Anti-IL-13 Prospects in Asthma

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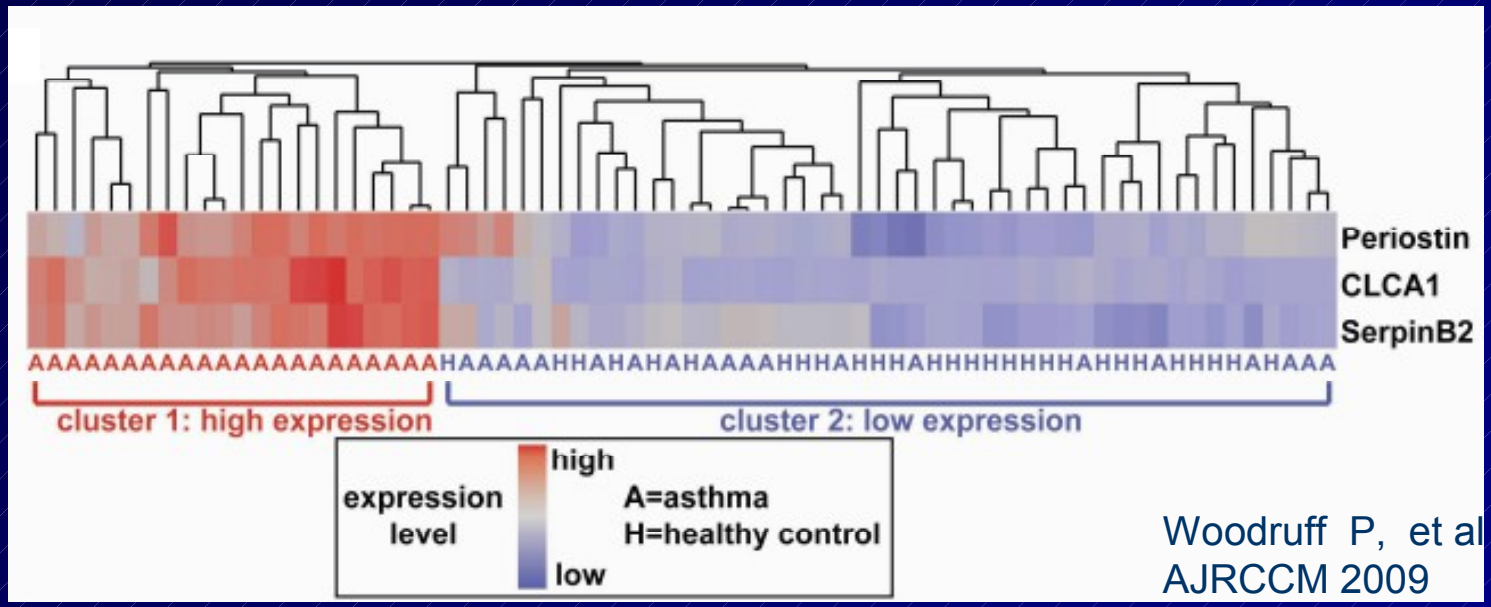
Disclosures

- Dr. Wenzel has received consulting fees from Actelion, Amgen, Gilead, GSK, MedImmune, Merck and Teva
- UPMC/Wenzel have received money to support multicenter clinical trials from Amgen, Array, GSK, MedImmune, Merck and Sanofi
- Dr. Wenzel has not received any funds from tobacco related sources

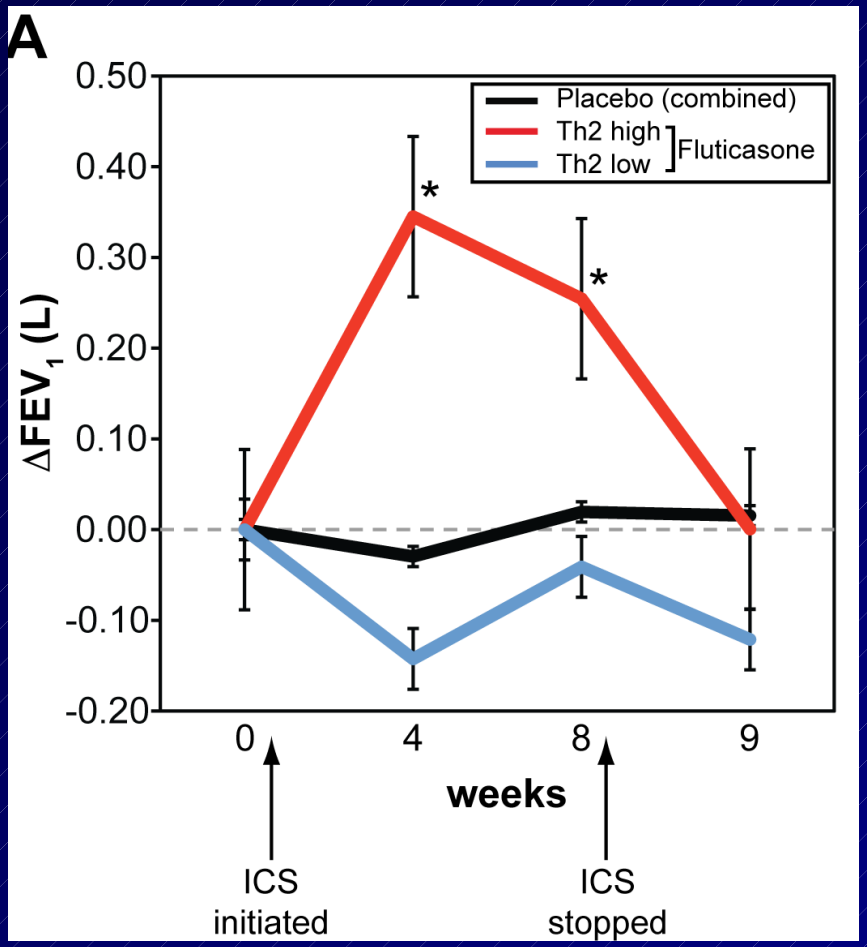
Molecular markers identify a Type-2 cytokine associated asthma



3 signature genes expressed *in vitro* in epithelial cells in response to IL-13 applied to *ex vivo* epithelial cells----"cluster' of mild asthmatics with:

- More atopy, eosinophils and BHR…
- More expression of canonical Type 2 cytokines IL-4, 5 and 13

“Th2 Hi” predicts responses to anti-inflammatory therapy



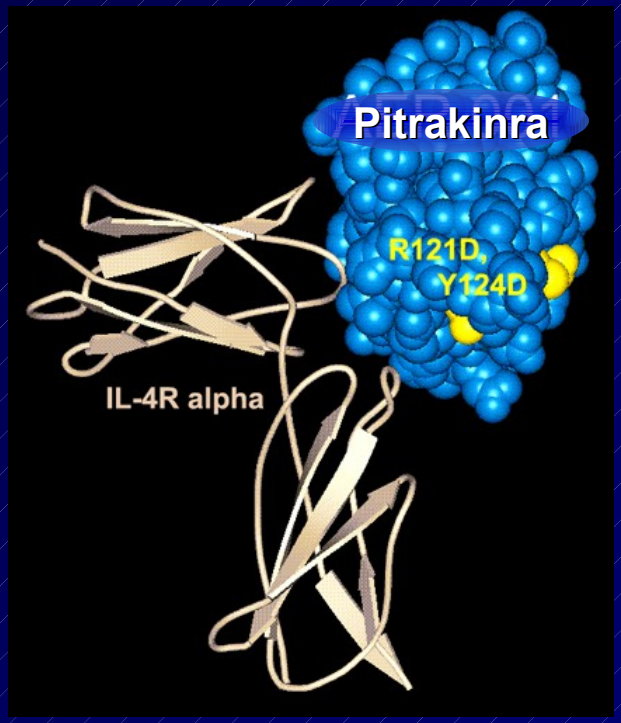
We think we are so smart….

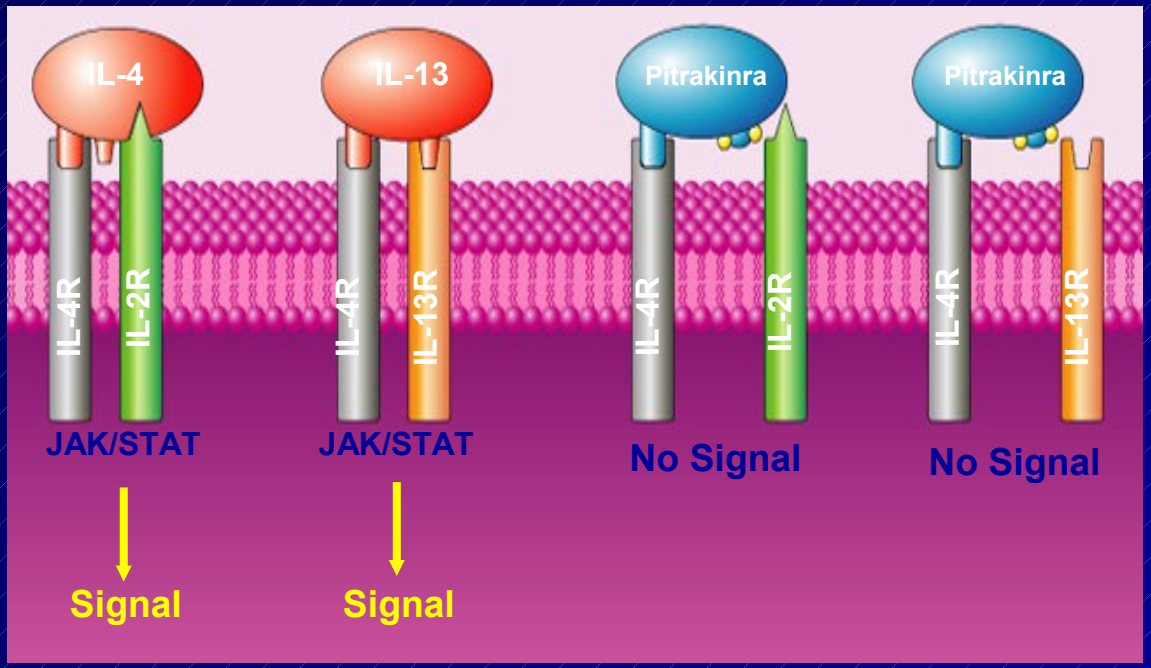
TREATMENT OF CHRONIC ASTHMA WITH PREDNISOLONE
SIGNIFICANCE OF EOSINOPHILS IN THE SPUTUM

H. MORROW BROWN
M.D. Edin., M.R.C.P.E.
CONSULTANT CHEST PHYSICIAN, DERBY CHEST CLINIC, AND DERWENT HOSPITAL, DERBY

Lancet Dec 13 1958!!

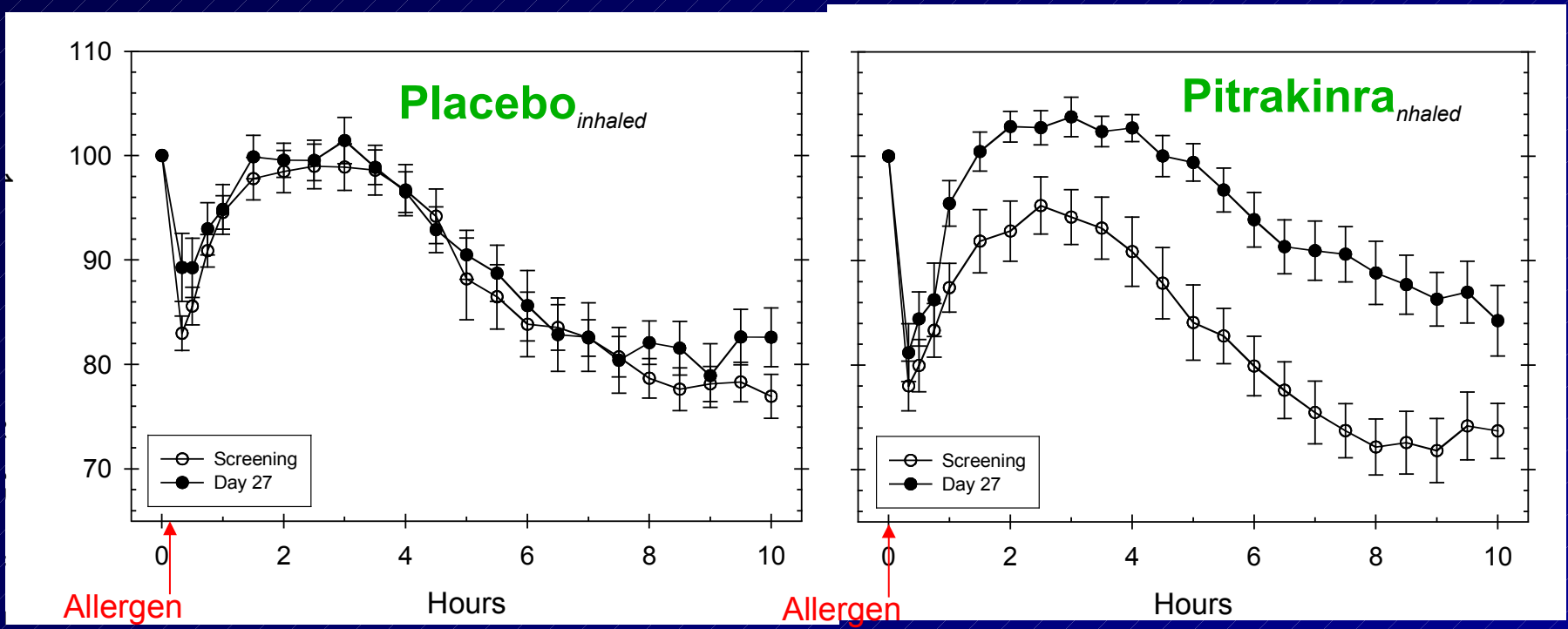
POC: MILD *allergic* asthma responds to IL-4/-13 antagonists





Pitrakinra is a 14 kDa IL-4 mutein that inhibits assembly of IL2R or IL13R into receptor complexes with IL-4R

IL4R alpha blockade decreased *allergen induced exacerbation*



3.7-fold reduction in average LAR FEV_1 %fall from pre-challenge baseline

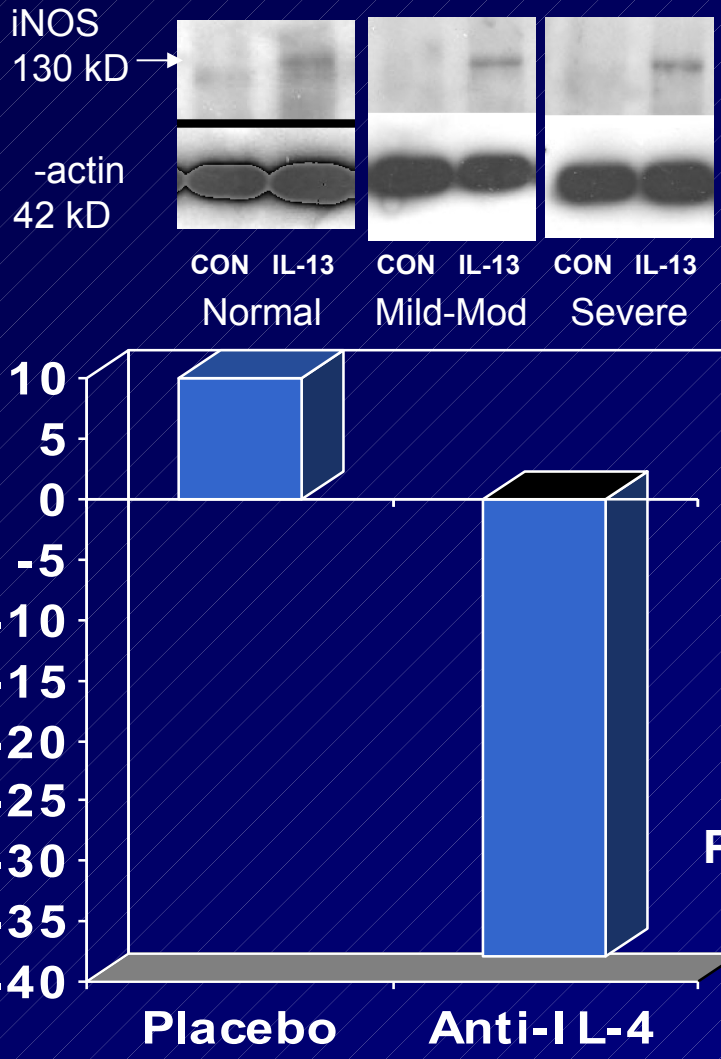
95% CI on ratio of ANCOVA-adjusted means, placebo / AEROVANT = (2.1, 6.3)

p < 0.001

Mean ± SEM (n = 14 placebo, 15 AEROVANT)

Wenzel, Lancet, October 2007

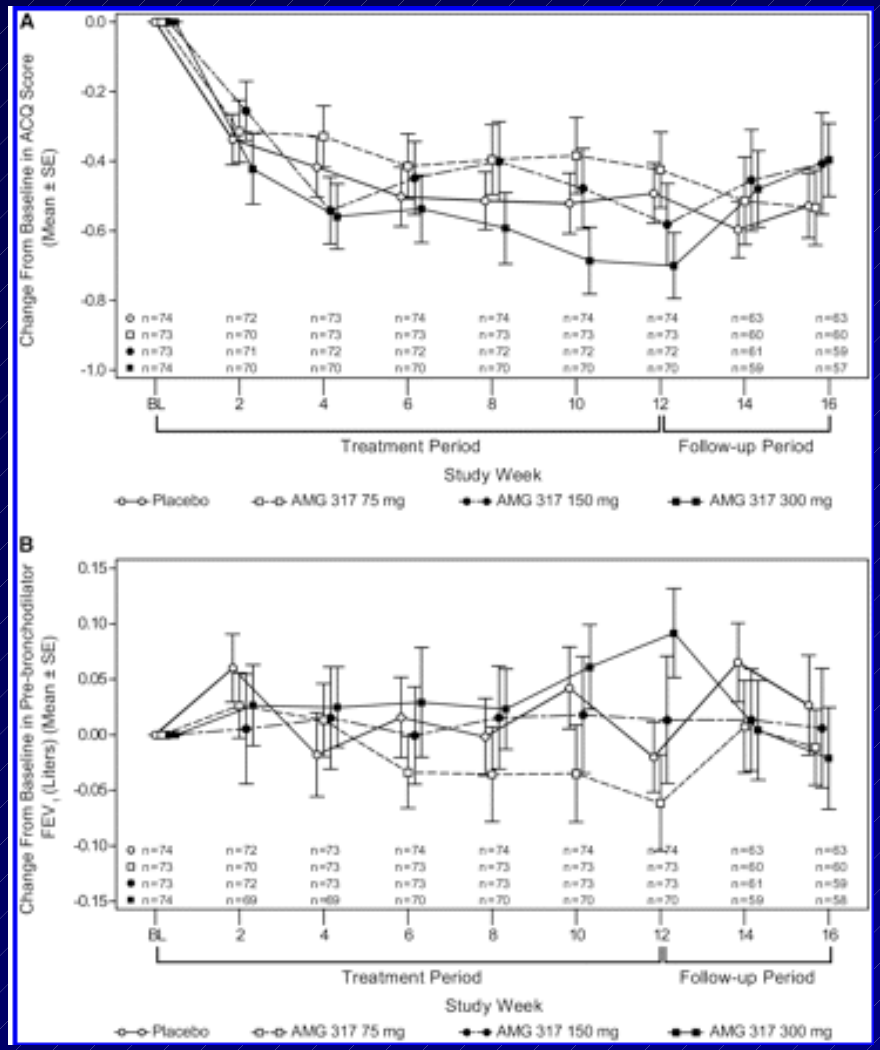
Inhibition of IL-4R pathway also improves allergic inflammation



- IL-13 stimulates iNOS expression (FeNO source) in human airway epithelial cells
- Nebulized blockade of IL-4R decreases FeNO at baseline confirming inhibition of biologic pathway

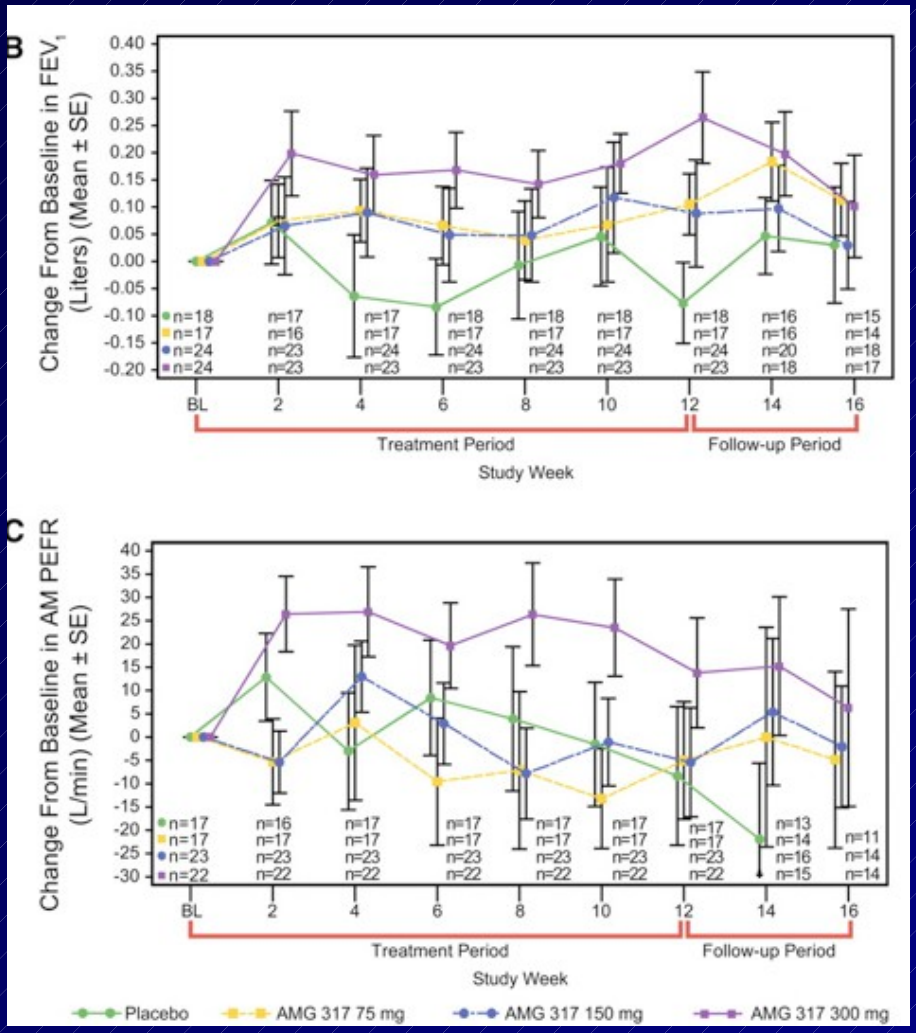
Wenzel, the Lancet Oct 2007
Chibana Clin Exp Allergy 2008

Amgen Anti-IL-4R antibody: Traditional approach



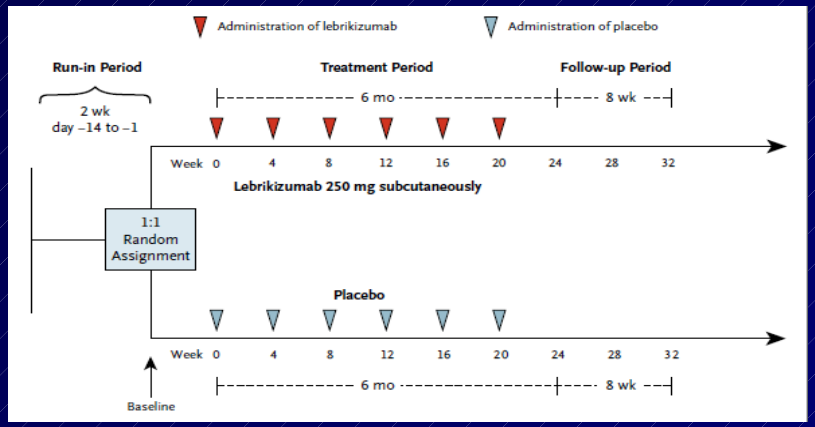
- Study of non-phenotyped moderate asthma patients *Corren et al Am J Resp Crit Care Med 2010*
- Endpoints ACQ and FEV1
  - Neither impacted by Rx
  - However, significant decrease in systemic IgE

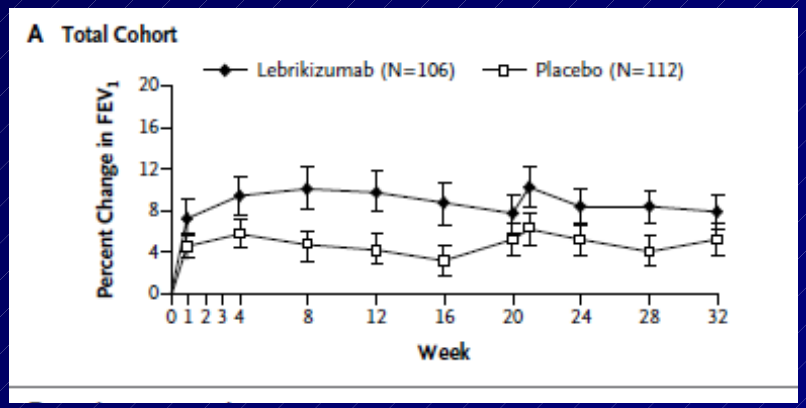
Is there subgroup that responds?



- Prespecified subgroup analysis of the lowest tertile of asthma control
- Improvements in FEV1, PEFR and in ACQ
- No biomarker phenotyping
- Drug was not taken forward

Targeting a Th2 gene signature with specific Th2 biologic approaches



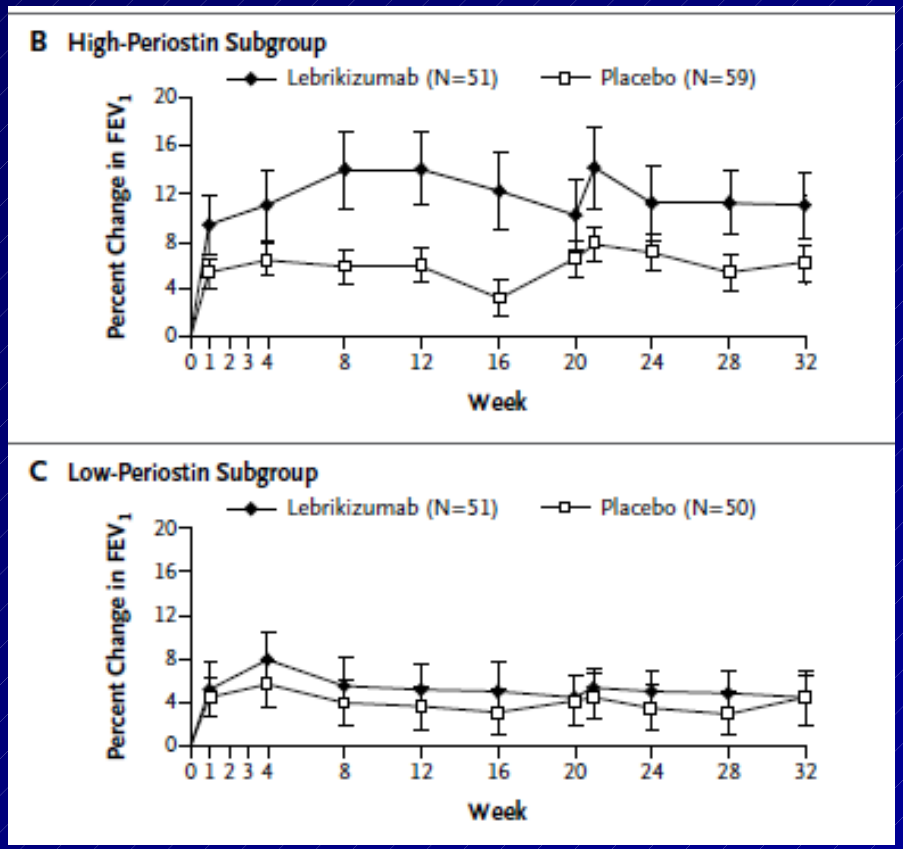


- 200+ pts with moderate to severe asthma on mid to high dose ICS, most with LABA randomized to Rx with anti-IL-13 vs placebo
- Anti-IL-13 was modestly effective in improving FEV1 in all comers
- However, 2ndary analysis was to target “Th2 Hi vs LO”
- Using blood eosinophils in combination with total serum IgE did not identify a responder subset

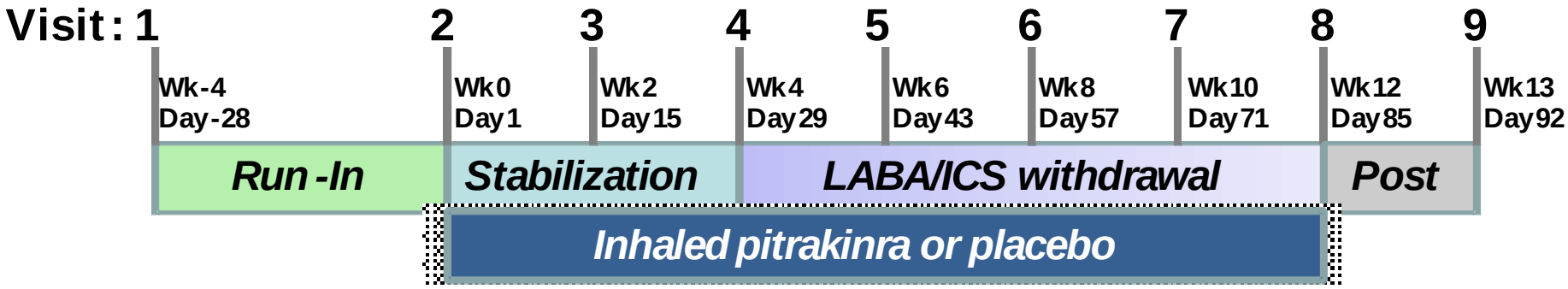
Corren J, Lemanske R, Hanania N et al *Lebrikizumab treatment in adults with asthma* N Engl J Med 2011 Sept 355: 1088-98

Th2 biomarker periostin appears to identify Th2 Hi asthma responsive to Rx

- Patients divided by median split of *serum* periostin levels
- Those with hi periostin had largest increase in FEV1 and borderline reduction in exacerbations
  - But no effect on ACQ or symptoms

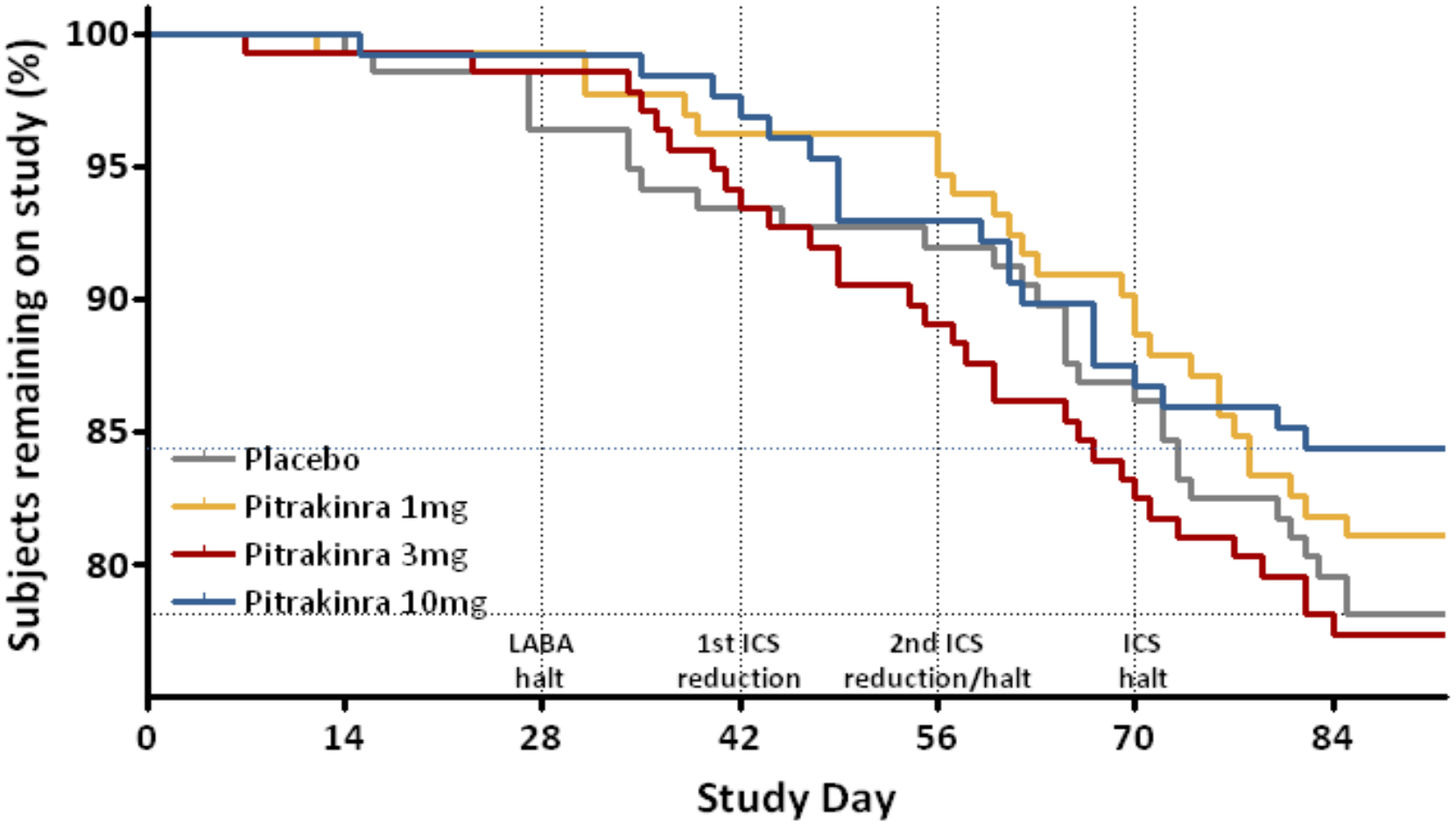


Can blood eosinophils define an Anti-IL-4/13 responsive population

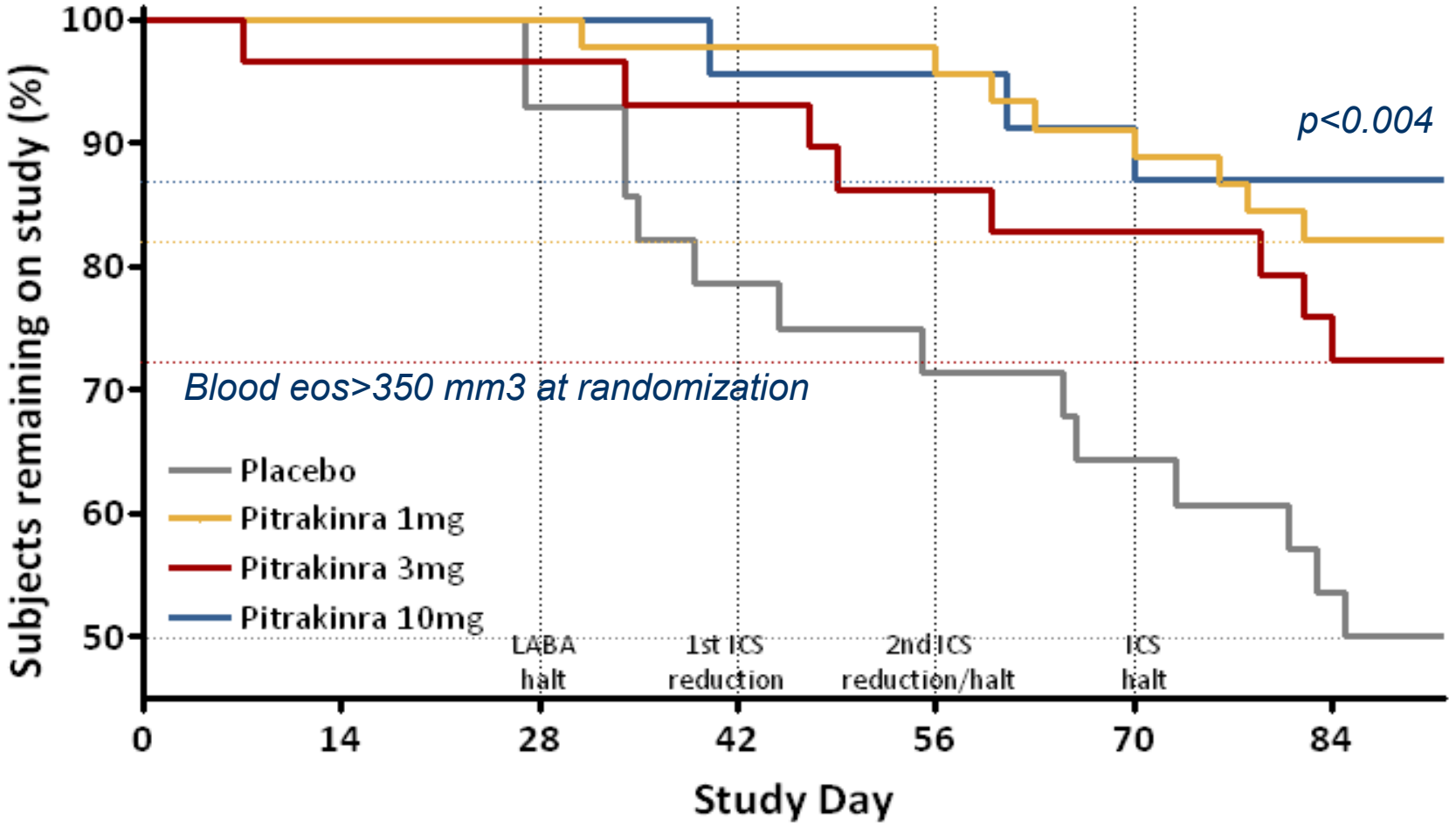


Wenzel et al, Eur Resp Soc meeting 2010

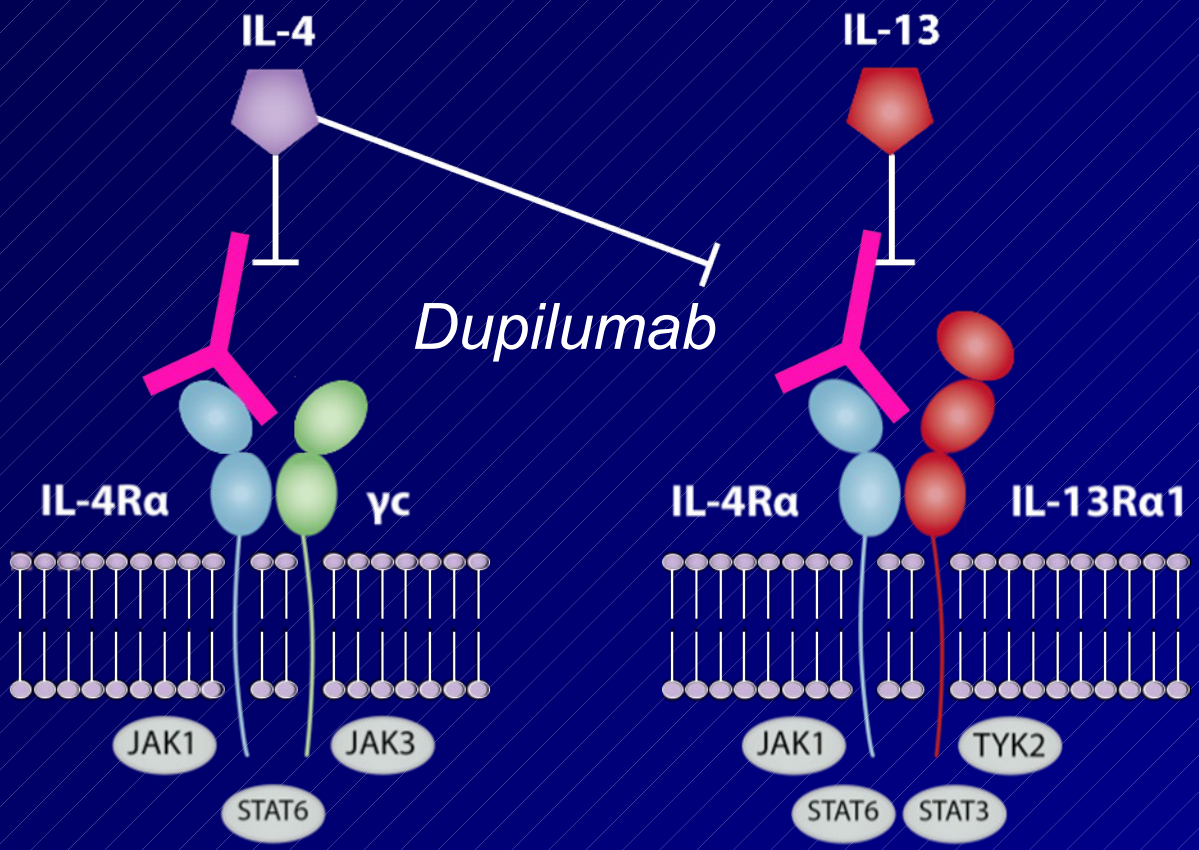
No significant impact in all comers



However, significant improvement in pre-defined BLOOD eos group



Prospective evaluation of eosinophilic phenotype



Type I Receptor

B cells, T cells, Monocytes, Eosinophils, Fibroblasts

Type II Receptor

Epithelial cells, Smooth muscle cells, Fibroblasts, Monocytes, Activated B cells

Mod to Severe *Type 2/Eosinophilic* Asthma

Variable	Placebo (n = 52)	Dupilumab 300 mg (n = 52)
Duration of asthma (yr), mean ± SD	26.9 ± 14.8	24.2 ± 12.6
No. asthma exacerbations in prior 2 yrs	1.4 ± 1.1	1.4 ± 1.0
High dose ICS/LABA use, no. (%)	41 (78.8)	42 (80.8)
FEV_1 (L)	2.54 ± 0.66	2.47 ± 0.65
FEV_1 (% of predicted value)	72.0 ± 12.7	72.0 ± 12.6
Blood eosinophils ($x10^{-9}$/L)	0.47 ± 0.21	0.55 ± 0.19*
ACQ5 score	2.1 ± 0.5	2.1 ± 0.5

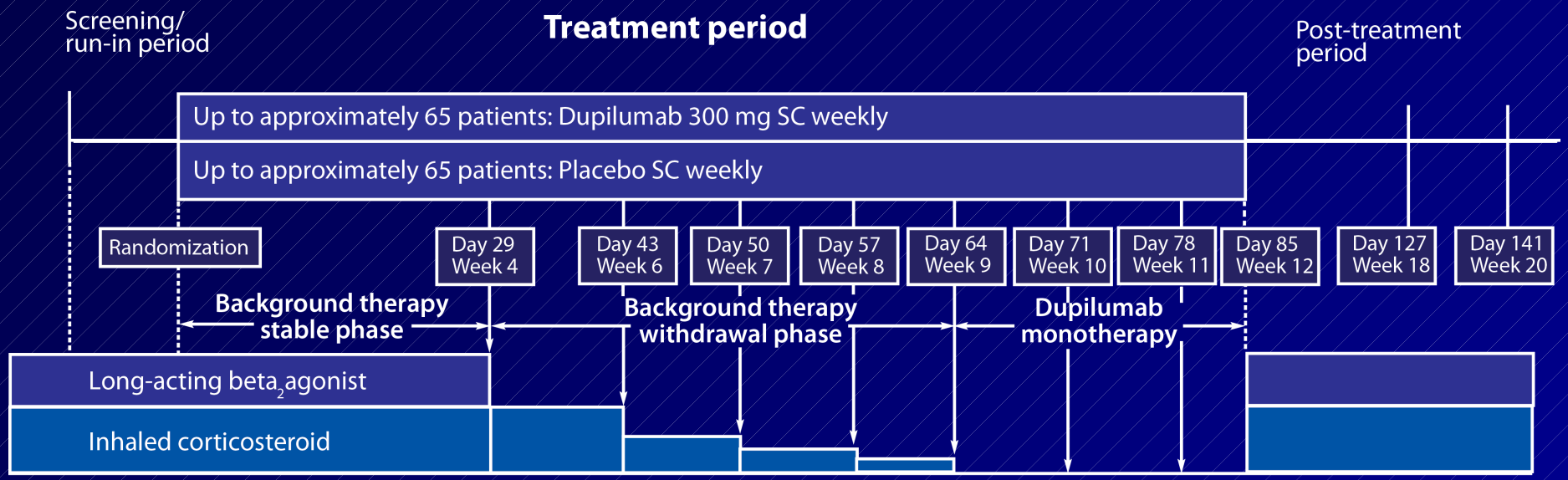
Data are mean ± SD unless noted otherwise.

**p = 0.04 for difference between groups. No other variables were significantly different at baseline.*

Wenzel S, et al. N Engl J Med. 2013;368:2455-66.

The NEW ENGLAND JOURNAL of MEDICINE

Proof of concept study design



Fluticasone/salmeterol

DPI: 250/50 µg BID
500/50 µg BID
MDI: 230/42 µg BID
460/42 µg BID

Fluticasone

250 µg BID → 100 µg BID → 50 µg BID → 0 µg BID
500 µg BID → 250 µg BID → 100 µg BID → 50 µg BID → 0 µg BID
220 µg BID → 110 µg BID → 44 µg BID → 0 µg BID
440 µg BID → 220 µg BID → 110 µg BID → 44 µg BID → 0 µg BID

Fluticasone/salmeterol

250/50 µg BID
500/50 µg BID
230/42 µg BID
460/42 µg BID

BID = twice daily doing; DPI = dry powder inhalation; MDI = metered dose inhalation; SC = subcutaneous

Wenzel, N Engl J Med June 2013

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Efficacy: 87% reduction in *induced* asthma exacerbations

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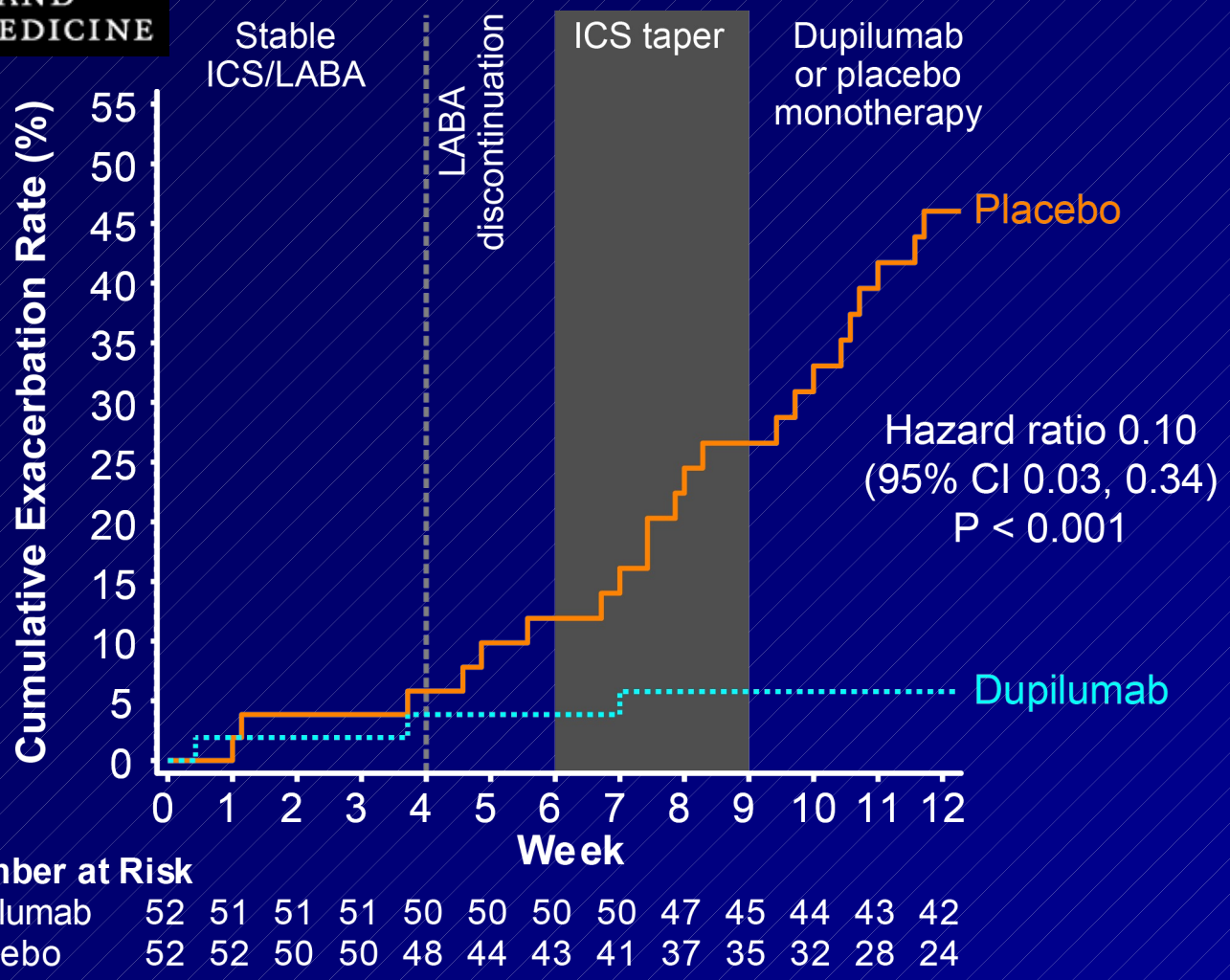
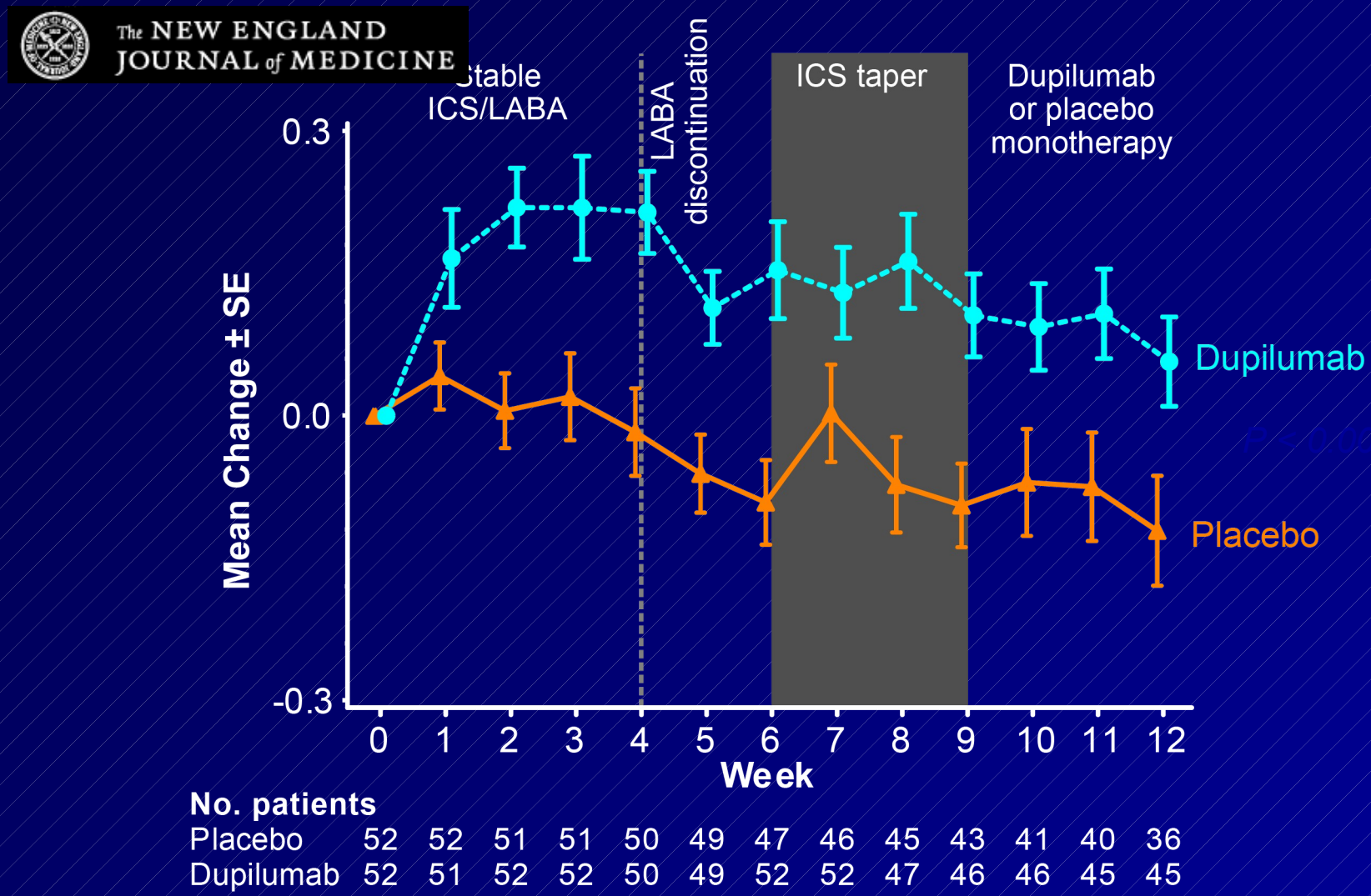
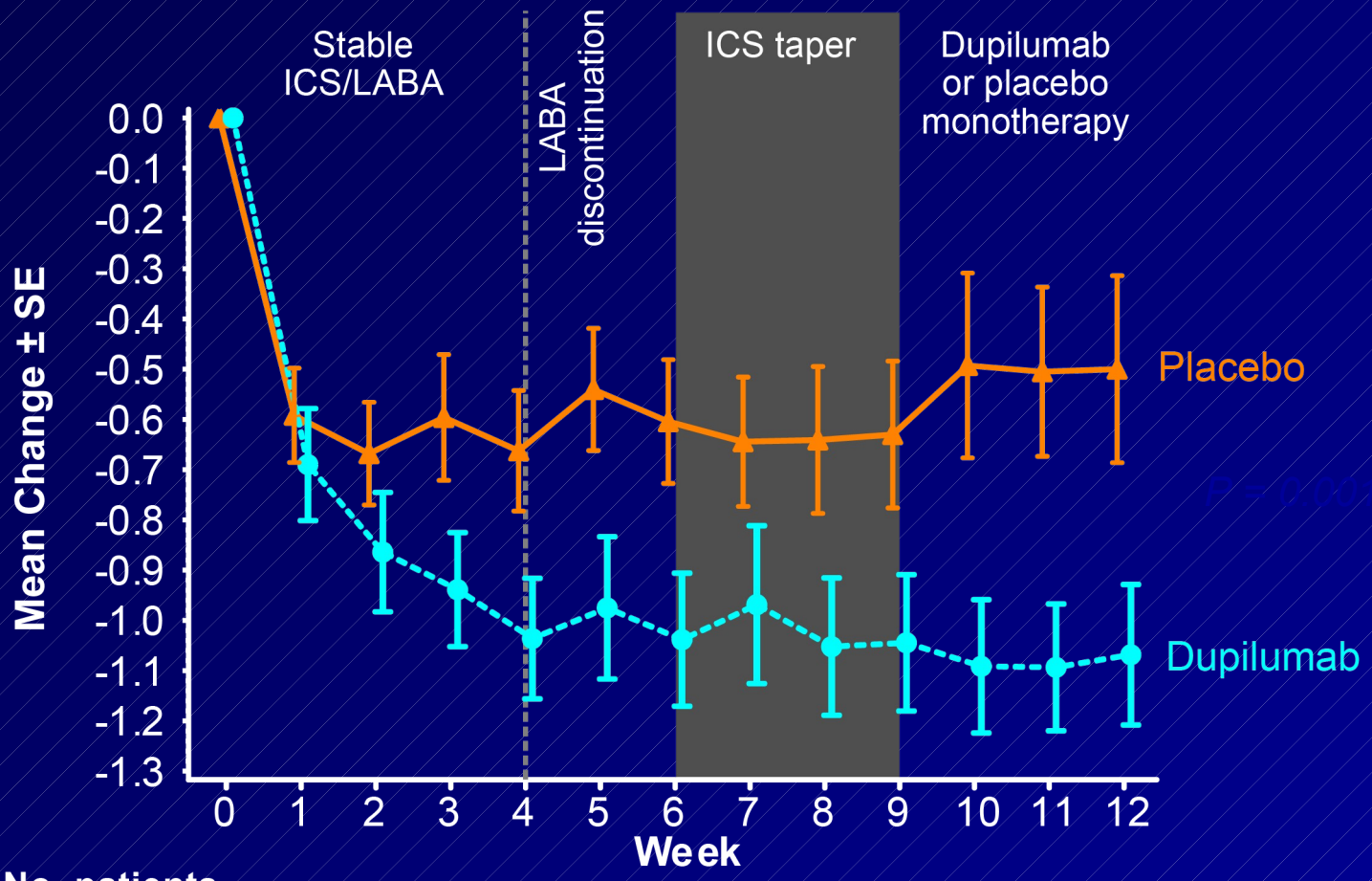


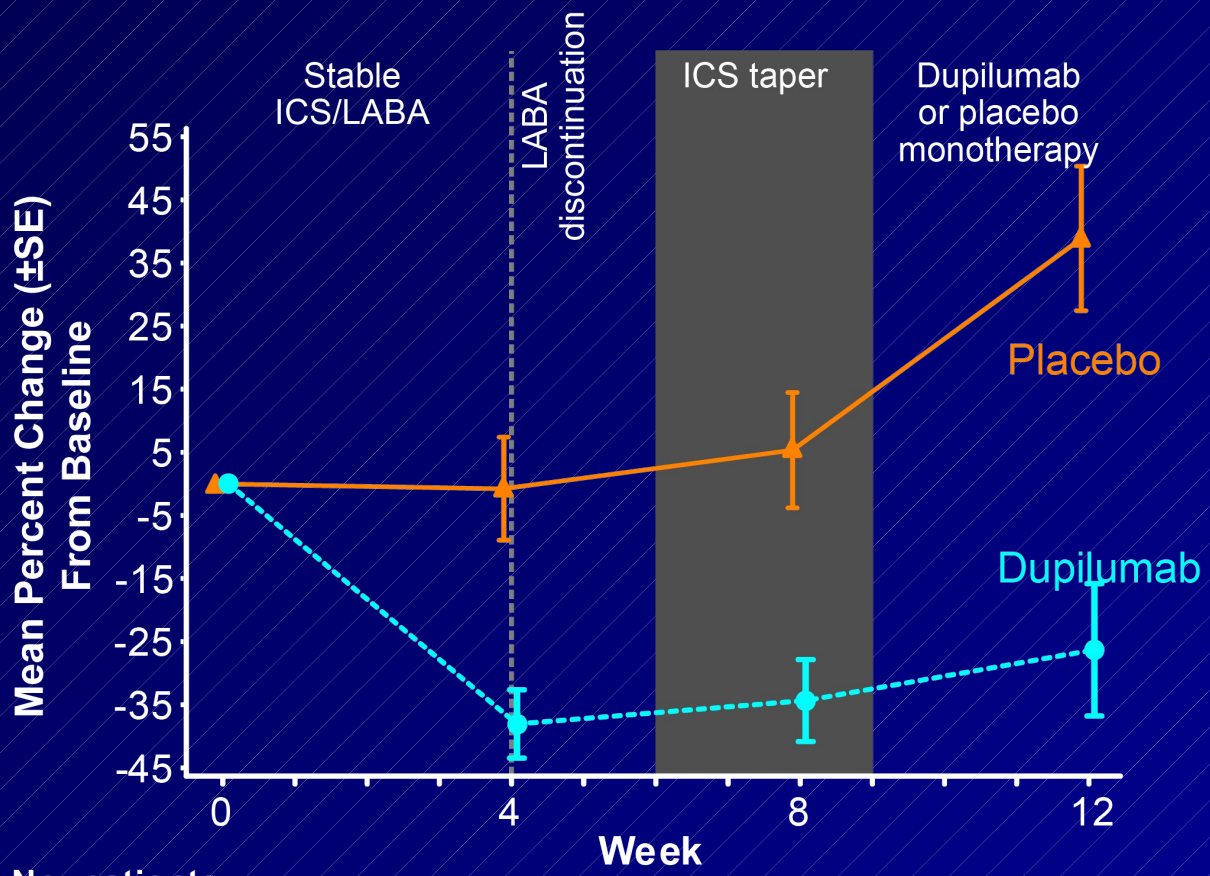
Improvement in lung function, on top of combination Rx



Improvement in Asthma Control

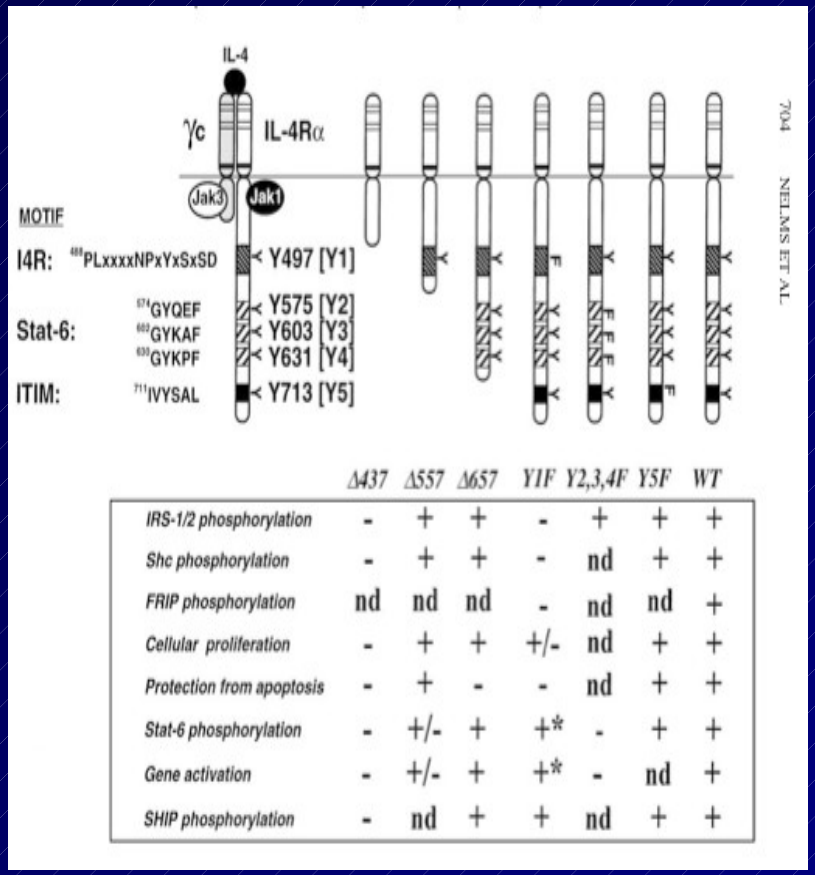


Proof of biologic mechanism: Change in FeNO correlated with change in FEV1



No. patients				
Placebo	52	51	47	44
Dupilumab	51	48	50	40

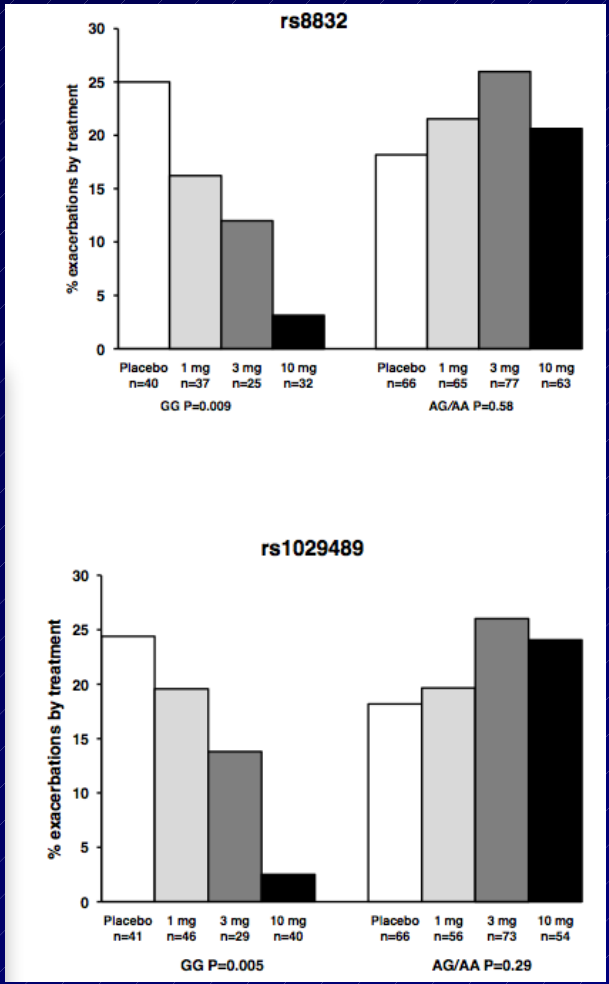
Pharmacogenetics: Will they influence response to targeted Rx?



	Δ437	Δ557	Δ657	YIF	Y2,3,4F	Y5F	WT
IRS-1/2 phosphorylation	-	+	+	-	+	+	+
Shc phosphorylation	-	+	+	-	nd	+	+
FRIP phosphorylation	nd	nd	nd	-	nd	nd	+
Cellular proliferation	-	+	+	+/-	nd	+	+
Protection from apoptosis	-	+	-	-	nd	+	+
Stat-6 phosphorylation	-	+/-	+	+*	-	+	+
Gene activation	-	+/-	+	+*	-	nd	+
SHIP phosphorylation	-	nd	+	+	nd	+	+

- *IL-4, IL-13, STAT6, IL-4R$^{\Delta}$* polymorphisms long associated with asthma/atopy
- Associated with severe exacerbating asthma/low lung function AND African racial background, but not usual descriptions of “severity”
  - Wenzel AJRCCM 2007
- Will genetic receptor differences impact response to Rx?

Genetics and responses



- Pitrakinra response in exacerbation study dependent on IL-4R genotype
- Clear dose response
- Common genotypes which account for up to 50% of population
  - Haplotypes of 40% population reduced exacerbations by 70%
- ?biomarker

Slager R, J Allergy Clin Immunol In press

Conclusions

- Molecular phenotyping allowed identification of Type-2 cytokine Hi asthma
  - Predicts response to IL-13 and IL-4/-13 targeted therapies
  - Not yet clear whether blockade of both IL-4 and IL-13 will lead to better responses than either alone
  - Similarly unclear with addition of IL-5 inhibition would add anything more
- Biomarker driven biologic therapies poised to have substantial impact in asthma