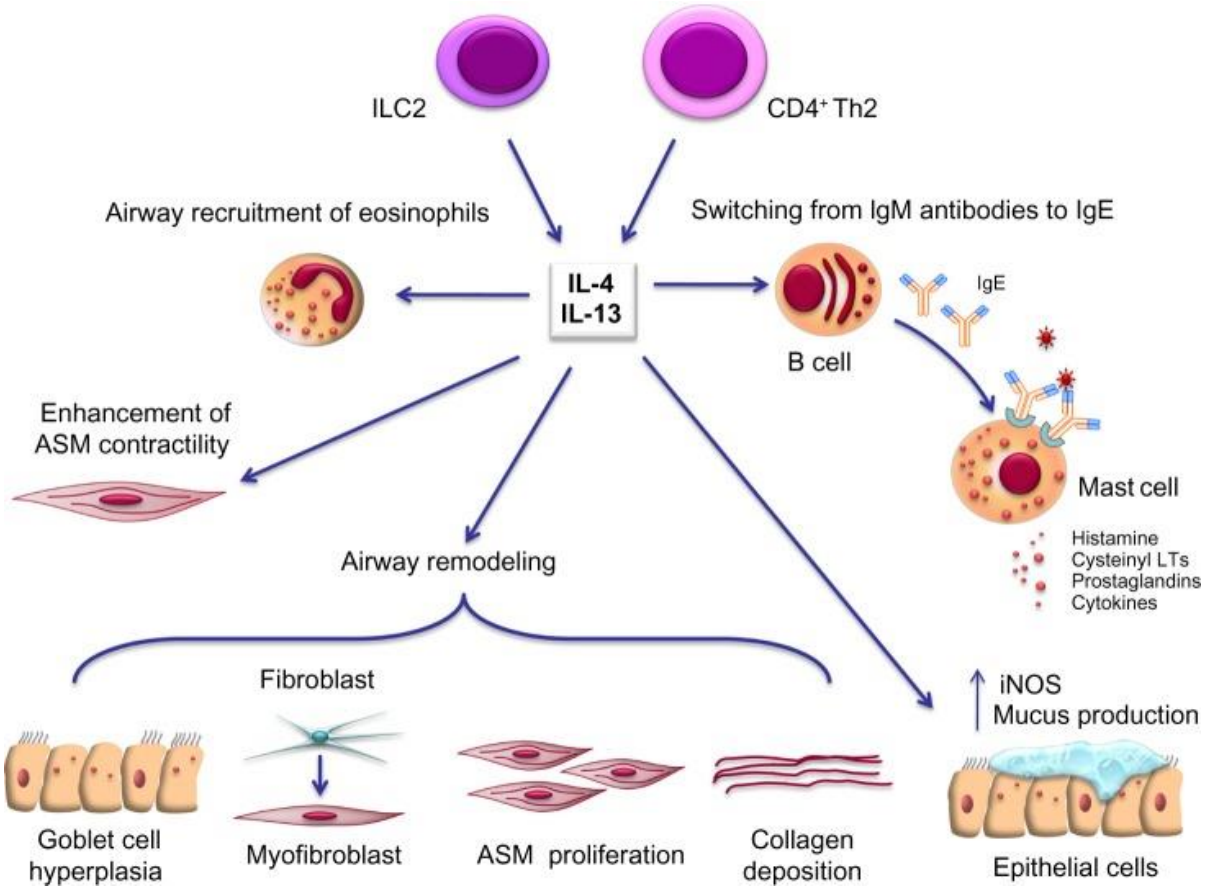


Fig. 8. Clinically significant exacerbations. Indirect comparisons of the rate of clinically significant exacerbations by baseline blood eosinophil subgroups and in the ITT population.
*p < 0.05, yp < 0.01, z Raw data that have not been adjusted for exacerbations and blood eosinophil threshold. Note: No comparisons with reslizumab were possible below 400 cells/
mL due to the inclusion criteria of those trials. BENRA, benralizumab; MEPO, mepolizumab; RESLI, reslizumab. Adapted from Busse W et al. J Allergy Clin Immunol 2019;
143:190e200.34

Lots of unknowns

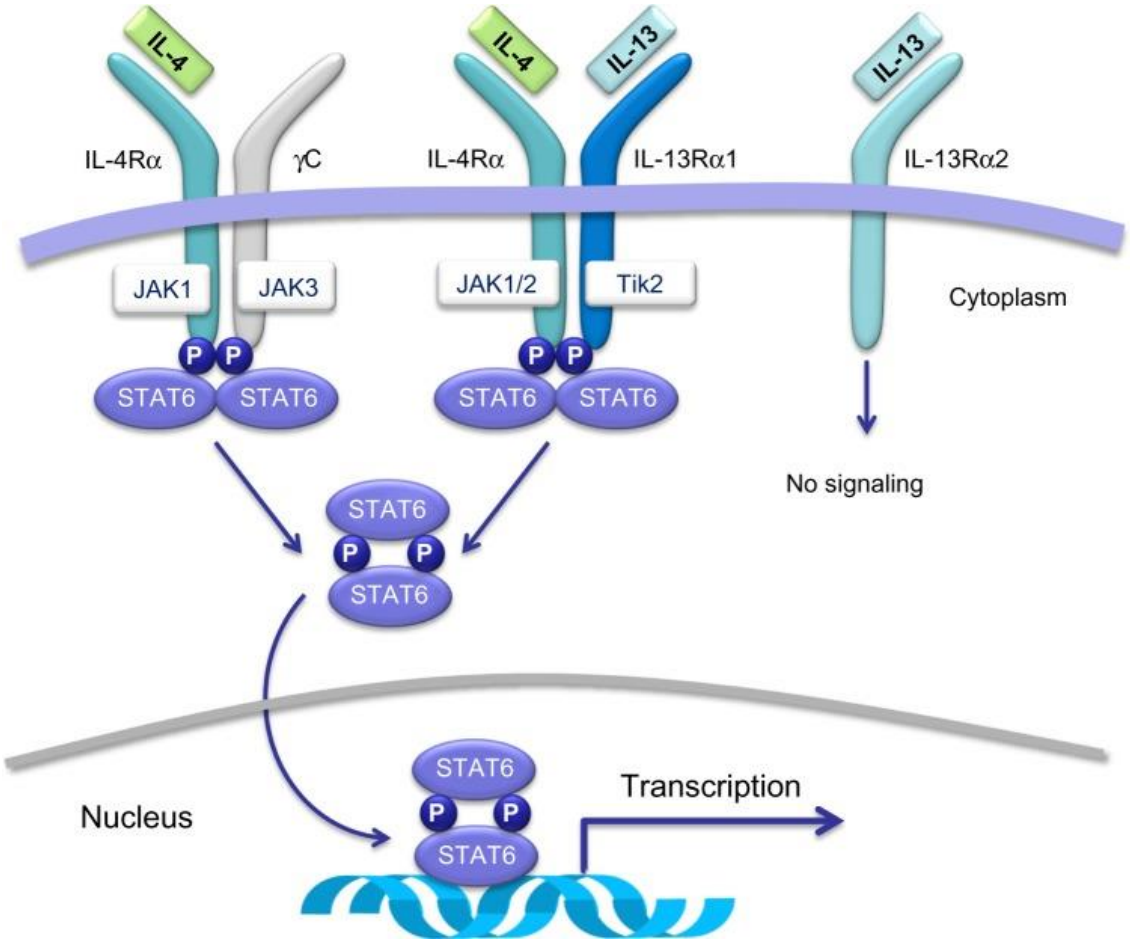
- What order?
- When to switch?
- What is good enough?
- What about the FeNO?




ILC2
CD4+ Th2
Airway recruitment of eosinophils
Switching from IgM antibodies to IgE
IL-4
IL-13
IgE
B cell
Enhancement of
ASM contractility
Mast cell
Histamine
Cysteinyl LTs
Prostaglandins
Cytokines
Airway remodeling
Fibroblast
iNOS
Mucus production
Goblet cell
hyperplasia
Myofibroblast
ASM proliferation
Collagen
deposition
Epithelial cells

Anti-IL13

- Lebrikizumab – mixed results from phase III trials, discontinued for asthma at present
- Tralokinumab – did not significantly reduce exacerbation rate in first of 2 phase III trials (STRATOS)


IL-4
IL-4Rα
γC
JAK1
JAK3
P
P
STAT6
STAT6
IL-4
IL-13
IL-4Rα
IL-13Rα1
JAK1/2
Tik2
P
P
STAT6
STAT6
IL-13
IL-13Rα2
Cytoplasm
No signaling
STAT6
P
P
STAT6
Nucleus
STAT6
P
P
STAT6
Transcription

Dupilumab

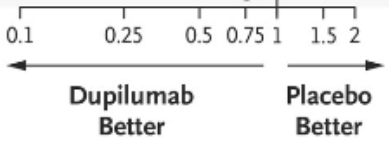
- Targeted against alpha subunit of the IL-4 receptor
- Given subcutaneously 2 weekly
- Already licensed in UK in atopic dermatitis
- Initial dose/subsequent doses dependant on whether steroid dependant vs mod-severe (as trial data differed)

Dupilumab

- Phase 2b promising (Wenzel et al, NEJM 2013)
  - Decreased exacerbations, improved control/lung function but withdrawal trial
- Phase 3 (LIBERTY trials)
  - Castro et al, NEJM 2018 Liberty Asthma quest
  - Liberty Venture (steroid sparing)

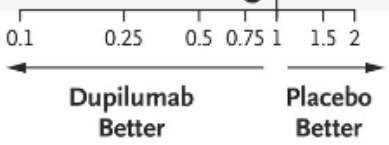
A Dupilumab, 200 mg Every 2 Wk, vs. Matched Placebo

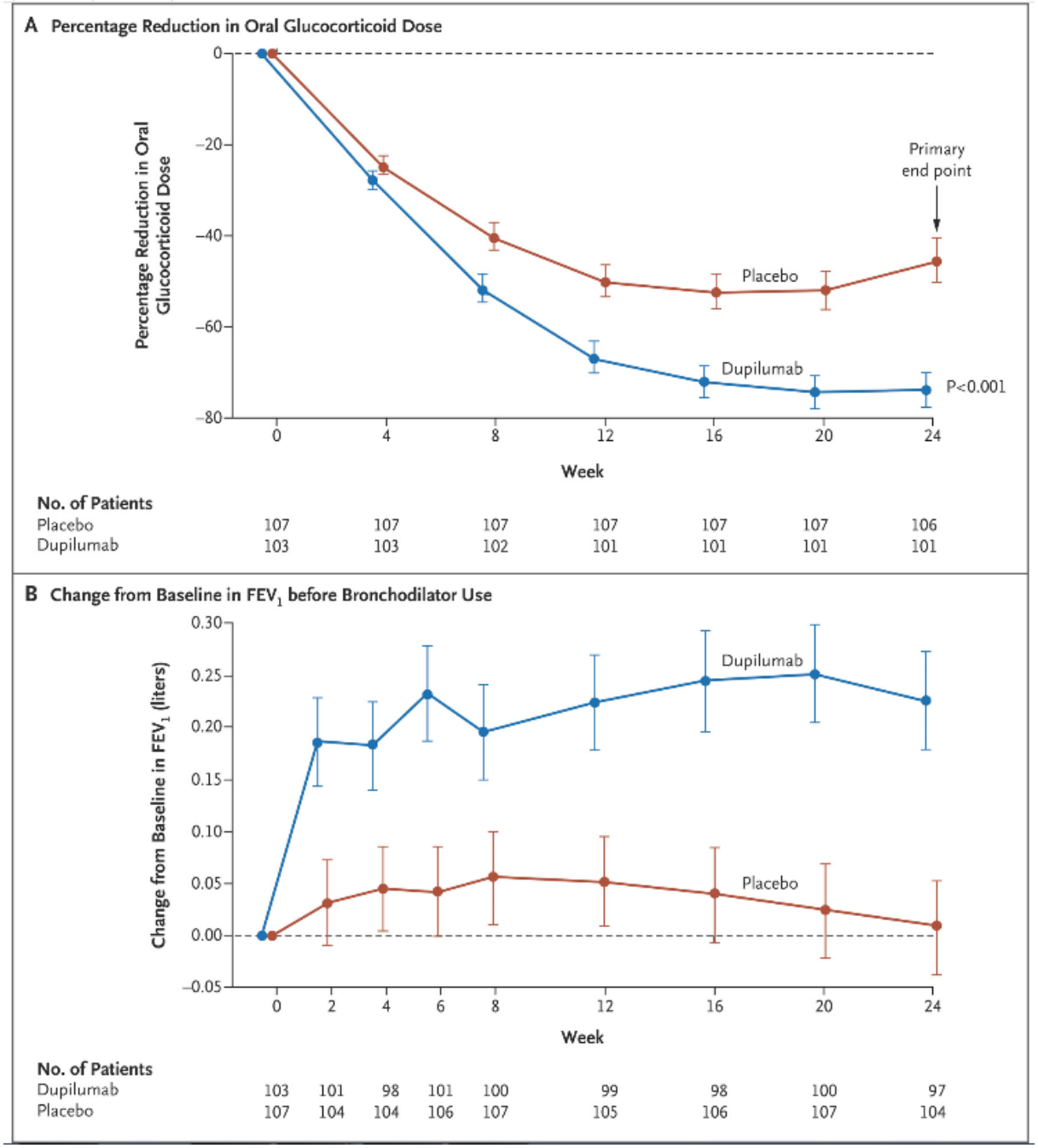
Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	317	631	0.52 (0.41–0.66)
Eosinophil count			
≥300 cells/mm³	148	264	0.34 (0.24–0.48)
≥150 to <300 cells/mm³	84	173	0.64 (0.41–1.02)
<150 cells/mm³	85	193	0.93 (0.58–1.47)
Fe_{NO}			
≥50 ppb	71	119	0.31 (0.18–0.52)
≥25 to <50 ppb	91	180	0.39 (0.24–0.62)
<25 ppb	149	325	0.75 (0.54–1.05)



B Dupilumab, 300 mg Every 2 Wk, vs. Matched Placebo

Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	321	633	0.54 (0.43–0.68)
Eosinophil count			
≥300 cells/mm³	142	277	0.33 (0.23–0.45)
≥150 to <300 cells/mm³	95	175	0.56 (0.35–0.89)
<150 cells/mm³	83	181	1.15 (0.75–1.77)
Fe_{NO}			
≥50 ppb	75	124	0.31 (0.19–0.49)
≥25 to <50 ppb	97	186	0.44 (0.28–0.69)
<25 ppb	144	317	0.79 (0.57–1.10)

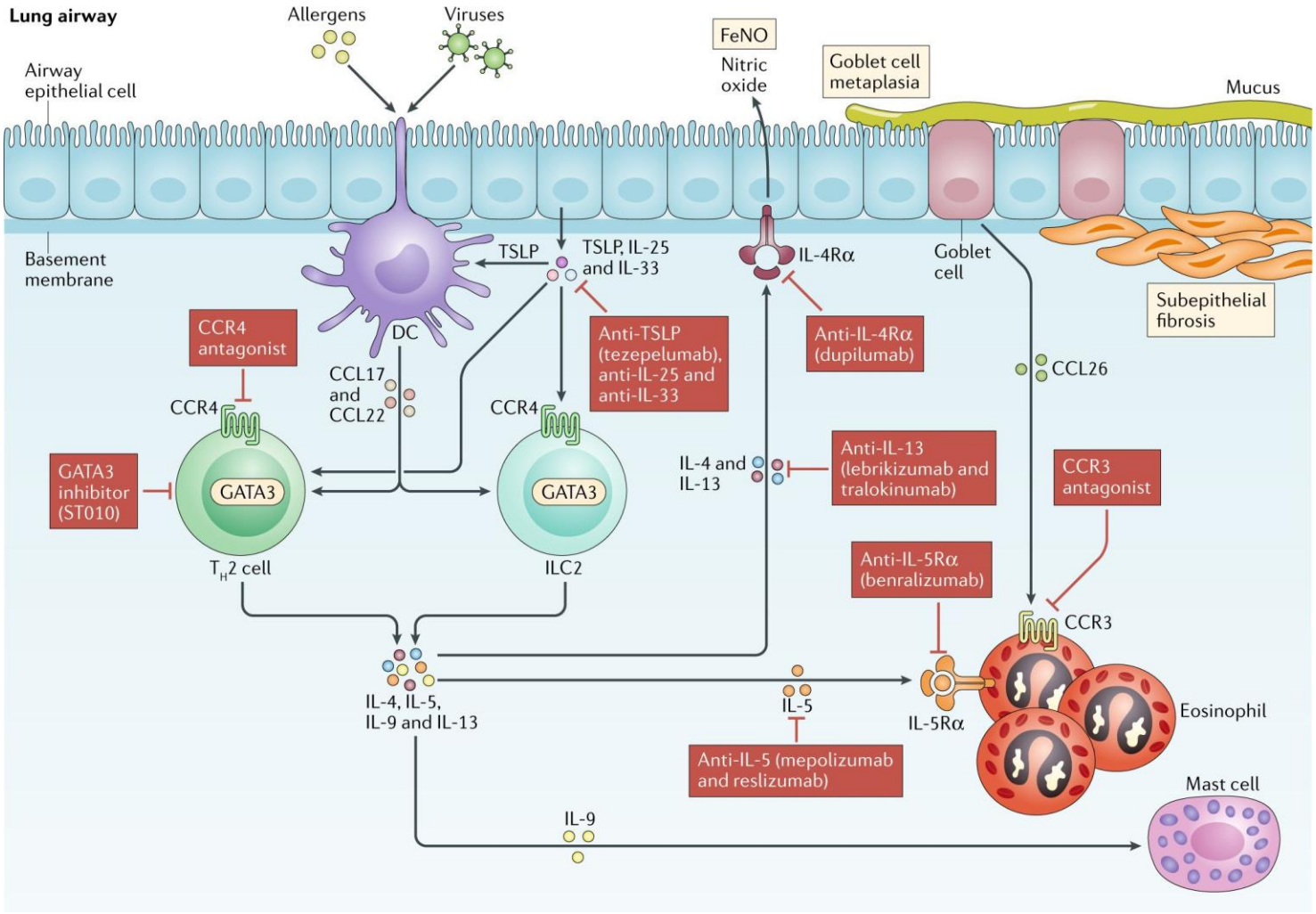



A Percentage Reduction in Oral Glucocorticoid Dose
Percentage Reduction in Oral Glucocorticoid Dose
0
−20
−40
−60
−80
Primary end point
Placebo
Dupilumab
P<0.001
0
4
8
12
16
20
24
Week
No. of Patients
Placebo 107 107 107 107 107 107 106
Dupilumab 103 103 102 101 101 101 101
B Change from Baseline in FEV1 before Bronchodilator Use
Change from Baseline in FEV1 (liters)
0.30
0.25
0.20
0.15
0.10
0.05
0.00
−0.05
Dupilumab
Placebo
0
2
4
6
8
12
16
20
24
Week
No. of Patients
Dupilumab 103 101 98 101 100 99 98 100 97
Placebo 107 104 104 106 107 105 106 107 104

Dupilumab

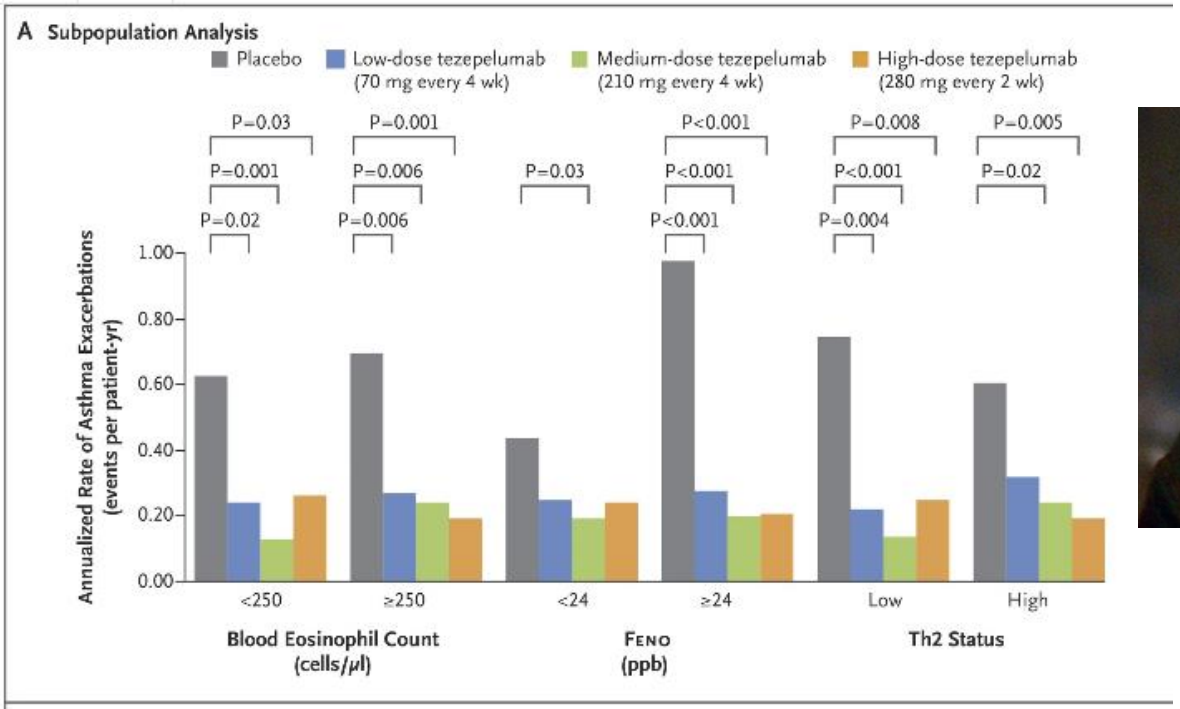
- FDA approved
- EMA approved
- NICE TA in progress ?expected 2020

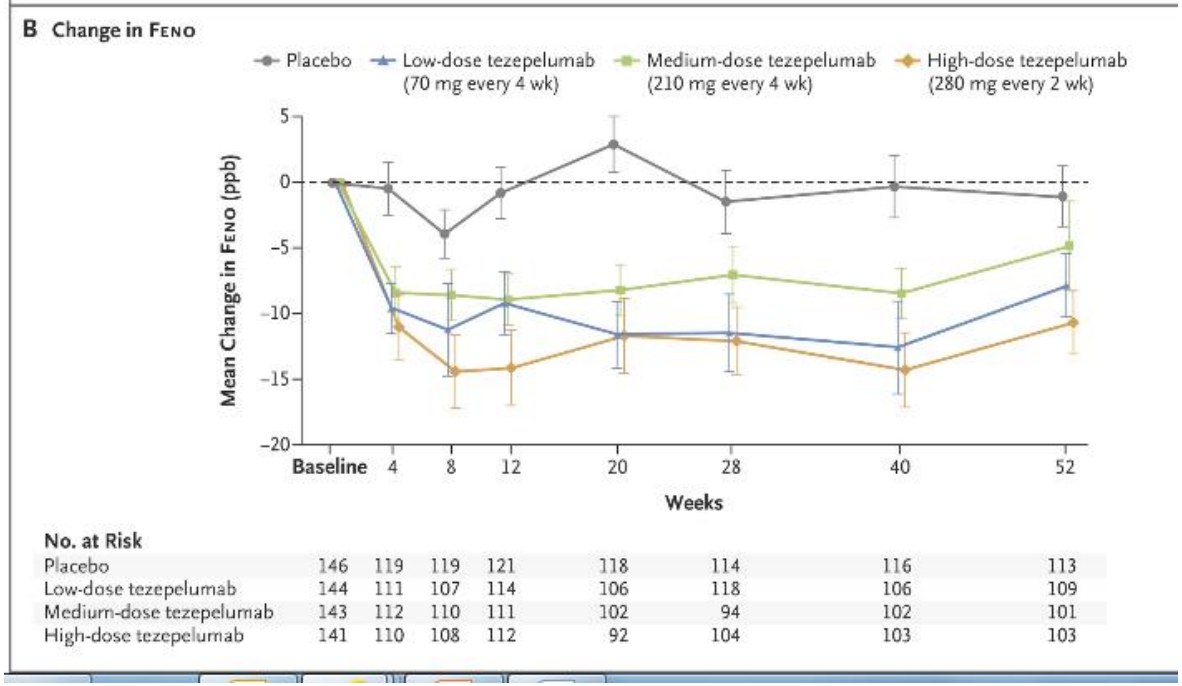
Tezepelumab



Tezepelumab

- Phase 2 trial (PATHWAY) Corren et al, NEJM 2017
  - ICS plus LABA pts
  - Reduced exacerbations, independent of eosinophil counts





No. at Risk

Placebo	146	119	119	121	118	114	116	113
Low-dose tezepelumab	144	111	107	114	106	118	106	109
Medium-dose tezepelumab	143	112	110	111	102	94	102	101
High-dose tezepelumab	141	110	108	112	92	104	103	103

Let's wait for phase 3 (ongoing)

Summary

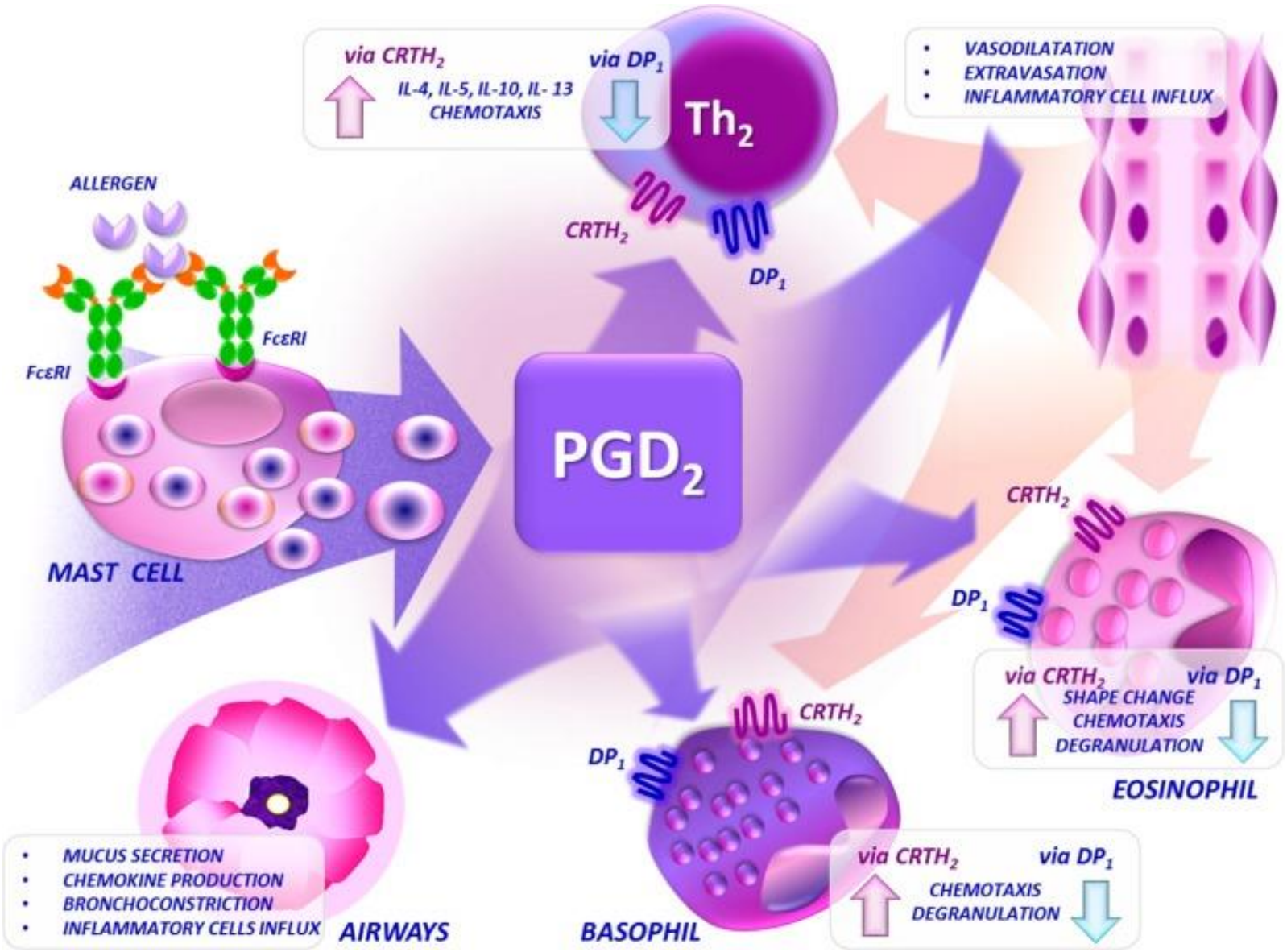
- Increasing use of monoclonals, targeting select populations of severe asthmatics
- Already target atopic
- IL-5/eosinophilic targeting now here, ~50% reduction, mainly in exacerbation/OCS dose, less impressive on lung function/questionnaires
  - Think of them in anyone having 3-4 exacerbations/year, with eosinophils > 0.3-0.4, ONCE ALL THE BASICS HAVE BEEN DONE
- Varied criteria, this and the treatments to come will make this a complex but interesting area.

Questions?

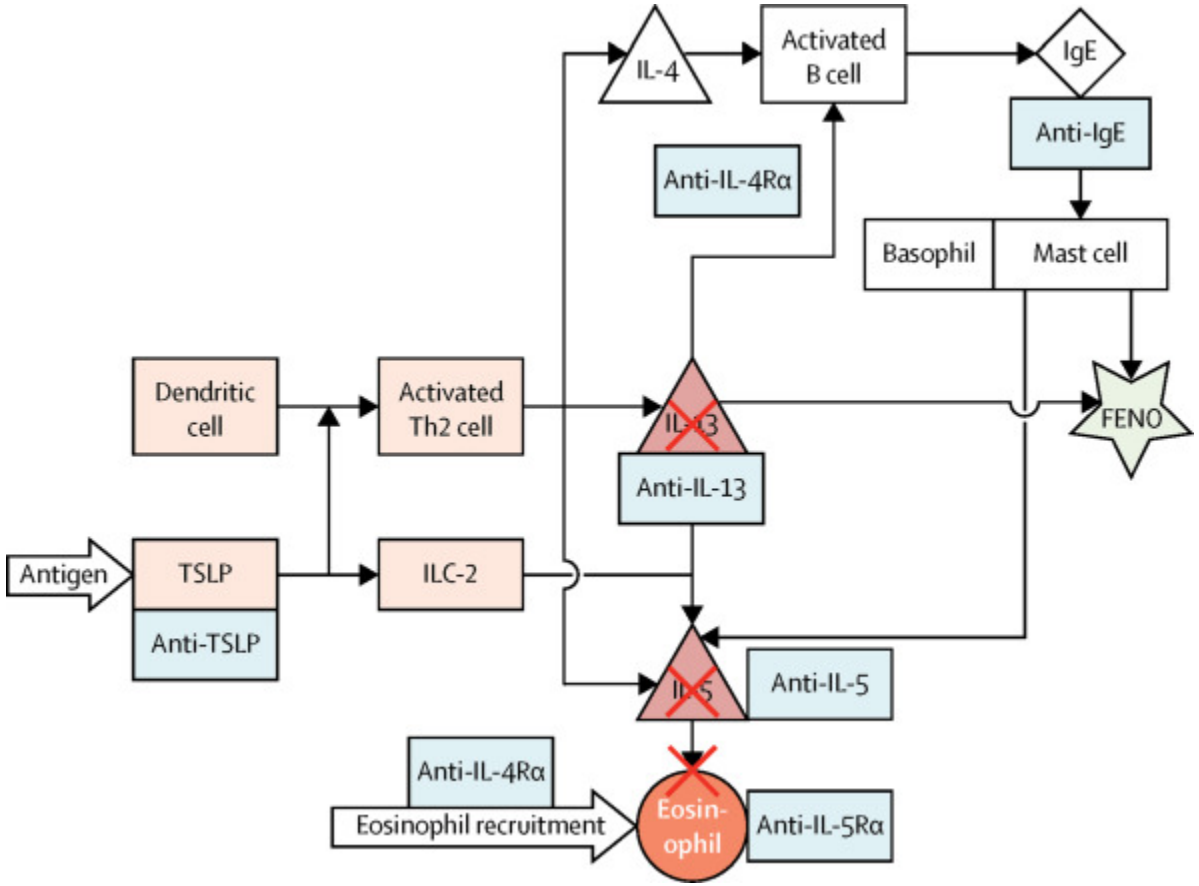

MABS
I LOVE
YOU
SO
MUCH

Fevpiprant/CRTH2 pathway blockers

- Arachidonic acid (AA) metabolized by COX enzymes, leading to prostaglandins, PGH2, which is then converted to PGD2.
- PGD2 produced by activated mast cells following allergen exposure, acts on 3 different receptors, DP1, DP2 (also known as CRTH2), and TP.
- DP and CRTH2 receptors implicated in allergic inflammation, possibly antagonistic


via CRTH2
via DP1
IL-4, IL-5, IL-10, IL- 13
CHEMOTAXIS
Th2
CRTH2
DP1
VASODILATATION
EXTRAVASATION
INFLAMMATORY CELL INFLUX
ALLERGEN
FcεRI
FcεRI
MAST CELL
PGD2
CRTH2
DP1
via CRTH2
via DP1
SHAPE CHANGE
CHEMOTAXIS
DEGRANULATION
EOSINOPHIL
CRTH2
DP1
MUCUS SECRETION
CHEMOKINE PRODUCTION
BRONCHOCONSTRICTION
INFLAMMATORY CELLS INFLUX
AIRWAYS
BASOPHIL
via CRTH2
via DP1
CHEMOTAXIS
DEGRANULATION

- Small molecule antagonists of CRTH2 receptor have been developed
- Oral administration
- Effect probably greater in eosinophilic phenotype
- Several in development e.g. Fevpiprant, Gossamer Bio (unnamed)
  - Phase II studies show promise (↓ exacerbations, possible improvement in FEV, although ACQ/AQLA unchanged)
  - Phase III in progress


IL-4
Activated B cell
IgE
Anti-IgE
Anti-IL-4Rα
Basophil
Mast cell
Dendritic cell
Activated Th2 cell
IL-13
FENO
Anti-IL-13
Antigen
TSLP
ILC-2
Anti-TSLP
IL-5
Anti-IL-5
Anti-IL-4Rα
Eosinophil recruitment
Eosin-ophil
Anti-IL-5Rα