Biothérapies dans l'asthme

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Conflits d’intérêt

J’ai actuellement, ou j’ai eu au cours des 3 dernières années, une affiliation ou des intérêts financiers ou intérêt de tout ordre avec les sociétés commerciales suivantes en lien avec la santé :

Astra Zeneca
Boehringer
Chiesi
GSK
Mundi Pharma
Novartis
Roche
Sanofi
Stallergene
Teva

List of stems for monoclonal antibody nomenclature[1][2][3]

Prefix	Target substem			Source substem		Stem
	old	new	meaning		meaning	
variable	-anibi-	—	angiogenesis (inhibitor)	-a-	rat	-mab -pab
	-ba(c)-	-b(a)-	bacterium	-e-	hamster	
	-ci(r)-	-c(i)-	circulatory system	-i-	primate	
	-fung-	-f(u)-	fungus	-o-	mouse	
	-gr(o)-	-gr(o)-	growth factor	-u-	human	
	-ki(n)-	-k(i)-	interleukin	-xi-	chimeric (human/foreign)	
	-les-	—	inflammatory lesions	-zu-	humanized	
	-li(m)-	-l(i)-	immune system	-vet-	veterinary	
	-mul-	—	musculoskeletal system	-xizu-*	chimeric/humanized hybrid	
	-ne(u)(r)-	-n(e)-*	nervous system	-axo-	rat/mouse hybrid (see *trifunctional antibody*)	
	-os-	-s(o)-	bone			
	-toxa-	-tox(a)-	toxin			
	-co(l)-	-t(u)-	colonic tumor			
	-go(t)-		testicular tumor			
	-go(v)-		ovarian tumor			
	-ma(r)-		mammary tumor			
	-me(l)-		melanoma			
	-pr(o)-		prostate tumor			
	-tu(m)-		miscellaneous tumor			
	-vi(r)-	-v(i)-	virus			

Benra-li-zu-mab
Tralo-kin-u-mab

Définition ERS/ATS 2014 de l'asthme sévère

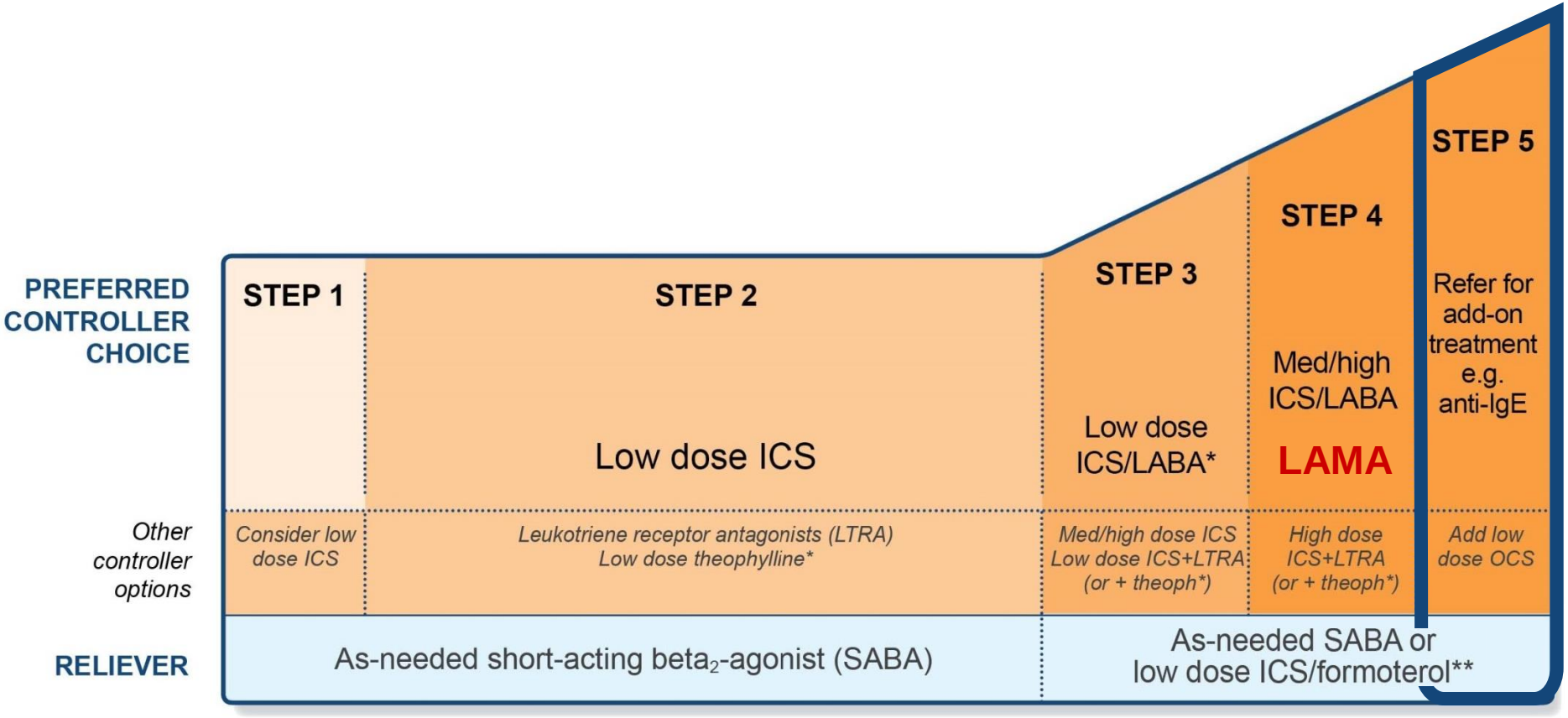
- Asthme nécessitant un traitement par corticostéroïdes inhalés à dose élevée et un β2 LDA +/- un autre traitement sur les 12 mois précédents

- et/ou corticostéroïdes *per os* > de 50% sur les 12 mois précédents

  - pour obtenir le contrôle des symptômes
  - et/ou qui s'aggrave en cas de réduction de ce traitement
  - et/ou qui demeure non contrôlé malgré ce traitement

Kian F. Chung et al. *Eur Respir J* 2014

Quand envisager les biothérapies dans l'asthme ?



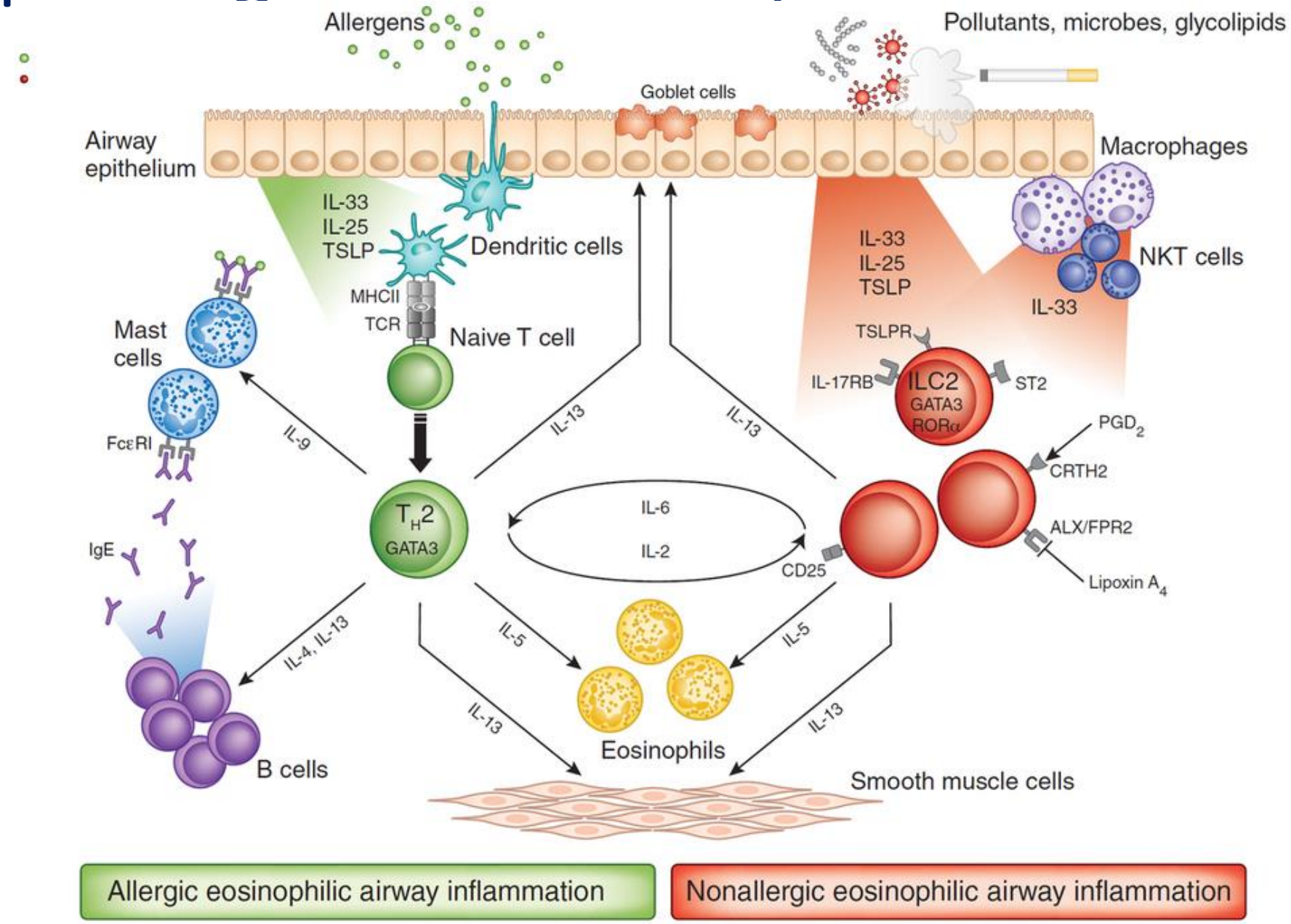
*For children 6-11 years, theophylline is not recommended, and preferred Step 3 is medium dose ICS
**For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy

Quand envisager une biothérapie dans l'asthme ?

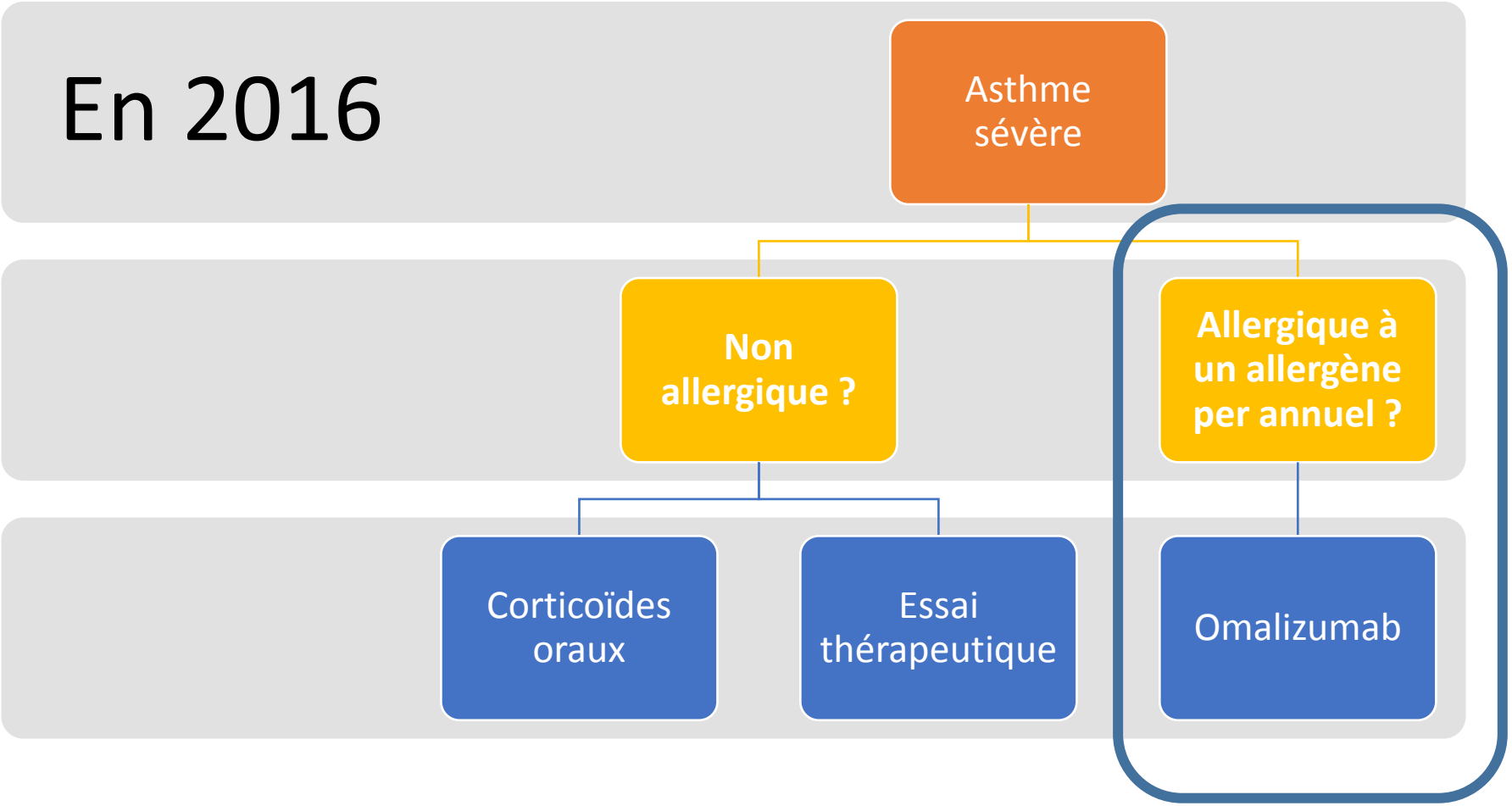
Regarder le patient prendre le traitement **Discuter l'observance et les barrières à l'observance**	**Utiliser une check list, Corriger les erreurs, revérifier régulièrement,** **Empathie pour parler des difficultés d'observance**
Confirmer le diagnostic d'asthme	**Scanner si obstruction persistante sous traitement**
Chercher et traiter les facteurs aggravants et comorbidités	**AINS, beta bloquants, allergènes, tabac,** **Rhinite, obésité, RGO, anxiété-dépression, SAOS**
Discuter augmentation de palier thérapeutique	**Décision partagée, évaluer le risque/bénéfice**
Adresser le patient à un centre spécialisé	**Si mauvais contrôle après 3-6 mois de traitement de palier 4, ou plus tôt si symptômes sévères ou doute sur le diagnostic**

GINA 2014

Physiopathologie de l'asthme : quelles cibles ?



Quelles caractéristiques de l'asthme peuvent influencer le choix du traitement ?

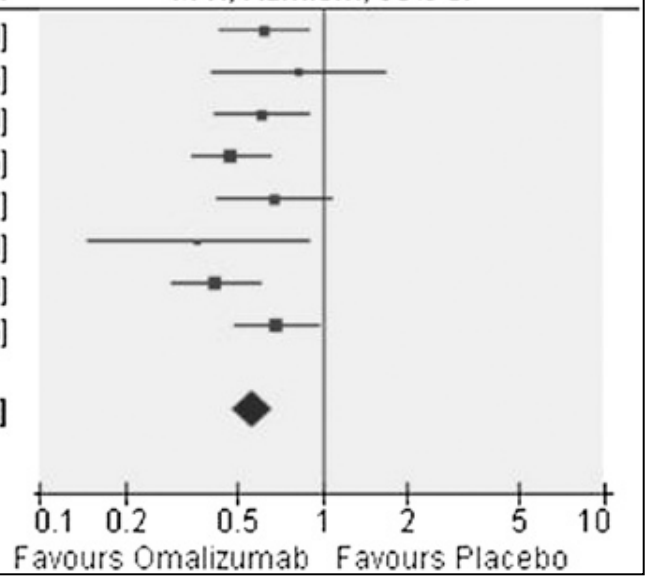


Anti IgE : omalizumab (Xolair®)

Study or Subgroup	Omalizumab Events	Omalizumab Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Busse 2001	39	268	60	257	15.5%	0.62 [0.43, 0.90]
Holgate 2004	13	126	15	120	4.8%	0.83 [0.41, 1.66]
Humbert 2005	35	246	55	236	14.2%	0.61 [0.42, 0.90]
Lanier 2009	56	384	59	192	18.9%	0.47 [0.34, 0.65]
Milgrom 2001	35	225	25	109	10.4%	0.68 [0.43, 1.07]
Ohta 2009	6	151	18	164	3.0%	0.36 [0.15, 0.89]
Soler 2001	35	274	83	272	16.0%	0.42 [0.29, 0.60]
Vignola 2004	43	209	59	196	17.2%	0.68 [0.49, 0.96]
Total (95% CI)		**1883**		**1546**	**100.0%**	**0.57 [0.48, 0.66]**
Total events	262		374			

Heterogeneity: Tau² = 0.01; Chi² = 8.15, df = 7 (P = 0.32); I² = 14%

Test for overall effect: Z = 7.06 (P < 0.00001)



- Réduit les exacerbations sévères , effet sur ACQ et AQLQL, consommation médicamenteuse
- Études de vraie vie : résultats similaires
- Coût-efficacité démontré

Rodrigo GJ *et al. Chest*. 2011 Jan;139(1):28-35

Omalizumab : quels répondeurs ?

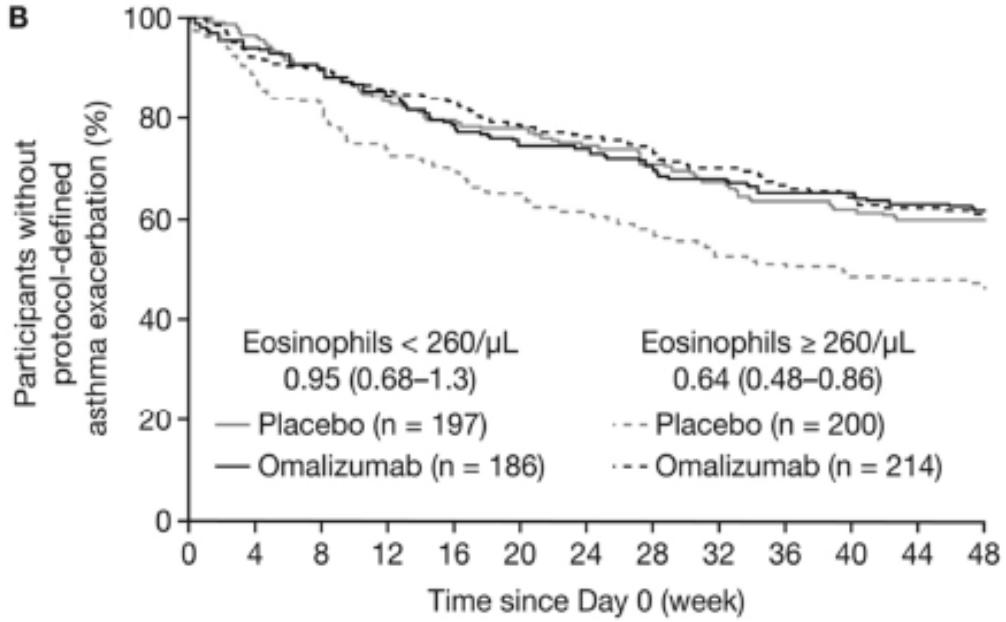
- 70 à 80% de répondeurs dans les essais cliniques et dans la « vraie vie »

- Facteurs prédictifs de réponse :

➢ Pas de différence sur les paramètres cliniques

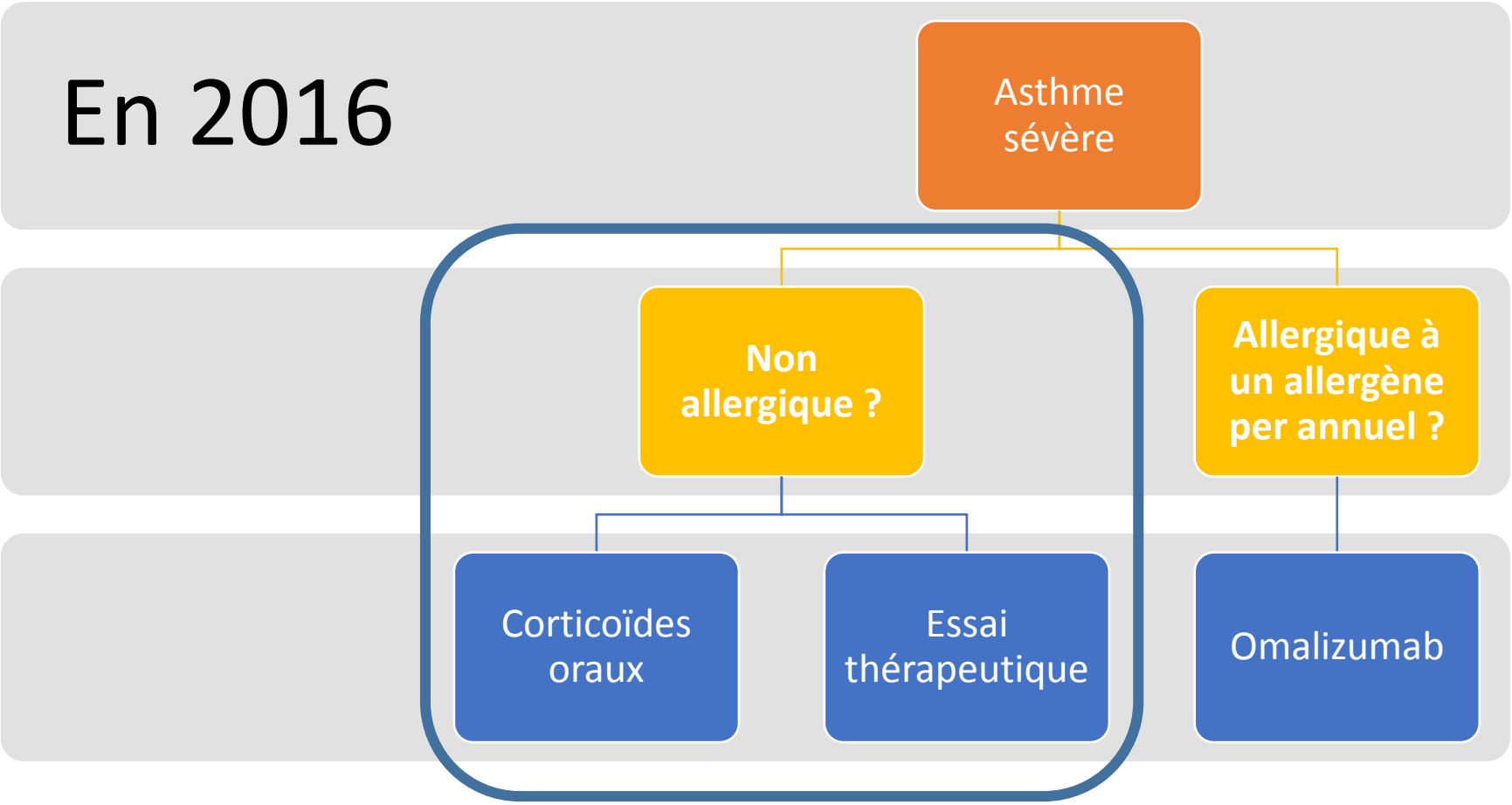
➢ Aucun biomarqueur n'a fait la preuve de son intérêt (baisse des IgE libres, baisse de l'expression du FcERI, diminution des basophiles…)

➢ Bonne réponse associée à l'éosinophilie ou au FeNO



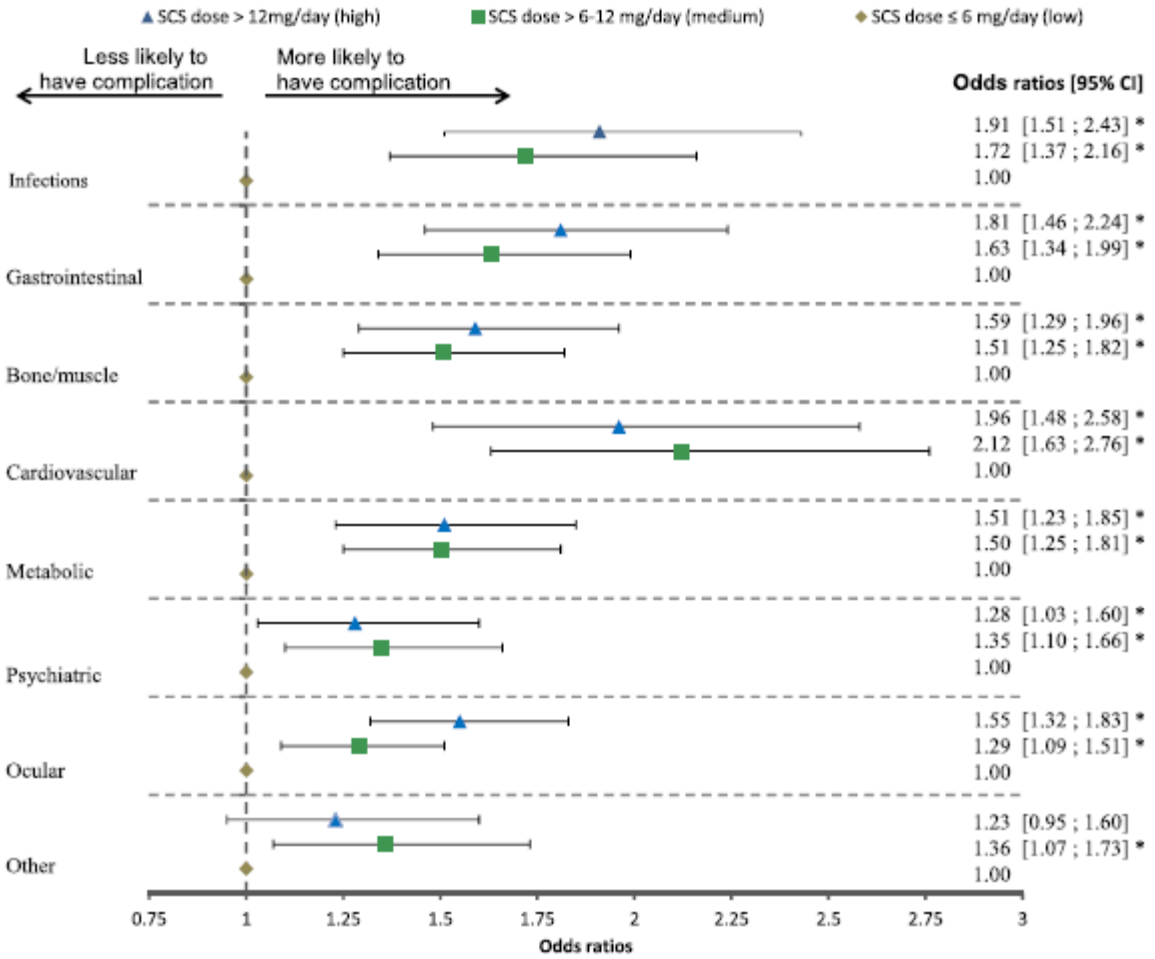
N. Hanania, AJRCCM, 2013

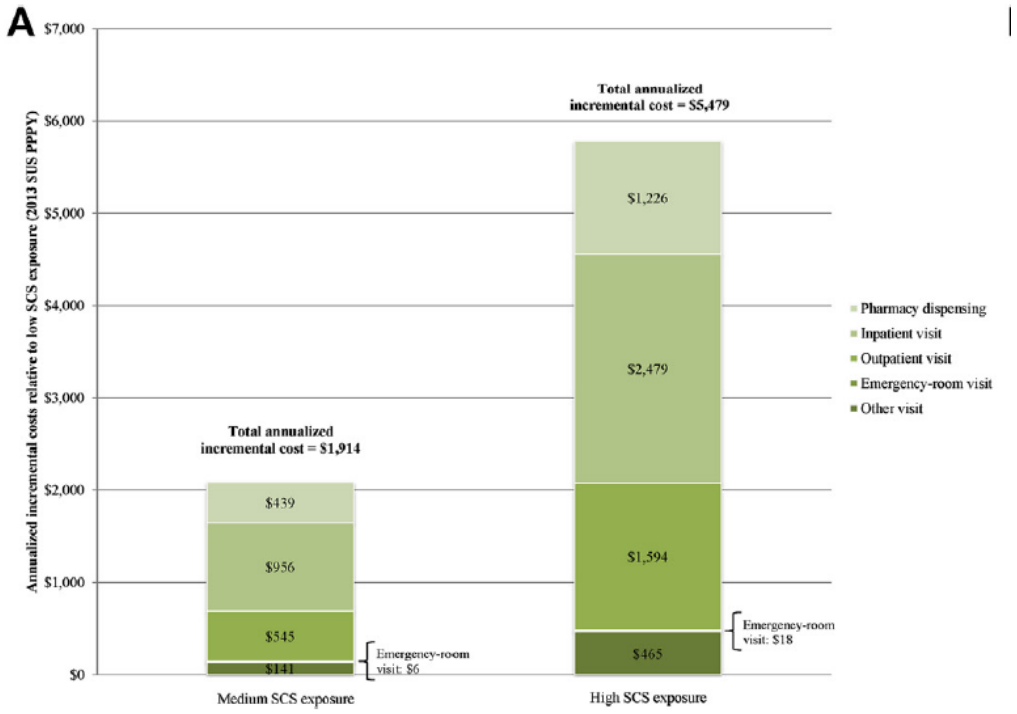
Quelles caractéristiques de l'asthme peuvent influencer le choix du traitement ?



Les corticoïdes oraux ?

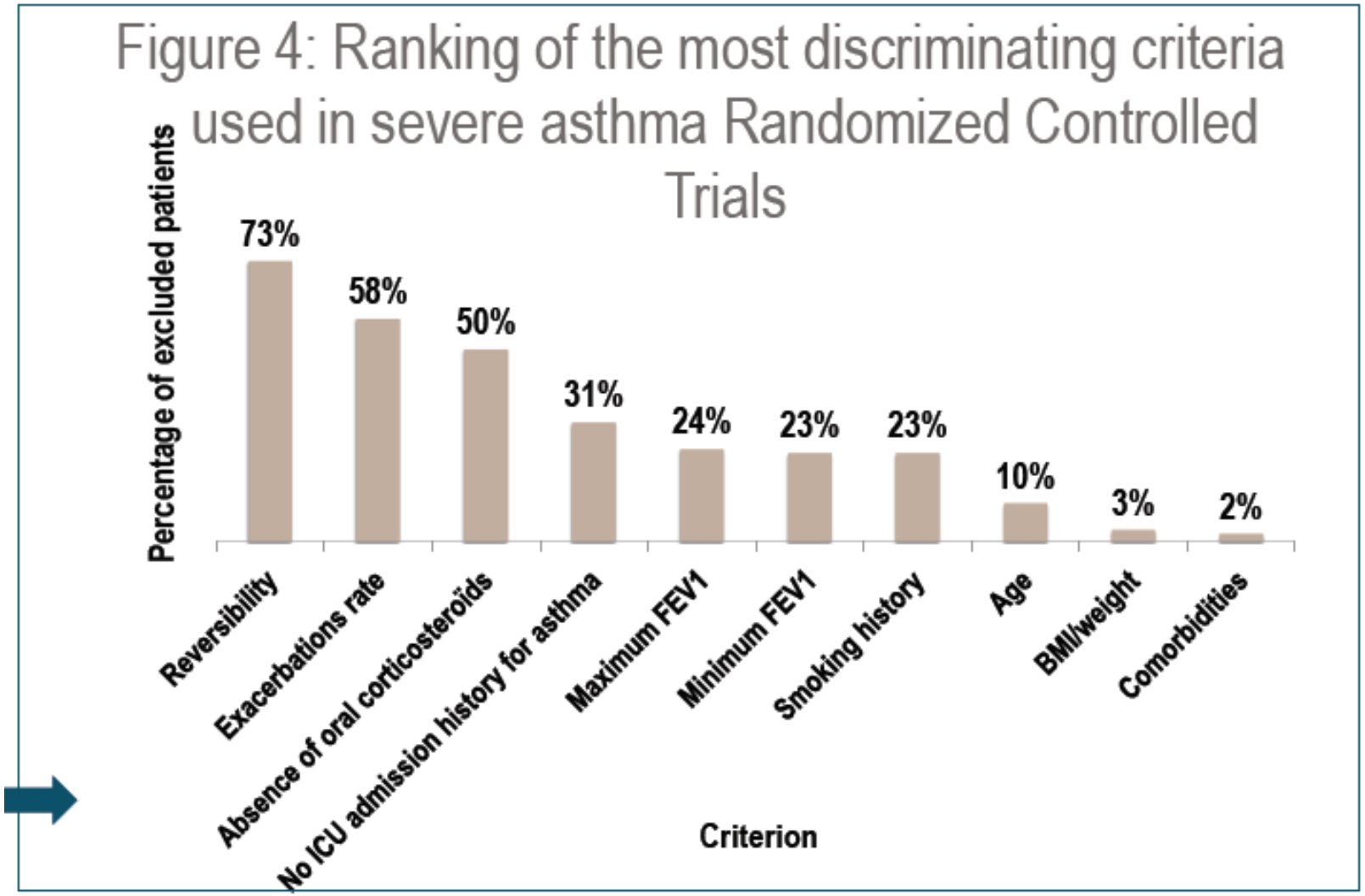
	Overall study population (n = 3628)	Low SCS exposure (n = 368)	Medium SCS exposure (n = 1630)	High SCS exposure (n = 1630)
Age at index date (y), mean ± SD (median)	57.6 ± 16.3 (57.7)	62.4 ± 16.9 (62.6)	60.0 ± 16.0 (60.6)	54.2 ± 15.7 (54.1)





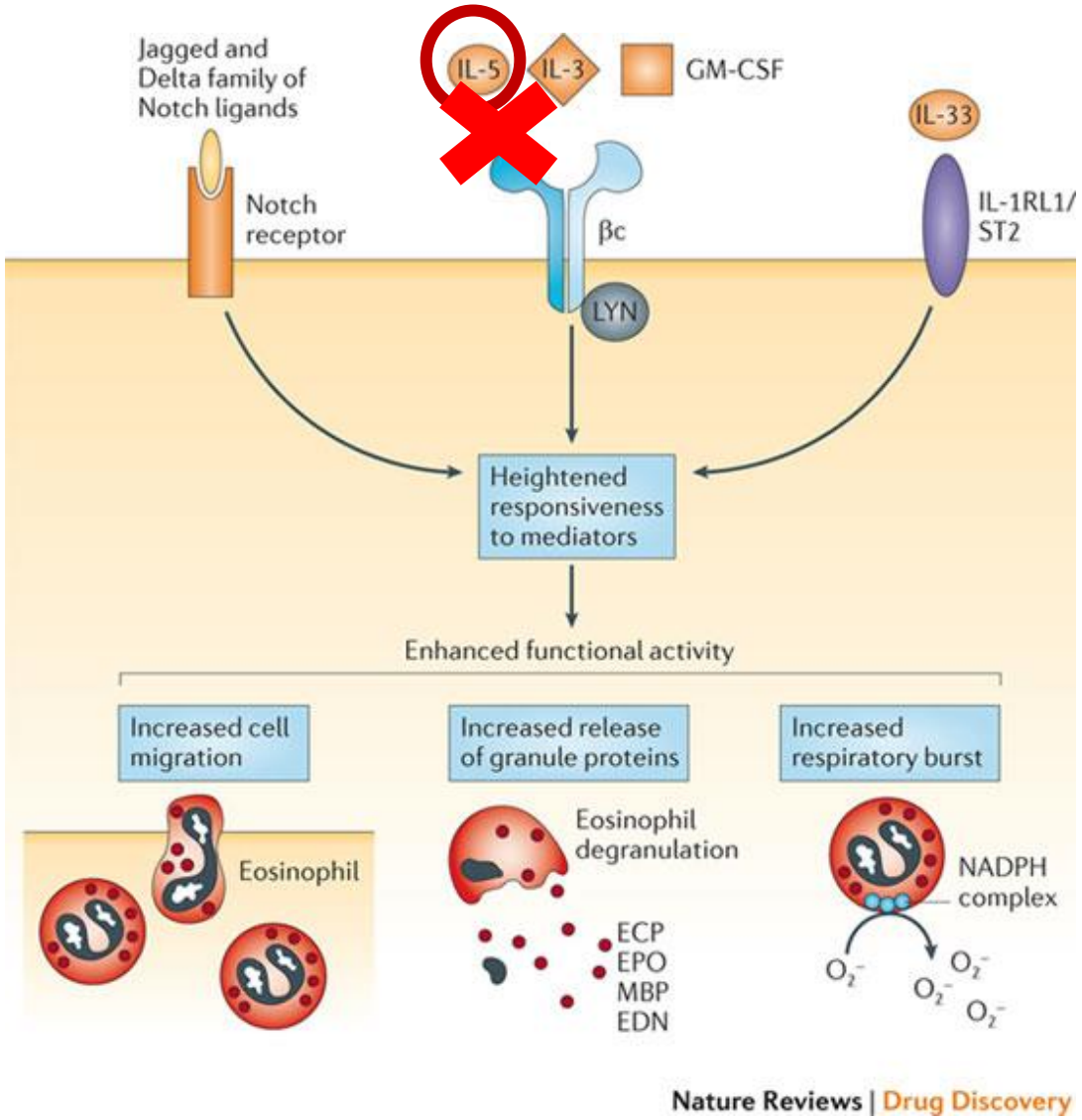
Lefebvre P, *J Allergy Clin Immunol*. **2015** Sep 20

Limitations à l'inclusion dans les essais



Pahus L. *Am J Respir Crit Care Med* 2014;**189:**A1294.

Anti IL-5 : mepolizumab (Nucala®)



- Autorisation de la FDA le 5.11.2015
- Indication : asthme sévère réfractaire éosinophile
- 100 mg/mois SC

Mepolizumab : quels bénéfices ?

Étude de phase III randomisée en double aveugle, groupes parallèles d'une durée d'1 an. PNE >300/ml dans les 12 mois ou 150 à la randomisation

Outcome	Placebo (N=191)	Intravenous Mepolizumab (N=191)	Difference from Placebo (95% CI)	P Value	Subcutaneous Mepolizumab (N=194)	Difference from Placebo (95% CI)	P Value
Mean rate of clinically significant exacerbations	1.75	0.93	47 (29 to 61)†	<0.001	0.81	53 (37 to 65)†	<0.001
Mean rate of exacerbations requiring hospitalization or emergency department visit	0.20	0.14	32 (–41 to 67)†	0.30	0.08	61 (17 to 82)†	0.02
Mean rate of exacerbations requiring hospitalization	0.10	0.06	39 (–66 to 77)†	0.33	0.03	69 (9 to 89)†	0.03
Change from baseline in FEV_1 — ml							
Before bronchodilation	86±31	186±32	100 (13 to 187)	0.02	183±31	98 (11 to 184)	0.03
After bronchodilation	30±34	176±34	146 (50 to 242)	0.003	167±33	138 (43 to 232)	0.004
Change from baseline in score on Asthma Control Questionnaire	–0.50±0.07	–0.92±0.07	–0.42 (–0.61 to –0.23)	<0.001	–0.94±0.07	–0.44 (–0.63 to –0.25)	<0.001
Change from baseline in score on St. George's Respiratory Questionnaire	–9.0±1.2	–15.4±1.2	–6.4 (–9.7 to –3.2)	<0.001	–16.0±1.1	–7.0 (–10.2 to –3.8)	<0.001

Ortega, *NEJM*, 2014

Mepolizumab : quels bénéfices ?

Étude de phase III randomisée en double aveugle, groupes parallèles d'une durée d'1 an. PNE >300/ml dans les 12 mois ou 150 à la randomisation

Outcome	Placebo (N=66)	Mepolizumab (N=69)	Odds Ratio (95% CI)*	P Value
Reduction in oral glucocorticoid dose at 20 to 24 wk: primary outcome — no. (%)†			2.39 (1.25–4.56)	0.008
90 to 100%	7 (11)	16 (23)		
75 to <90%	5 (8)	12 (17)		
50 to <75%	10 (15)	9 (13)		
>0 to <50%	7 (11)	7 (10)		
No decrease in oral glucocorticoid dose, a lack of asthma control, or withdrawal from treatment	37 (56)	25 (36)		
Secondary outcomes				
Reduction in daily oral glucocorticoid dose of ≥50% — no. (%)‡	22 (33)	37 (54)	2.26 (1.10–4.65)	0.03
Reduction in daily oral glucocorticoid dose to a level ≤5 mg — no. (%)‡	21 (32)	37 (54)	2.45 (1.12– 5.37)	0.02
Reduction of 100% in oral glucocorticoid dose — no. (%)‡	5 (8)	10 (14)	1.67 (0.49–5.75)	0.41
Median percent reduction from baseline in daily oral glucocorticoid dose (95% CI)§	0.0 (–20.0 to 33.3)	50.0 (20.0 to 75.0)	NA	0.007

Bel, *NEJM*, 2014

Mepolizumab : quels répondeurs ?

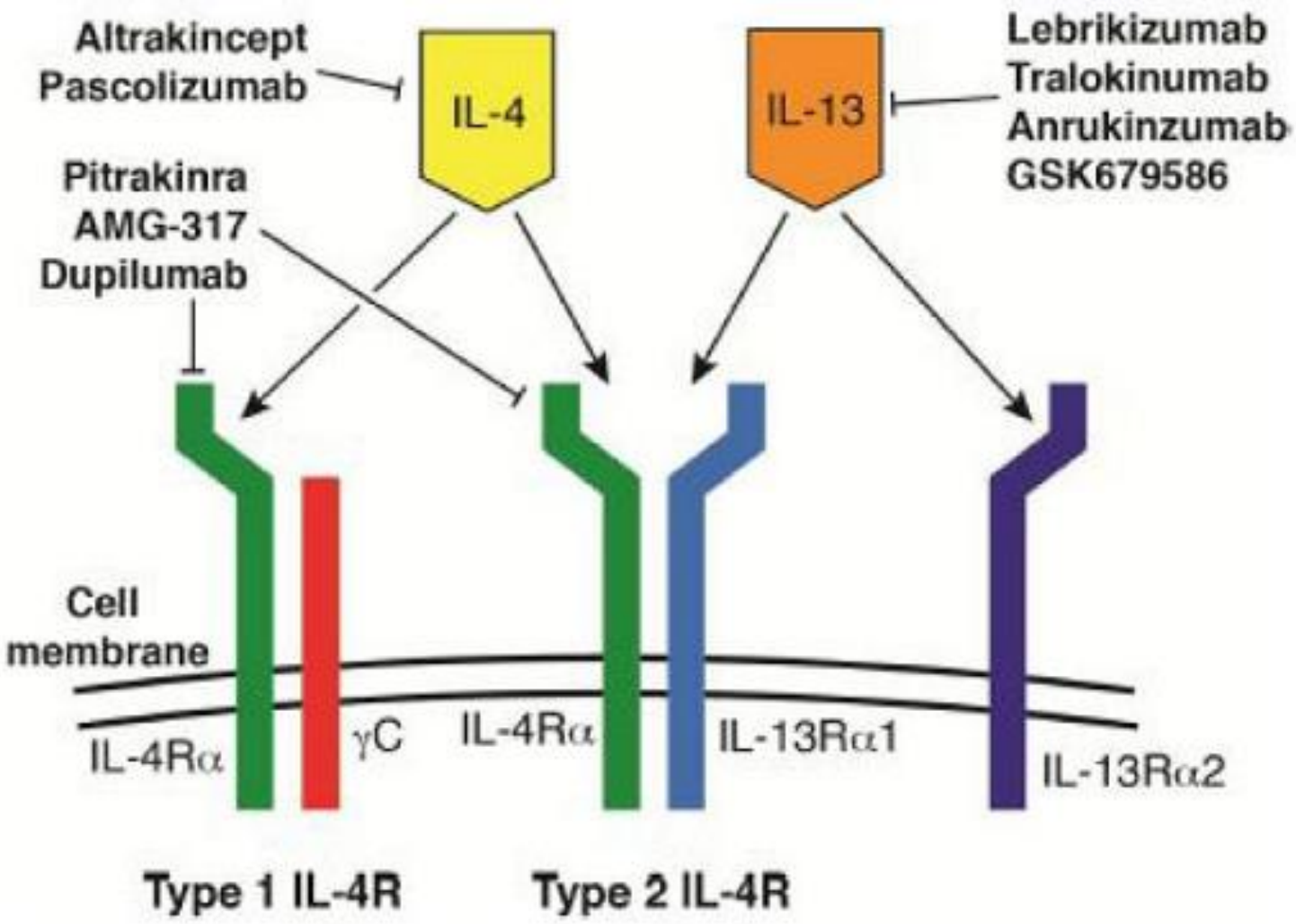
- Critères d'inclusion dans les essais :
- Éosinophiles sanguins >300/mm^3 dans les 12 mois précédents
- Ou éosinophilie >150/mm^3 à l'inclusion
- Ou éosinophiles >3% dans l'expectoration induite

Benralizumab, reslizumab : quelle population cible ? quels bénéfices ?

	Benralizumab (IL5R)	Reslizumab
Nbre d'essais de phase III publiés	1	3
Nbre de patients inclus	609	311 +395 +953
Phénotype éosinophile	Eos>400 ou 2% ou FeNO>50	Eosinophile >400/mm^3 à l'inclusion
Dose	SC 1 fois par mois	3 mg/kg IV une fois par mois
Effet	VEMS	VEMS
	ACQ6	ACQ
	Exacerbations si éos >400	Exacerbations

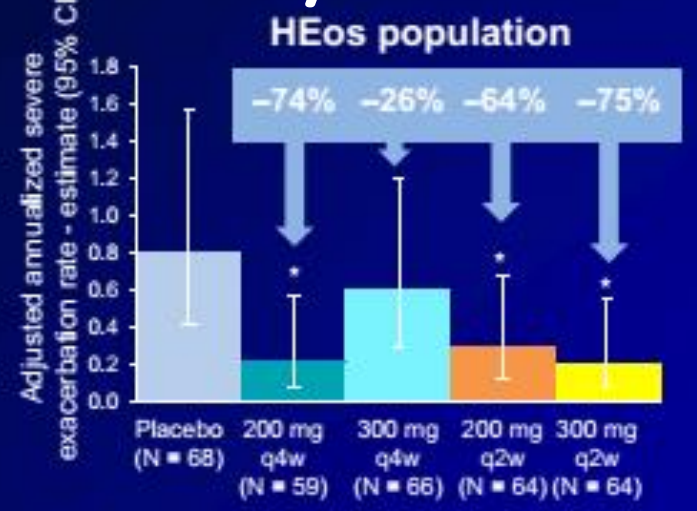
Mukherjeeet al. *World Allergy Organization Journal* 2014,7:32

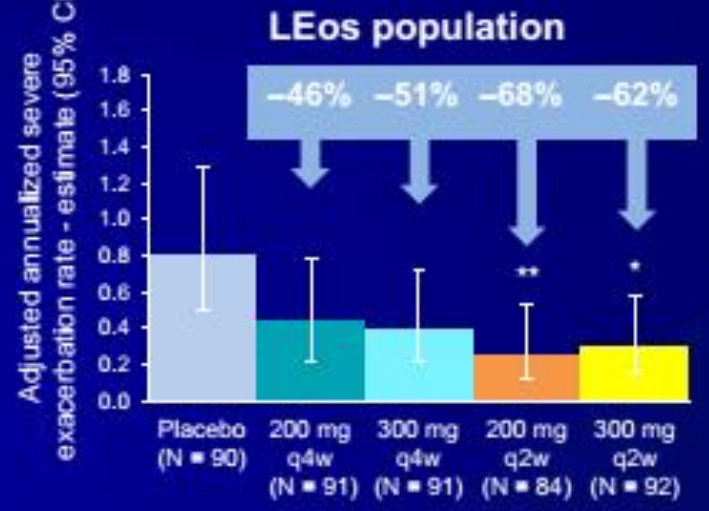
Anti IL-13, anti IL-4/13R

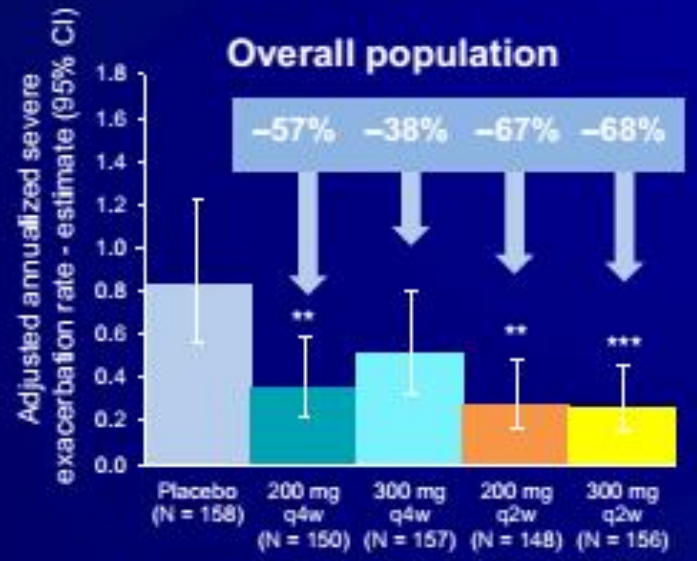


Adjusted Annual Severe Exacerbation Event Rate

Anti IL-4/13 R : dupilumab







- In the HEos and overall populations, significant decreases in severe asthma exacerbation rates were observed for all dupilumab regimens versus placebo, except the 300 mg q4w
- In the LEos population, significant decreases in severe asthma exacerbation rates were observed for the dupilumab q2w regimens versus placebo

The annualized rate of asthma exacerbation events (eg, LOAC, severe exacerbation) was analyzed using a negative binomial regression model. The model included the total number of events occurring during the double-blind treatment period as the response variable, with treatment group, pooled countries/regions, and number of asthma events prior to the study as covariates. **Arrows represent percent change compared to placebo.** *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ vs placebo; CI, confidence interval.

Anti IL-13 : lebrikizumab

Table 1 Studies of lebrikizumab in asthma

Study	Study design	Number of patients	Population	Regimen	Main findings
Corren et al (2011)[24]	Randomized, double-blind, multicenter	219	Uncontrolled asthmatics despite ICS, 80% using LABA	Lebrikizumab 250 mg SQ monthly for 6 months or placebo	Overall improvement of pulmonary function; response was more pronounced in patients with high periostin levels. Patients with a Th2 inflammatory profile had a decrease in exacerbation rates
Noonan et al (2013)[25]	Randomized, double-blind	212	Mild asthmatics not using ICS	Lebrikizumab 125 mg, 250 mg, 500 mg, or placebo SQ monthly for 3 months	No significant difference in the FEV_1 between groups. There was a reduction in the rate of protocol-defined treatment failure compared to placebo
Scheerens et al (2014)[26]	Randomized, double-blind, parallel-group	29	Mild asthmatics	Lebrikizumab 5 mg/kg SQ monthly for 4 months or placebo	Overall, there was no significant reduction in the LAR. Patients with a Th2 inflammatory profile had a greater reduction in LAR
Hanania et al (2014)[29]	Two replicate studies, randomized, double-blind, multicenter	463	Uncontrolled asthmatics despite ICS and a second controller	Lebrikizumab 37.5 mg, 125 mg, 250 mg, or placebo SQ monthly for an average of 6 months	Treatment reduced the exacerbation rate and increased FEV_1, particularly in those with high periostin levels

Maselli, Journal of Asthma and Allergy, 2015

Anti IL-13 : lebrikizumab

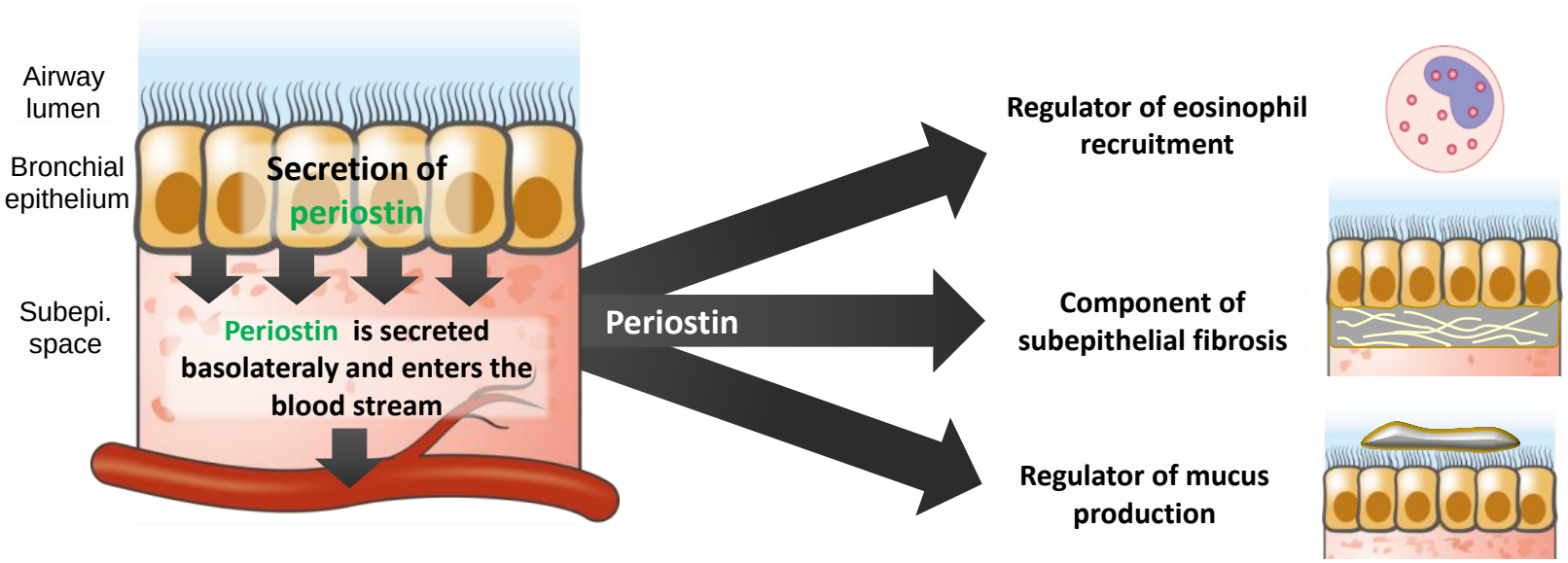
The LAVOLTA I and LAVOLTA II Phase 3 trials were two multicenter, randomized, double-blind, placebo-controlled studies that together included more than 2,100 people across 28 countries. The primary endpoint of both trials was the rate of asthma exacerbations over a period of 52 weeks.

The results of the LAVOLTA I trial showed that treatment with lebrikizumab significantly reduced the rate of asthma exacerbations in people with higher levels of serum periostin or blood eosinophils, both airway inflammation biomarkers. There was also a significant improvement in lung function (assessed by forced expiratory volume in one second, called FEV_1). However, the observed effects were inferior to the ones previously reported in Phase 2 trials assessing lebrikizumab.

In the LAVOLTA II trial, the exacerbation reduction did not meet statistical significance. There were no safety concerns reported in either trial.

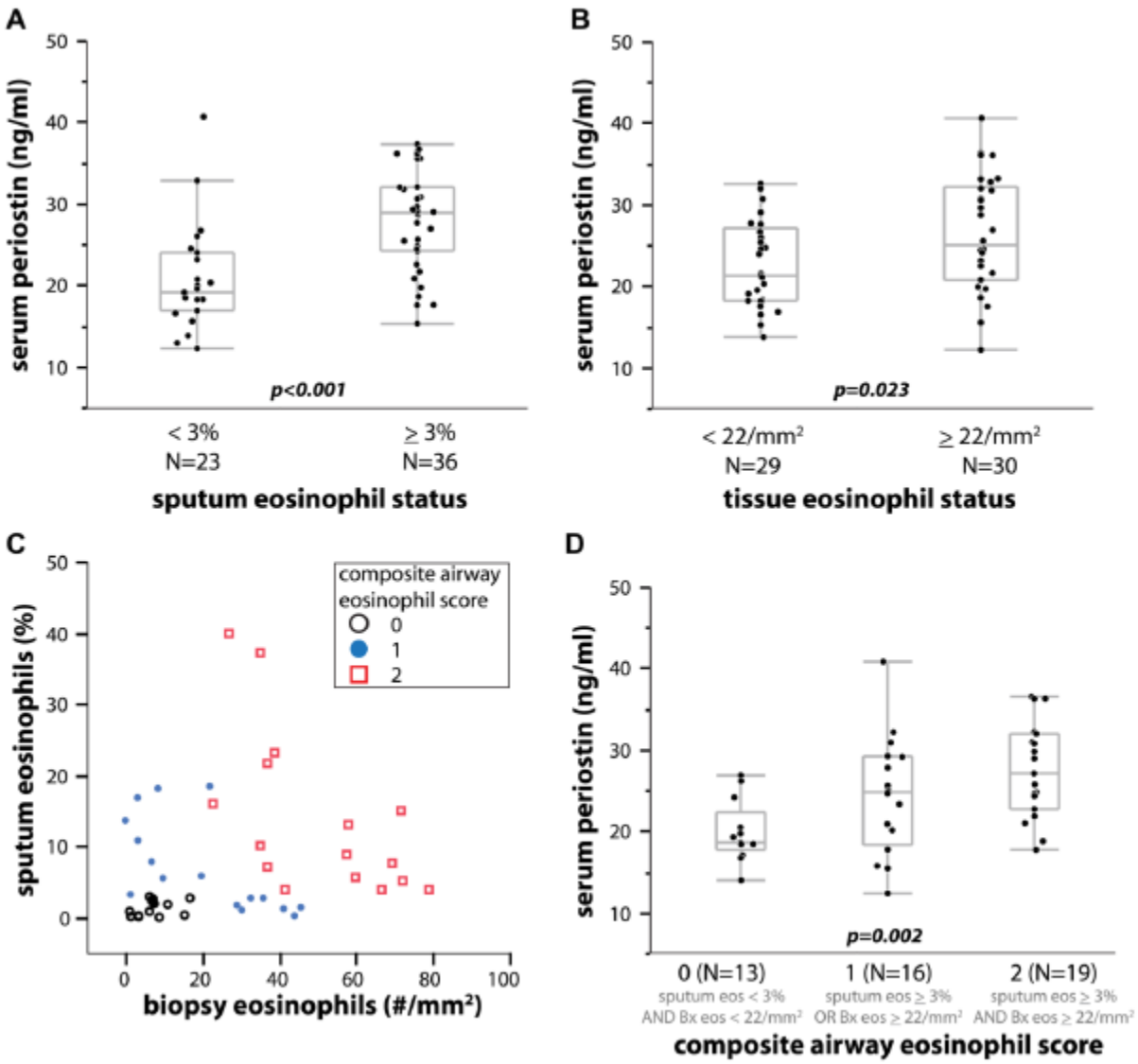
http://lungdiseasenews.com/2016/03/07/two-phase-3-trials-asthma-drug-lebrikizumab-differing-results-genentech-reports/

La périostine



1. Woodruff PG, *et al. Proc Natl Acad Sci USA* 2007; 104:15858–15863; 2. Takayama G, *et al. J Allergy Clin Immunol* 2006; 118:98–104; 3.
2. Hayashi N, *et al. Proc Natl Acad Sci USA* 2007; 104:14765–14770; 4. Sidhu S, *et al. Proc Natl Acad Sci USA* 2010; 107:14170–14175; 5. Blanchard C, *et al. Mucosal Immunol* 2008; 1:289–296;
3. 6. Sehra S, *et al. J Immunol* 2011; 186:4959–4966

La périostine, un futur marqueur du phénotype Th2?



Jia, JACI 2012 September ; 130(3): 647–654.

L'asthme éosinophile: quelle fréquence ?

	Rate ratio (95% CI)*		Odds ratio (95% CI)*	
	Severe exacerbations	Acute respiratory events	Risk-domain asthma control	Overall asthma control
>200 cells per µL (n=28 477)	1·13 (1·08–1·19)	1·09 (1·05–1·13)	0·89 (0·86–0·92)	0·80 (0·77–0·82)
>250 cells per µL (n=22 241)	1·21 (1·16–1·27)	1·13 (1·09–1·17)	0·88 (0·85–0·91)	0·79 (0·77–0·82)
>300 cells per µL (n=16 602)	1·30 (1·23–1·37)	1·18 (1·13–1·23)	0·85 (0·82–0·89)	0·78 (0·75–0·81)
>350 cells per µL (n=12 791)	1·34 (1·27–1·41)	1·21 (1·16–1·27)	0·83 (0·80–0·87)	0·77 (0·74–0·80)
>400 cells per µL (n=9495)	1·41 (1·32–1·50)	1·28 (1·22–1·34)	0·79 (0·75–0·83)	0·75 (0·71–0·78)
>450 cells per µL (n=7416)	1·50 (1·40–1·60)	1·35 (1·28–1·42)	0·75 (0·71–0·79)	0·73 (0·69–0·77)
>500 cells per µL (n=5511)	1·57 (1·46–1·69)	1·41 (1·32–1·49)	0·72 (0·68–0·77)	0·70 (0·66–0·74)

*All comparisons p<0·0001; adjusted for age, sex, body-mass index, smoking status, and Charlson comorbidity index score.

Table 3: Results for asthma-related endpoints at different blood eosinophil cutoff values: subpopulation (n=54 072)

52%

30%

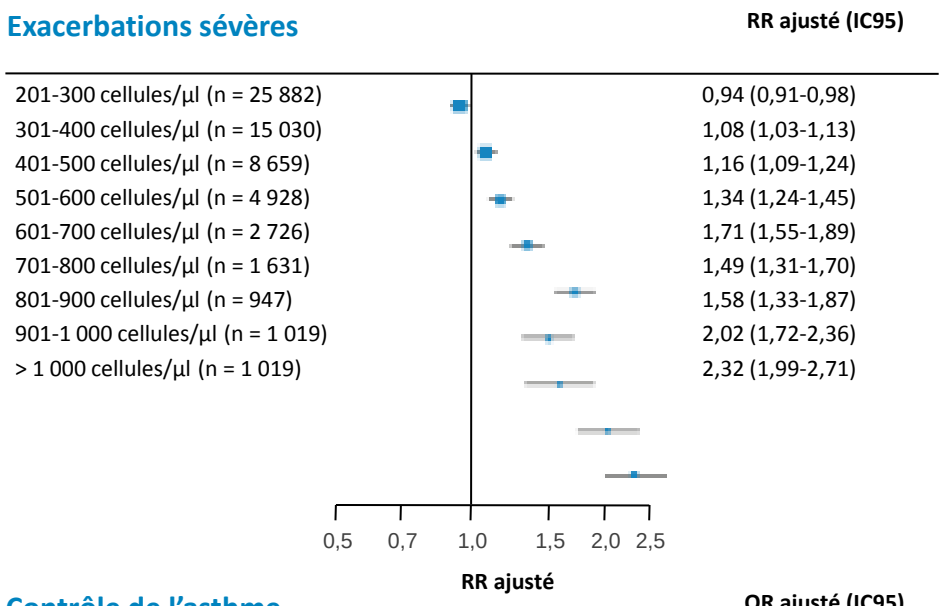
17%

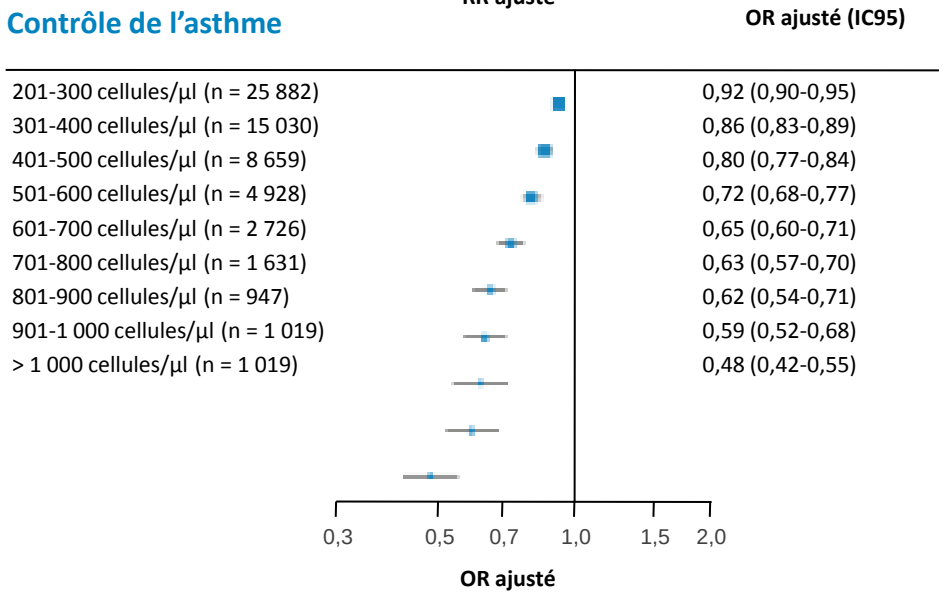
10%

0,3% ont > 1500/mm^3

Price, *Lancet Respir Med*, 2015

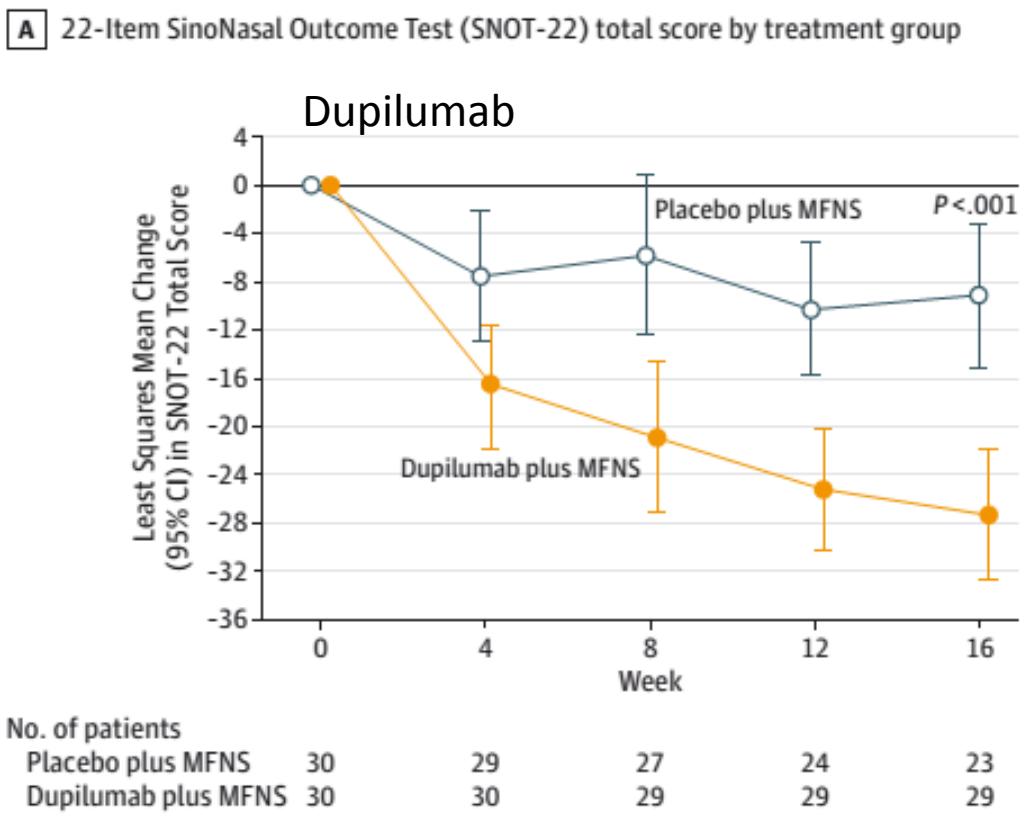
Asthme éosinophile : contrôle et exacerbations ?





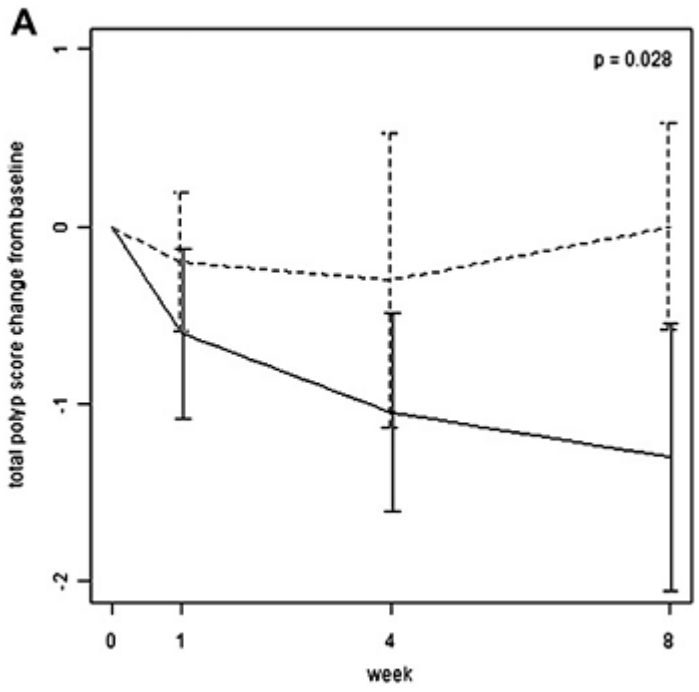
Price, *Lancet Respir Med*, 2015

La polypose : nouvelle cible pour les biothérapies ?



Bachert, JAMA, 2016

Mépolizumab



Gevaert, JACI, 2011

Quels critères pour choisir une biothérapie ?

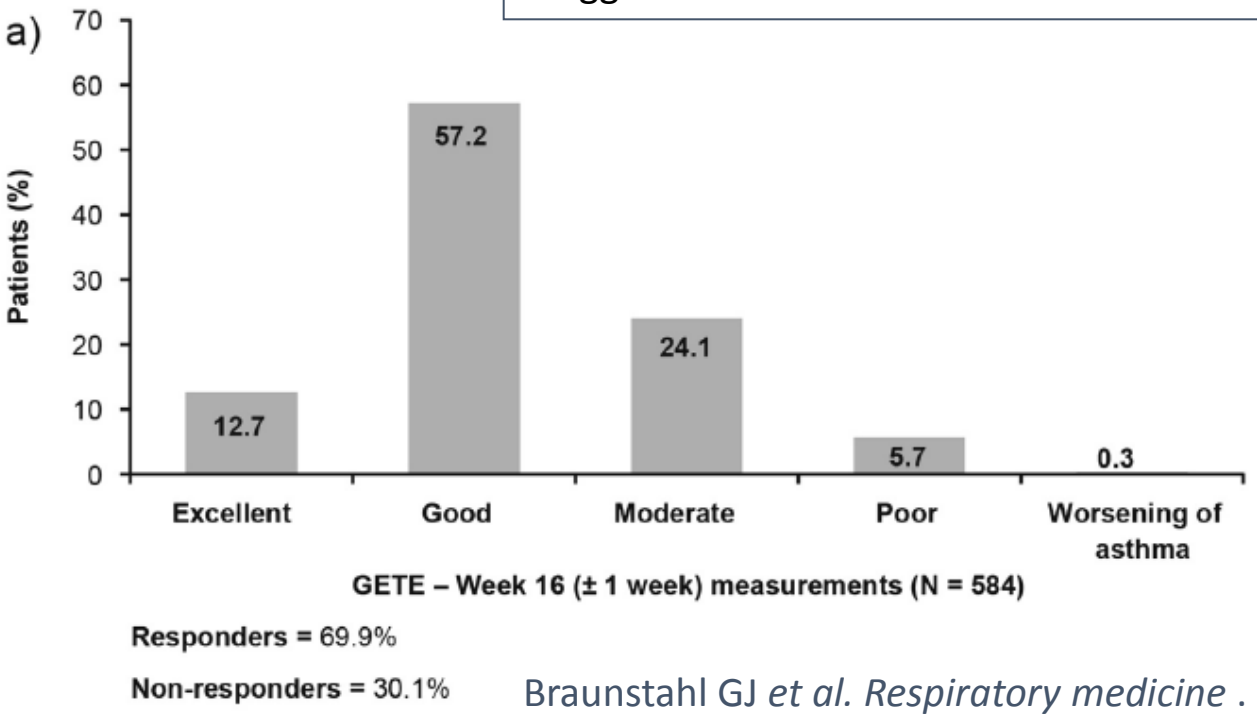
- Se référer à l'AMM…
- … et se référer aux critères d'inclusion dans les essais pour la valeur du seuil du biomarqueur
- Particularités cliniques (polypose ? atopie ?)

- Profil de tolérance
- Voie d'administration
- Coût
- Etudes comparatives entre biothérapies ?

Comment définir la réponse ?

- 70 à 80% de répondeurs avec l'omalizumab
- Omalizumab : pas de définition d 'une "bonne réponse"
  - GETE 1 ou 2 ?
  - ACT +5 points ? ACQ +0.5 point ?
  - Définir les objectifs avant de débuter
  - ACT
  - VEMS
  - Nombre d'exacerbations, consommation
  - de stéroides

1 Excellent (contrôle complet),
2 Bon (amélioration notable),
3 Modéré (amélioration limitée)
4 Pauvre (pas de modification significative)
5 Aggravation

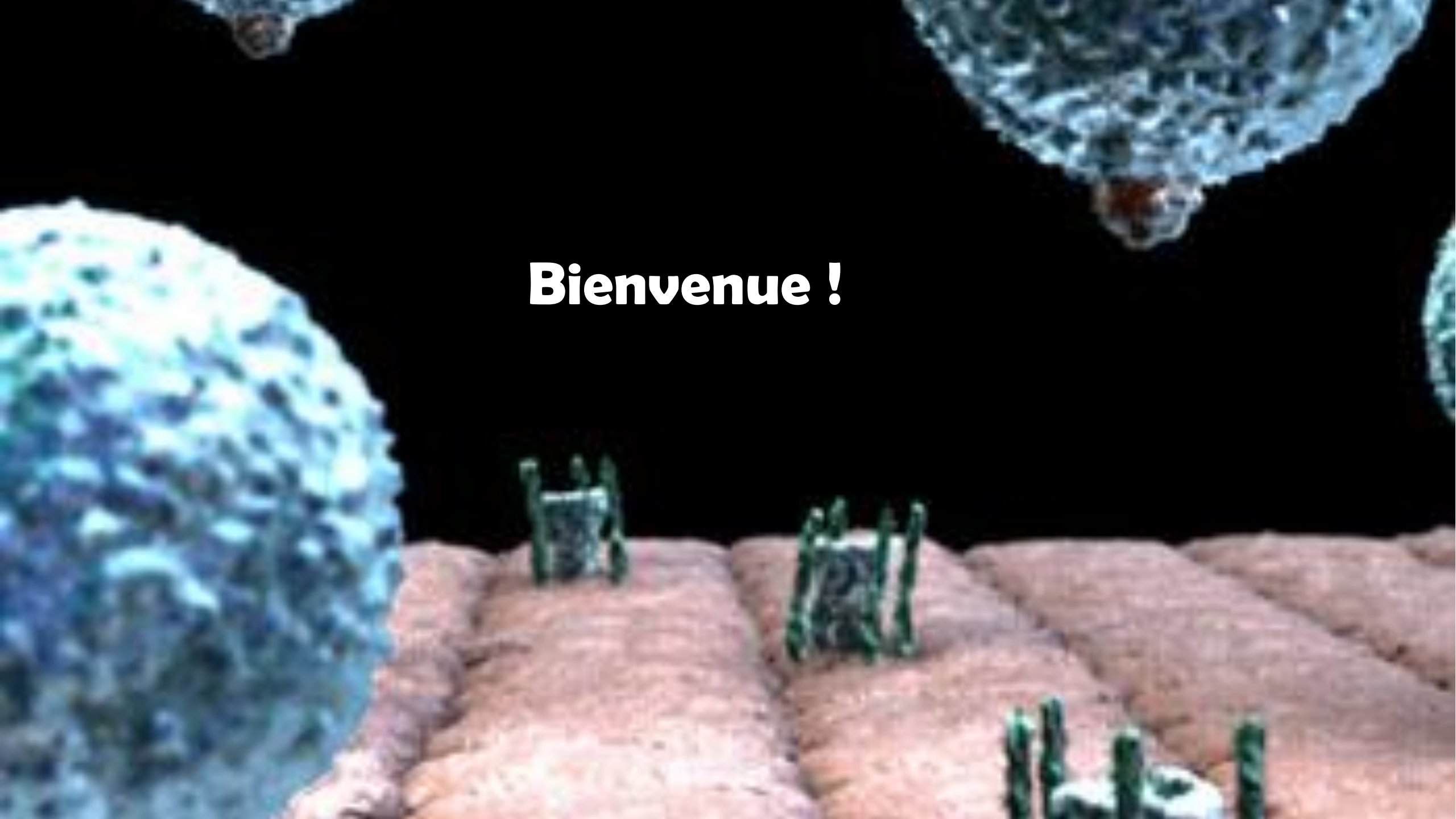


Braunstahl GJ *et al. Respiratory medicine* . 2013

Résumé

- Les nouvelles biothérapies dans l'asthme sévère ciblent la voie T2
- Les populations cibles sont identifiées par des biomarqueurs : éosinophilie sanguine et/ou périostine.
- La connaissance de la valeur de ces biomarqueurs encore incomplète mais indispensable à acquérir : seuil, stabilité du phénotype, variabilité (traitement, exacerbations…), combinaisons de biomarqueurs…..

- Recherche sur les asthmes « non Th2 » encore balbutiante (anti IL23, anti IL17..)



Bienvenue !