Monoclonal antibodies

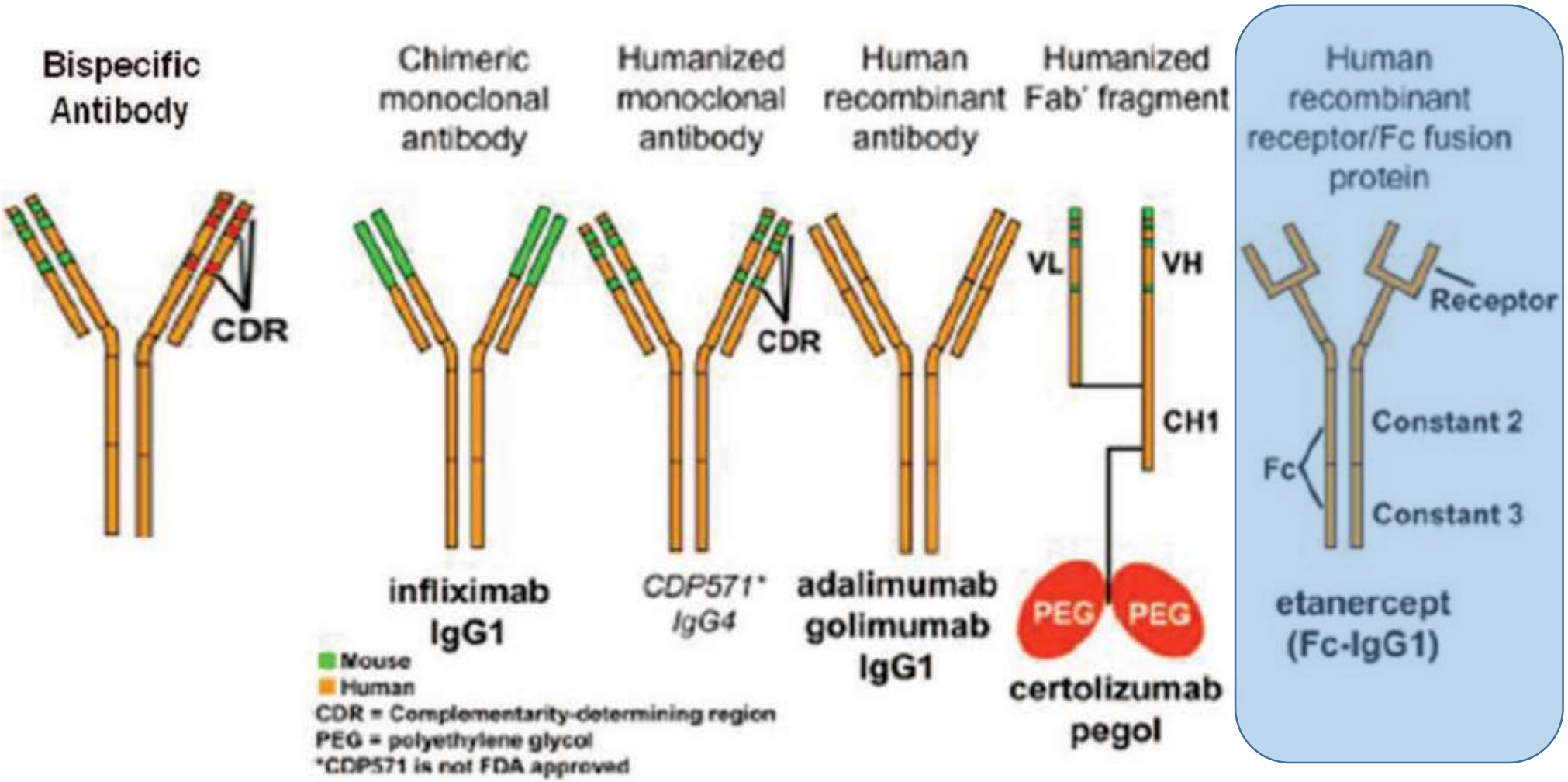
Emerging role in pulmonary medicine

Seminar outline

- Basics of monoclonal antibodies
- Role of monoclonal antibodies in:
  - Asthma
  - Lung cancer
  - Pulmonary vasculitis
  - Sarcoidosis
- Pulmonary disorders induced by monoclonal antibodies

Monoclonal vs Polyclonal antibodies

- Antibodies that arise in an animal in response to typical antigens are heterogeneous, because they are formed by several different clones of plasma cells (i.e., they are polyclonal).
- Antibodies that arise from a single clone of cells are homogeneous (i.e., they are monoclonal).



WAO Journal 2010; 3:188–194

Prefix
Random

Substem B
Target class

-b(a)-	bacterial
-c(i)-	cardiovascular
-f(u)-	fungal
-k(i)-	interleukin
-l(i)-	immunomodulating
-n(e)- (under discussion	neural
-s(o)-	bone
-tox(a)	toxin
t(u)	tumour
-v(i)-	viral

Substem A
Source species

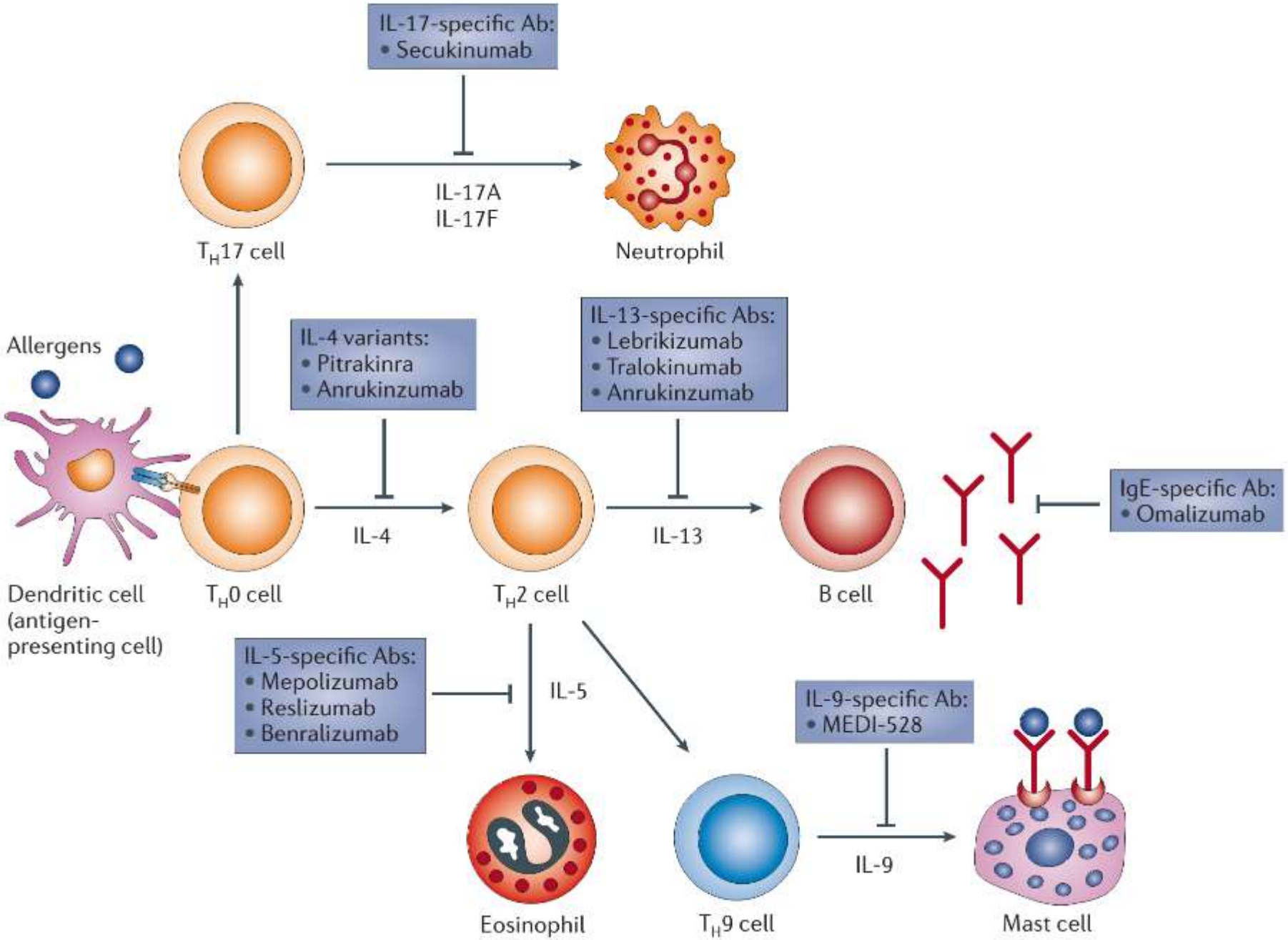
a	rat
axo (pre-sub-stem)	rat/mouse
e	hamster
i	primate
o	mouse
u	human
xi	chimeric
-xizu- (under discussion)	chimeric/humanized
zu	humanized

Suffix
-mab

Rituximab = Ri + tu + xi + mab
Omalizumab = Oma + li + zu + mab

WHO 2009 General policies for monoclonal antibodies

Asthma



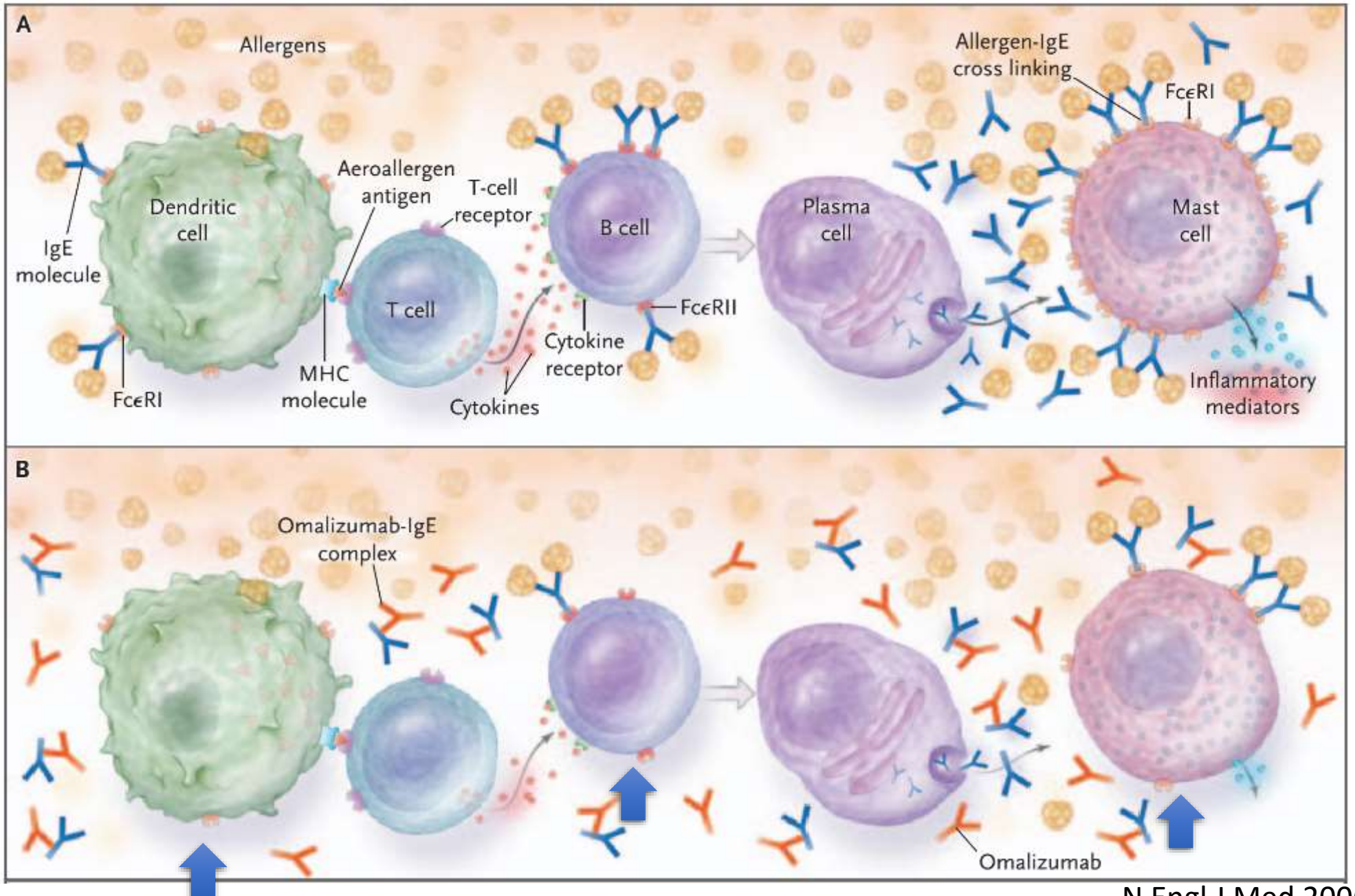
Nat Rev Drug Discov. 2012 Dec;11(12):958-72

Drug	Mechanism of action	Effects	Development*
Omalizumab	Binds free IgE	Reduces exacerbations, improves symptoms and quality of life	FDA- and EMA-approved
Mepolizumab	Blocks IL-5	Decreases the number of eosinophils and frequency of exacerbations, as well as prednisone consumption	Phase II/III
Reslizumab	Blocks IL-5	Decreases the number of sputum eosinophils and enhances FEV1	Phase II
Benralizumab	Inhibits binding of IL-5 to IL-5Rα	Depletes the number of peripheral blood eosinophils	Phase I/II
Pascolizumab	Blocks IL-4	No significant clinical efficacy	Phase II
Altrakincept	Soluble IL-4R	No significant clinical efficacy	Phase II
Pitrakinra	Inhibits binding of IL-4 and/or IL-13 to IL-4Rα	May prevent a decrease in FEV1 after allergen challenge	Phase II
Tralokinumab	Blocks IL-13	Reduces airway eosinophilia	Phase I/II
Anrukinzumab	Blocks IL-13	Inhibits allergen-induced late-phase asthmatic responses	Phase II
Lebrikizumab	Blocks IL-13	Enhances FEV1 in patients with high serum levels of periostin	Phase II
MEDI-528	Blocks IL-9	Reduces airway inflammation and hyper-responsiveness in mice	Phase II
MT203	Blocks GM-CSF	Decreases survival and activation of eosinophils	Phase II
Secukinumab	Blocks IL-17	Data not yet available	Phase II; NCT01478360
Golimumab	Blocks TNFα	May increase the risk of infections and malignancies	Suspended
Infliximab	Blocks TNFα	Reduces PEF oscillations and asthma exacerbations	Phase II
Etanercept	Soluble TNFα receptor	Conflicting data; see main text	Phase II

Nat Rev Drug Discov. 2012 Dec;11(12):958-72

Asthma: Anti-IgE Rx

Omalizumab (rhuMab-E25)



N Engl J Med 2006;354:2689-95

TREATMENT OF ALLERGIC ASTHMA WITH MONOCLONAL ANTI-IgE ANTIBODY

HENRY MILGROM, M.D., ROBERT B. FICK, JR., M.D., JOHN Q. SU, PH.D., JAMES D. REIMANN, PH.D., ROBERT K. BUSH, M.D., MARC L. WATROUS, PH.D., AND W. JAMES METZGER, M.D., FOR THE RHUMAB-E25 STUDY GROUP*

- Subjects had **moderate to severe asthma** (FEV1 <71%, asthma symptom score of 4 or more, daily reliever use) and had positive skin-prick test to at least 2 perennial allergens
- 317 subjects who required inhaled or oral corticosteroids (or both) to receive **either placebo or one of two regimens of IV rhuMAb-E25**: high-dose rhuMAb-E25 (5.8 µg/kg/ng of IgE per ml) or low-dose rhuMAb-E25 (2.5µg/kg/ng of IgE per ml) on days 0 (half a dose), 4 (half a dose), and 7 (full dose) and then once every 2 weeks thereafter for 20 weeks.
- For the first 12 weeks of the study, the subjects continued the regimen of corticosteroids they had received before enrollment. **During the following eight weeks, the doses of corticosteroids were tapered in an effort to discontinue this therapy**.

N Engl J Med 1999;341:1966-73

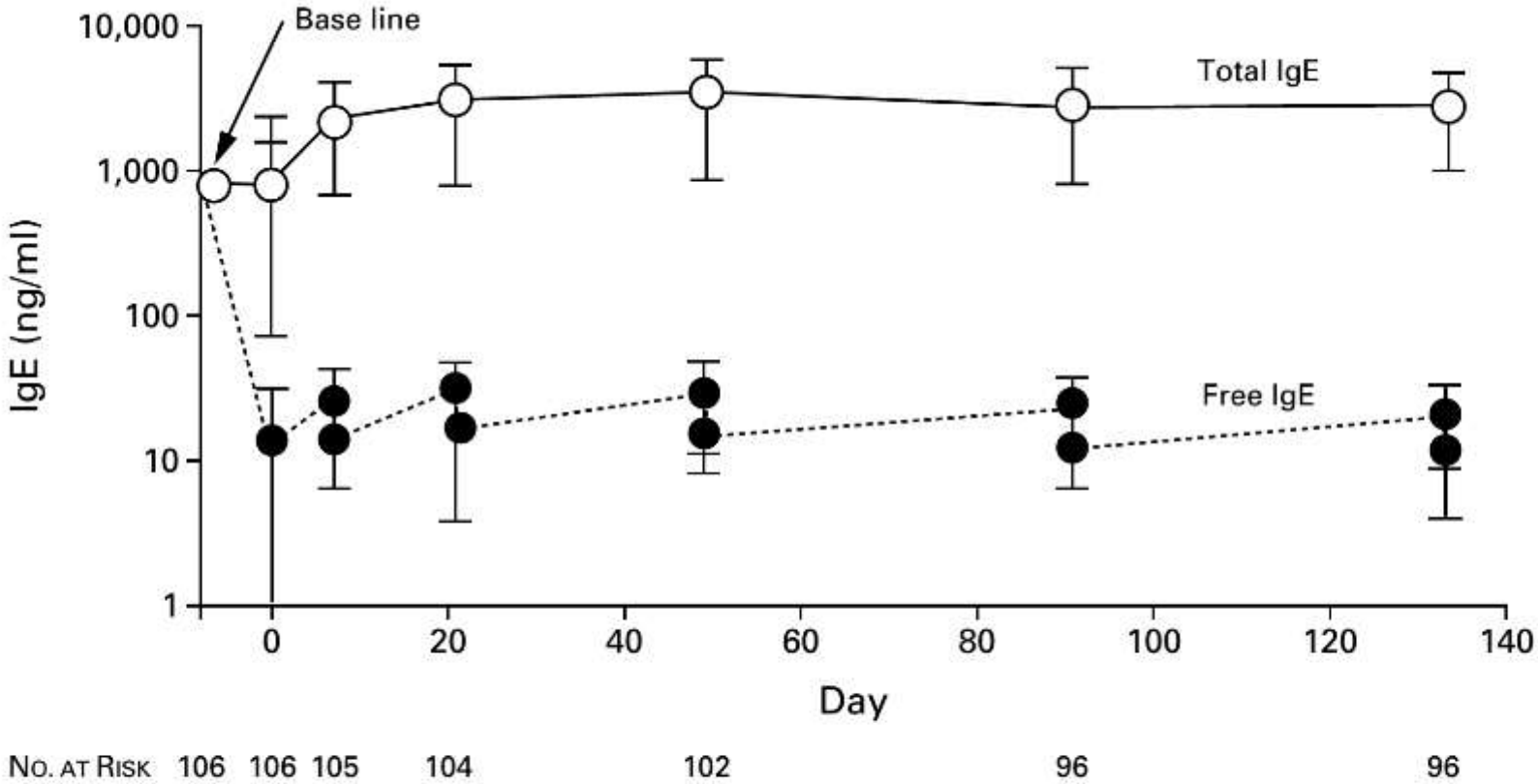


Figure 1. Mean (±SD) Serum Concentrations of Total and Free IgE in Subjects Given a Low Dose of rhuMAb-E25 for 20 Weeks.

Serum free IgE concentrations decreased rapidly by more than 95 percent (base-line level, 1060 ng per milliliter [441.7 IU per milliliter]). To convert values to international units per milliliter, divide by 2.4. A log (base 10) scale is shown.

N Engl J Med 1999;341:1966-73

TABLE 2. REDUCTIONS IN OVERALL ASTHMA SYMPTOM SCORES.*

SCORE	HIGH-DOSE rhuMAb-E25 (N=103)	LOW-DOSE rhuMAb-E25 (N=103)	PLACEBO (N=100)
Base line			
Mean	4.1±0.1	4.0±0.1	4.0±0.1
Median	3.8	4.0	3.8
Week 12			
Mean	2.8±0.1	2.8±0.1	3.1±0.1
P value	0.008	0.005	
>50% Reduction in scores — no. of subjects (%)	50 (49)	48 (47)	24 (24)
P value	<0.001	<0.001	
Week 20			
Mean	2.7±0.1	2.7±0.1	2.9±0.1
P value	0.048	0.14	
>50% Reduction in scores — no. of subjects (%)	51 (50)	48 (47)	34 (34)
P value	0.03	0.07	

*Plus–minus values are means ±SE. Data are presented for the 306 subjects with at least four weeks of treatment. Subjects who left the study after at least four weeks of treatment had their last value carried forward. Asthma symptoms are scored on a 7-point scale, with a score of 1 indicating no symptoms and a score of 7 indicating maximal symptoms. The P values are for the comparison with placebo.

- Subjects had moderate to severe asthma (FEV1 <71%, asthma symptom score of 4 or more, daily reliever use) and had positive skin-prick test to at least 2 perennial allergens
- Primary outcome measure was improvement in the asthma symptom score at 12 weeks
- Improvement was marginal, but statistically significant

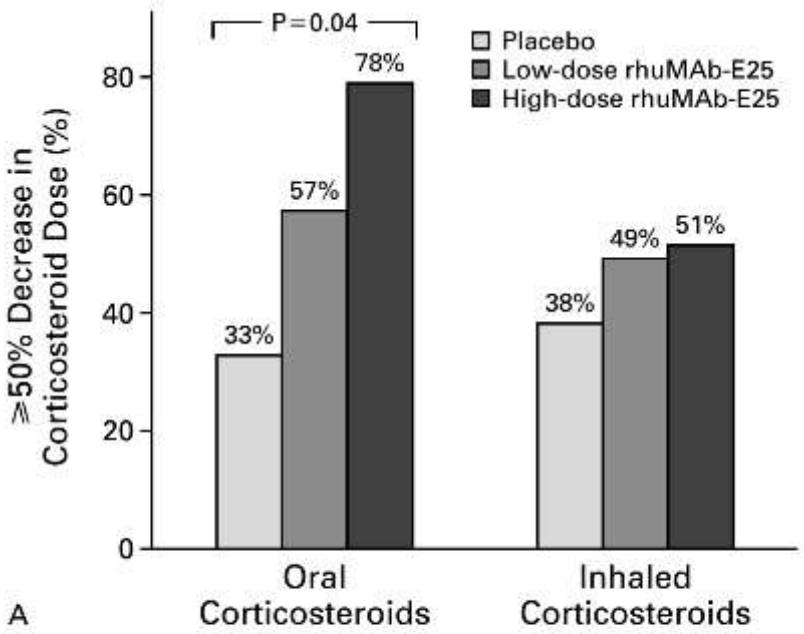
N Engl J Med 1999;341:1966-73

043 THE (AB)USE OF SYMPTOM SCORES IN ASTHMA CLINICAL TRIALS: EVIDENCE FROM A SYSTEMATIC REVIEW

G Frampton, J Shepherd. *Southampton Health Technology Assessments Centre (SHTAC), School of Medicine, University of Southampton, Epsilon House, Southampton Science Park, Southampton, UK*

- The numerical interpretation of scores seems detached from considering the real importance of symptoms to patients
- No single standard scale (different studies have used different scales)
- Most are unvalidated
- Difficult to compare across studies (as in meta-analyses)
- Clinically significant change not clear

J Epidemiol Community Health 2009;63:43



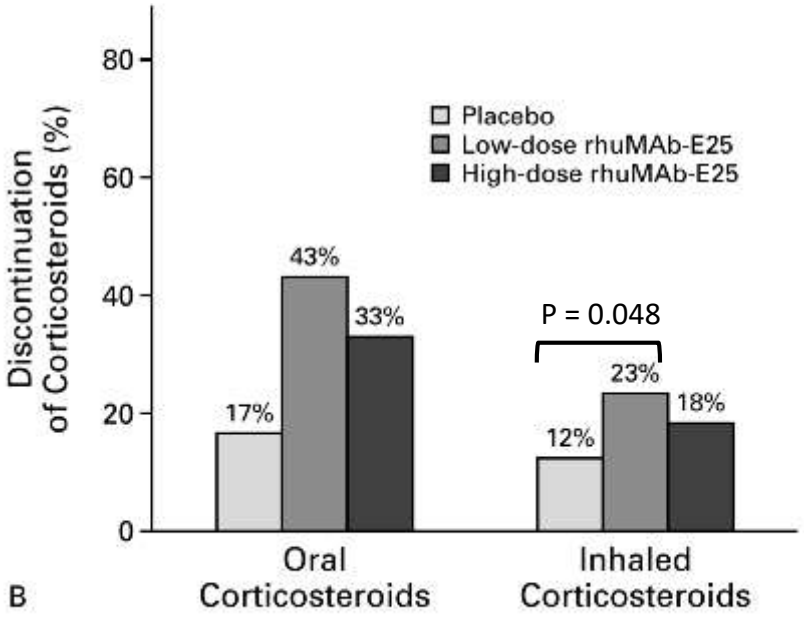


Figure 2. Results of Efforts to Taper the Dose of Corticosteroids.

- First 12 weeks of the study, omalizumab as an add-on to baseline corticosteroids
- Next 8 weeks, corticosteroids were tapered

- More subjects in the two omalizumab groups were able to decrease or discontinue corticosteroids than in the placebo group (but only some of the differences were significant)

N Engl J Med 1999;341:1966-73

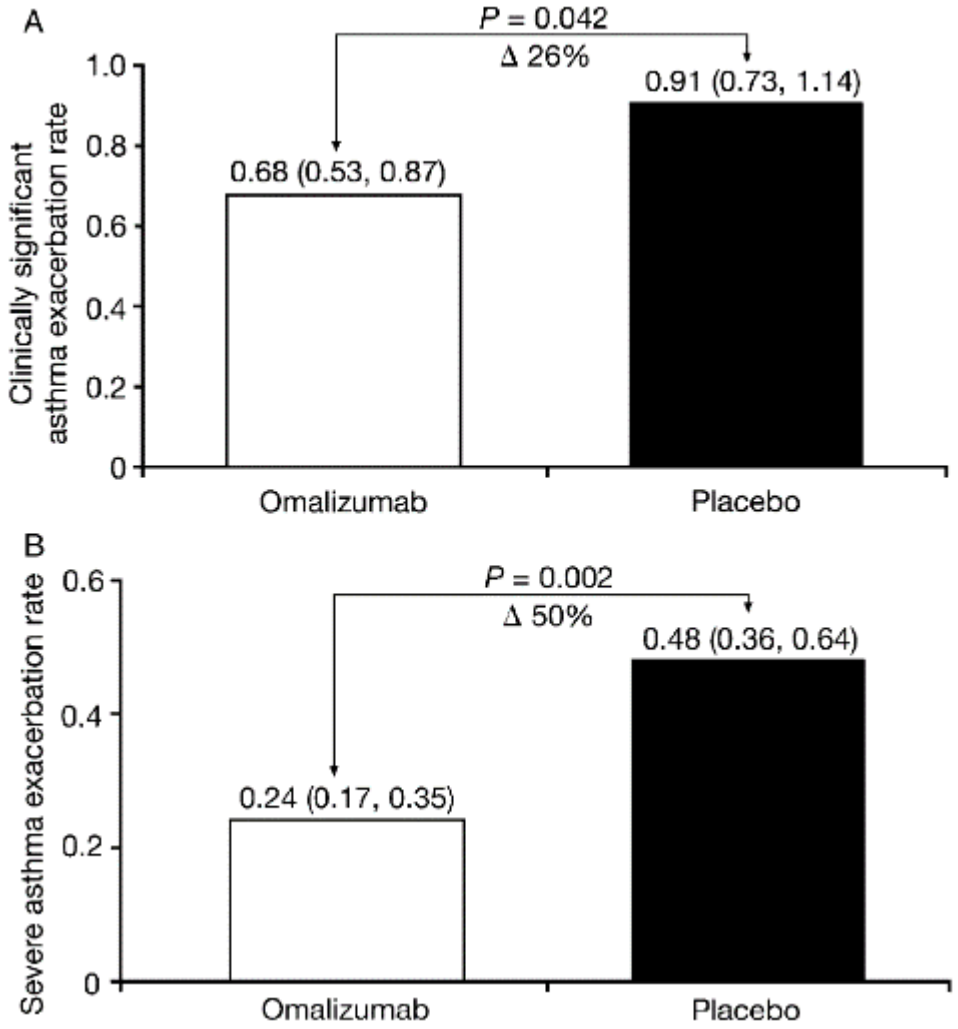
Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE

GINA 2002 Step 4 (Severe Persistent Asthma): Inhaled glucocorticosteroid (> 1,000 µg BDP or equivalent) plus inhaled LABA, plus one or more of the following, if needed: Sustained-release theophylline, Leukotriene modifier, oral LABA, Oral glucocorticosteroid

Patients at baseline receiving, *n* (%)†	Omalizumab (n =209)	Placebo (n =210)
Inhaled corticosteroids plus LABA	209 (100)	210 (100)
Antileukotrienes	74 (35.4)	72 (34.3)
Theophyllines	64 (30.6)	51 (24.3)
Maintenance oral steroids	49 (23.4)	42 (20.0)
Oral β_2-agonists	1 (0.5)	3 (1.4)

Allergy 2005: 60: 309–316

Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE



Clinically significant exacerbation was defined as worsening of asthma symptoms requiring treatment with systemic corticosteroids

Severe exacerbation was defined as PEF or FEV1 <60% of personal best, requiring treatment with systemic corticosteroids

Allergy 2005: 60: 309–316

Omalizumab: Dosing

Table 1. Dosing Schedule for Subcutaneously Administered Omalizumab, According to the Baseline Serum IgE Level and Body Weight.*

Baseline Serum IgE Level	Body Weight				
	30–60 kg	61–70 kg	71–80 kg	81–90 kg	91–150 kg
IU/ml	*dose in milligrams*				
30–100	*150*	*150*	*150*	*150*	*300*
101–200	*300*	*300*	*300*	*300*	225
201–300	*300*	225	225	225	300
301–400	225	225	300	300	—
401–500	300	300	375	375	—
501–600	300	375	—	—	—
601–700	375	—	—	—	—

* Adapted from the Xolair package insert.[32] The recommended dose is 0.016 mg per kilogram of body weight per international unit of IgE every four weeks, administered subcutaneously at either four-week (italic) or two-week (roman) intervals for adults and adolescents (persons 12 years of age and older) with allergic asthma. Dashes indicate that no dose should be prescribed.

- Clinical benefit with omalizumab is observed when free IgE levels in serum are reduced to 50 ng/ml (20.8 IU/ml) or less
- Omaluzimab must be given in molar excess of 15:1 to 20:1 relative to total baseline IgE in order to obtain adequate reduction in IgE

Ther Adv Resp Dis. 2011;5(3):183-194
N Engl J Med 2006;354:2689-95

Omalizumab: Duration of Rx

- In one study which analyzed patients who had responded by 16 weeks of Rx, only 61% had responded after 4 weeks of therapy; however, 87% did so at 12 weeks
- A **minimum duration of 12 weeks is advisable** before determining the degree of omalizumab's therapeutic response
- After omalizumab cessation, the levels of free IgE, basophil FcεRI expression, and allergen-induced histamine release return to pretreatment levels within approximately 2–10 months often with recrudescence of disease
- Some authors recommend **life-long treatment** because of this reason

Ther Adv Resp Dis. 2011;5(3):183-194

Omalizumab: Adverse effects

- Injection site pain (19.9% vs 13.2%)
- Possibly increased risk for infection (OR 1.96; 0.88–4.36)
- Potential for higher risk of geohelminth infection (51% vs 40%)
- Increased risk of anaphylaxis (0.09–0.2%) (Note: Many cases were delayed, however, occurred within 2 hours of injection)
- Possibly higher incidence of malignancies (0.5% vs. 0.2%)
- Churg–Strauss syndrome (?)

Chest 2011; 139(1):28–35
Ther Adv Resp Dis. 2011;5(3):183-194
Clin Exp Allergy. 2007 Feb;37(2):197-207
Clin Exp Allergy. 2009 Jun;39(6):788-97
Curr Opin Allergy Clin Immunol2013, 13:19–24

CHEST Original Research

ASTHMA

Churg-Strauss Syndrome in Patients Treated With Omalizumab

Michael E. Wechsler, MD, MMSc; Dennis A. Wong, MD; Mary K. Miller, MS; and Lisa Lawrence-Miyasaki, RN, BSN, MA

Retrospective analysis of data from Novartis global database

34 potential cases of CSS

- 17 were not CSS
- 13 definite/probable CSS (ACR criteria met)
  - 8 had prior symptoms or onset just after steroid weaning
- 4 possible CSS (ACR criteria not met)

Omalizumab treatment may unmask CSS due to the weaning of corticosteroids in some asthma patients or may delay corticosteroid treatment allowing for CSS to manifest

Chest. 2009;136(2):507-518

Anti-IgE for chronic asthma in adults and children (Review)

Walker S, Monteil M, Phelan K, Lasserson TJ, Walters EH

THE COCHRANE COLLABORATION®

- 14 RCTs (Omalizumab):
  - 13 adult/adolescents, one pediatric
  - 7 as an adjunct to treatment with inhaled and oral corticosteroids (attempts were made to reduce steroids in 5 trials after 12-28 weeks of stable steroid phase)
  - 7 without background steroid Rx
- Route: 10 SC, 3 IV, 1 inhaled
- Frequency & duration: Every 2-4 weeks for 12-28 weeks
- Asthma severity (as per Cochrane reviewer): Mild 7, moderate/severe 5, severe 2
- Inclusion criteria
  - Positive skin tests to common aero-allergens (required in all trials)
  - Threshold IgE level required in 8 trials (141.5 to 1300 IU/mL)
  - Nearly 1/3rd to 1/2 of screened patients had to be excluded in the trials because of failure to meet these inclusion criteria

Cochrane Database Syst Rev. 2006 Apr 19;(2):CD003559

Background steroid	Yes (Oral/Inhaled)		No (Milder disease; BTS Step 1)		
Anti-IgE therapy	**SC**	**IV**	**SC**	**IV**	**Inhaled**
Reduction in IgE from baseline	89-99%	89-99%	0	Yes (90%)	no
Exacerbation risk	OR 0.55 (0.45 to 0.69)	32/106 vs 47/105 (1)	0	0	0
Rescue medication use (puffs/d)	-0.63 (-0.90 to -0.36)	0.8 vs 1.2 (1)	0	ns	0
PEF at end of Rx	ns	0	0	ns	ns
Change in PEF (L/min) from baseline	0	30.7 vs 11.3 (1)	0	0	0
FEV1 at end of Rx	ns	ns	ns	ns	ns
Change in FEV1 from baseline	73ml (1), 2.8% (1)	0	0	0	0
Symptom scores at end of Rx	-0.46 (-0.75 to -0.29)	2.8 vs 3.1 (1)	0	ns	0
Change in symp scores from baseline	-1.8 (1)	0	0	0	0
Asthma control (Good or Excellent)	59% vs 41% (1); OR 2.58 (2)	0	0	0	0
AQLQ (Change from baseline)	0.32 (0.22 to 0.43)	1.4 vs 0.8 (1)	0	0	0
ICS withdrawal	OR 2.50 (2.00 to 3.13)	ns	-	-	-
ICS reduction (BDP equivalent/day)	-118 mcg (-154 to -84)	0	-	-	-
>50% ICS reduction	OR 2.50 (2.02 to 3.10)	51.6% vs 37.6% (1)	-	-	-
OCS withdrawal/reduction	ns	0	-	-	-

ns = not significant, green = significant improvement, 0 = data not available, - = not applicable

Cochrane Database Syst Rev. 2006 Apr 19;(2):CD003559

Results: Efficacy

- Omalizumab produced significant reduction in serum free IgE (89% to 99%) (in all trials, except one trial which used inhaled route)
- Omalizumab reduced asthma exacerbations and need for rescue medications when used as an adjunctive therapy to steroids
- Omalizumab use allowed significant reduction of ICS dose
- In the subgroup of patients requiring oral steroids, Omalizumab had no significant effect on asthma exacerbations or reduction in daily oral steroid dose
- Omalizumab significantly improved HRQoL
- There was no consistent effect of Omalizumab on lung function

Cochrane Database Syst Rev. 2006 Apr 19;(2):CD003559

Results: Safety

- Side effects following treatment with Omalizumab were mild to moderate and did not differ significantly from placebo with the exception of injection site reactions
- Antibodies to Omalizumab did not develop in participants treated with subcutaneous or intravenous Omalizumab

Cochrane Database Syst Rev. 2006 Apr 19;(2):CD003559

CHEST

Original Research

ASTHMA

Efficacy and Safety of Subcutaneous Omalizumab vs Placebo as Add-on Therapy to Corticosteroids for Children and Adults With Asthma

A Systematic Review

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

Gustavo J. Rodrigo, MD; Hugo Neffen, MD; and José A. Castro-Rodriguez, MD, PhD

- Included 8 studies on moderate to severe asthma
- Had included 2 additional studies (compared to the previous Cochrane review) published in 2009
- Results similar to the Cochrane review
- 1 RCT published after both these meta-analyses (Hanania NA et al, 2011) also yielded similar results

Asthma: Anti-IL Rx

Mepolizumab (IL-5), Dupilumab (IL-4), Lebrikizumab (IL-13)

A Study to Evaluate Safety and Efficacy of Mepolizumab in Patients with Moderate Persistent Asthma

Patrick Flood-Page[1], Cheri Swenson[2], Isidore Faiferman[3], John Matthews[3], Michael Williams[3], Lesley Brannick[3], Douglas Robinson[4], Sally Wenzel[5], William Busse[2], Trevor T. Hansel[4], and Neil C. Barnes[6], on behalf of the International Mepolizumab Study Group*

[1]Royal Gwent Hospital, Newport, Wales, United Kingdom; [2]Allergy and Asthma Clinical Research Unit, University of Wisconsin-Madison, Madison, Wisconsin; [3]Respiratory and Inflammation Discovery Medicine, GlaxoSmithKline, Greenford, United Kingdom; [4]National Heart and Lung Institute, Imperial College London, London, United Kingdom; [5]National Jewish Medical and Research Center, Denver, Colorado; and [6]London Chest Hospital, London, United Kingdom

- Mepolizumab is a monoclonal antibody against interleukin-5
- 362 patients with **asthma experiencing persistent symptoms despite ICS** (400-1,000 mcg of beclomethasone or equivalent)
- Three 'monthly' IV infusions of Mepolizumab 250mg or 750mg vs placebo
- Follow-up: Till 8wks after last infusion
- Mepolizumab was associated with a significant reduction in blood and sputum eosinophils in both treatment groups
- There were no statistically significant changes in any of the clinical end points measured.

Am J Respir Crit Care Med Vol 176. pp 1062–1071, 2007

Mepolizumab for Prednisone-Dependent Asthma with Sputum Eosinophilia

Parameswaran Nair, M.D., Ph.D., Marcia M.M. Pizzichini, M.D., Ph.D.,
Melanie Kjarsgaard, R.R.T., Mark D. Inman, M.D., Ph.D.,
Ann Efthimiadis, M.L.T., Emilio Pizzichini, M.D., Ph.D.,
Frederick E. Hargreave, M.D., and Paul M. O'Byrne, M.B.

- Randomized, double-blind, parallel-group trial
- Enrolled 20 patients with **persistent sputum eosinophilia (>3%) and symptoms despite steroid Rx** (Prednisone 5-25mg and ICS 600-2000mcg fluticasone for 4 wks). **(<3% of 800 patients from asthma clinics)**
- 9 patients were assigned to receive mepolizumab (5 monthly infusions of 750 mg each) and 11 patients to receive placebo. (2 patients without sputum eosinophilia were included by error)
- Prednisone tapered to 2.5-5mg between 6-22wks
- Follow-up: 8wks after last infusion
- There were 12 asthma exacerbations in 10 patients who received placebo, 9 of whom had sputum eosinophilia at the time of exacerbation. In comparison, only one patient who received mepolizumab had an asthma exacerbation, and this episode was not associated with sputum eosinophilia (P = 0.002)

N Engl J Med 2009; 360:985-993

Mepolizumab and Exacerbations of Refractory Eosinophilic Asthma

Pranabashis Haldar, M.R.C.P., Christopher E. Brightling, Ph.D., F.R.C.P., Beverley Hargadon, R.G.N., Sumit Gupta, M.R.C.P., William Monteiro, M.Sc., Ana Sousa, Ph.D., Richard P. Marshall, Ph.D., M.R.C.P., Peter Bradding, D.M., F.R.C.P., Ruth H. Green, M.D., F.R.C.P., Andrew J. Wardlaw, Ph.D., F.R.C.P., and Ian D. Pavord, D.M., F.R.C.P.

- Randomized, double-blind, placebo-controlled, parallel-group study
- 61 subjects who had **refractory eosinophilic asthma and a history of recurrent severe exacerbations**
- Inclusion criteria
  - Diagnosis of refractory asthma according to ATS criteria
  - Sputum eosinophil more than 3% on at least one occasion in the previous 2 years despite high-dose corticosteroid Rx, and
  - At least two exacerbations requiring rescue prednisolone in the previous 12 months
- 12 infusions (monthly) of either 750 mg of IV mepolizumab or matched placebo
- Background asthma medications not changed during study
- Mepolizumab was associated with **significantly fewer severe exacerbations** than placebo over 50 weeks (2.0 vs. 3.4 mean exacerbations per subject; RR, 0.57; 95% CI, 0.32 to 0.92; P = 0.02)

N Engl J Med 2009;360:973-84

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

- Multicentre, double-blind, placebo-controlled trial
- Patients had a **history of recurrent severe asthma exacerbations, and had signs of eosinophilic inflammation**
- Patients had evidence of eosinophilic inflammation as shown by one or more criteria at study entry or in the previous year:
  - Sputum eosinophil count of 3% or more
  - Exhaled nitric oxide concentration (FENO) of 50 ppb or more
  - Asthma-related peripheral blood eosinophil count of $0{\cdot}3\times10^9$ per L or more, or
  - Prompt deterioration of asthma control after a 25% or less reduction in regular maintenance inhaled or oral corticosteroids
- Patients met the ATS criteria for a diagnosis of **refractory asthma**
- 621 patients were randomised: 159 were assigned to placebo, 154 to 75 mg mepolizumab, 152 to 250 mg mepolizumab, and 156 to 750 mg mepolizumab (13 infusions at 4-weekly intervals)

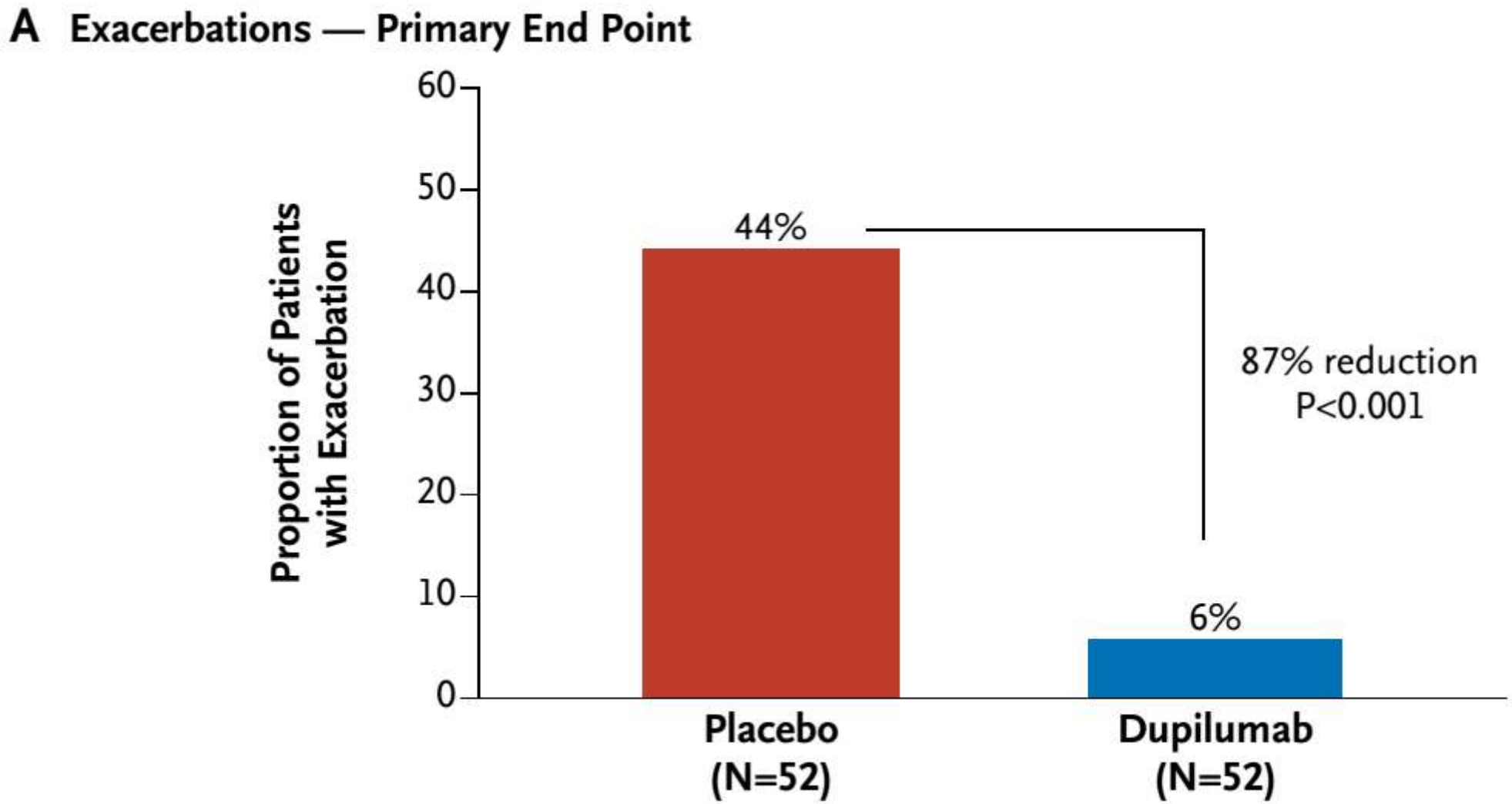
Lancet 2012; 380: 651–59

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.

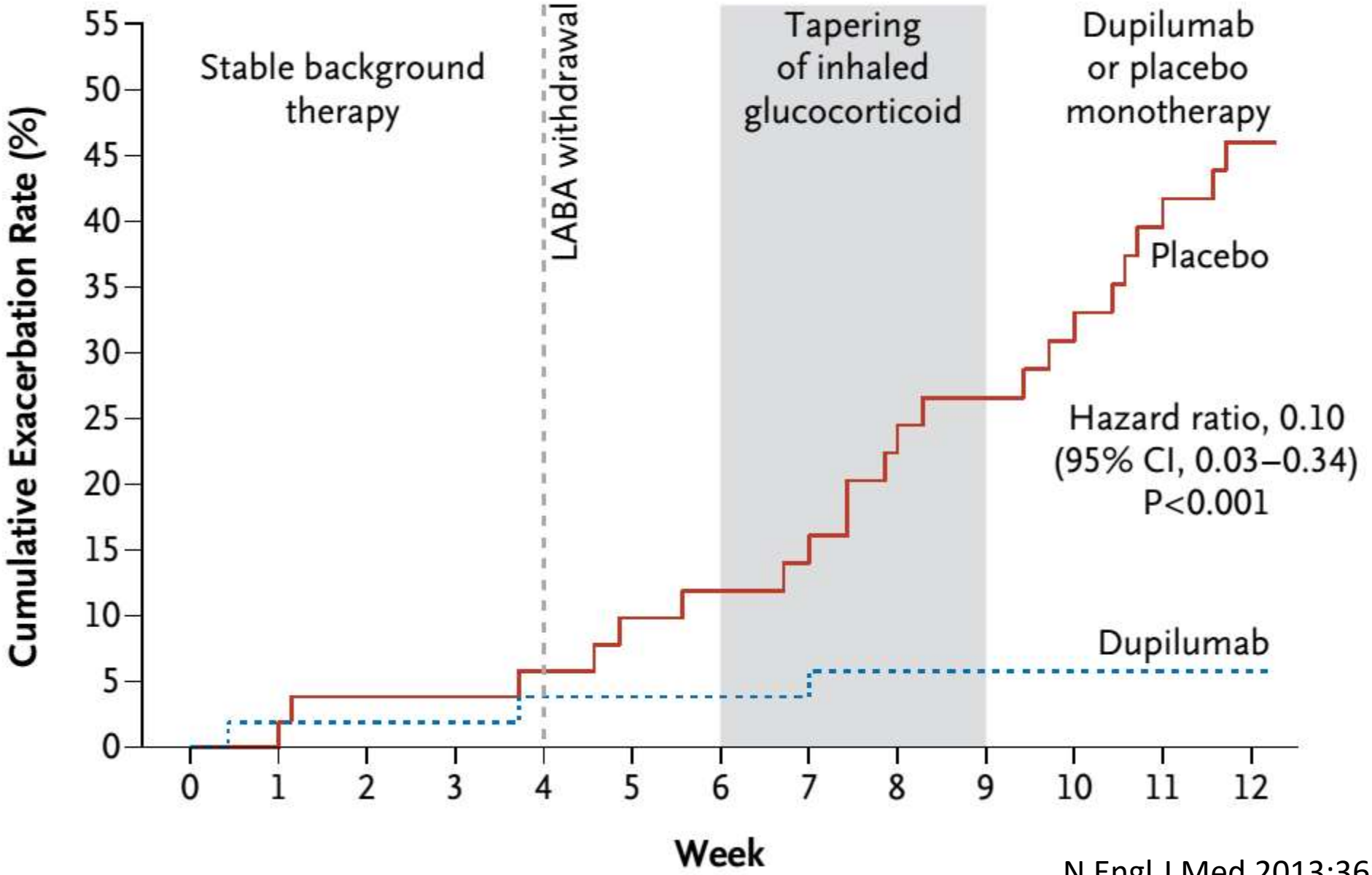
- Dupilumab is a fully human monoclonal antibody to the alpha subunit of the interleukin-4 receptor
- Patients with **persistent, moderate-to-severe "eosinophilic" asthma** (blood eosinophil count of at least 300 cells per microliter or a sputum eosinophil level of at least 3%) who used medium-dose to high-dose ICS plus LABAs were enrolled.
- Dupilumab (300 mg) or placebo (n = 104; 52 vs 52) was administered subcutaneously once weekly for 12 weeks or until a protocol-defined asthma exacerbation occurred.
- Patients were instructed to discontinue LABAs at week 4 and to taper and discontinue inhaled glucocorticoids during weeks 6 through 9.

N Engl J Med 2013;368:2455-66

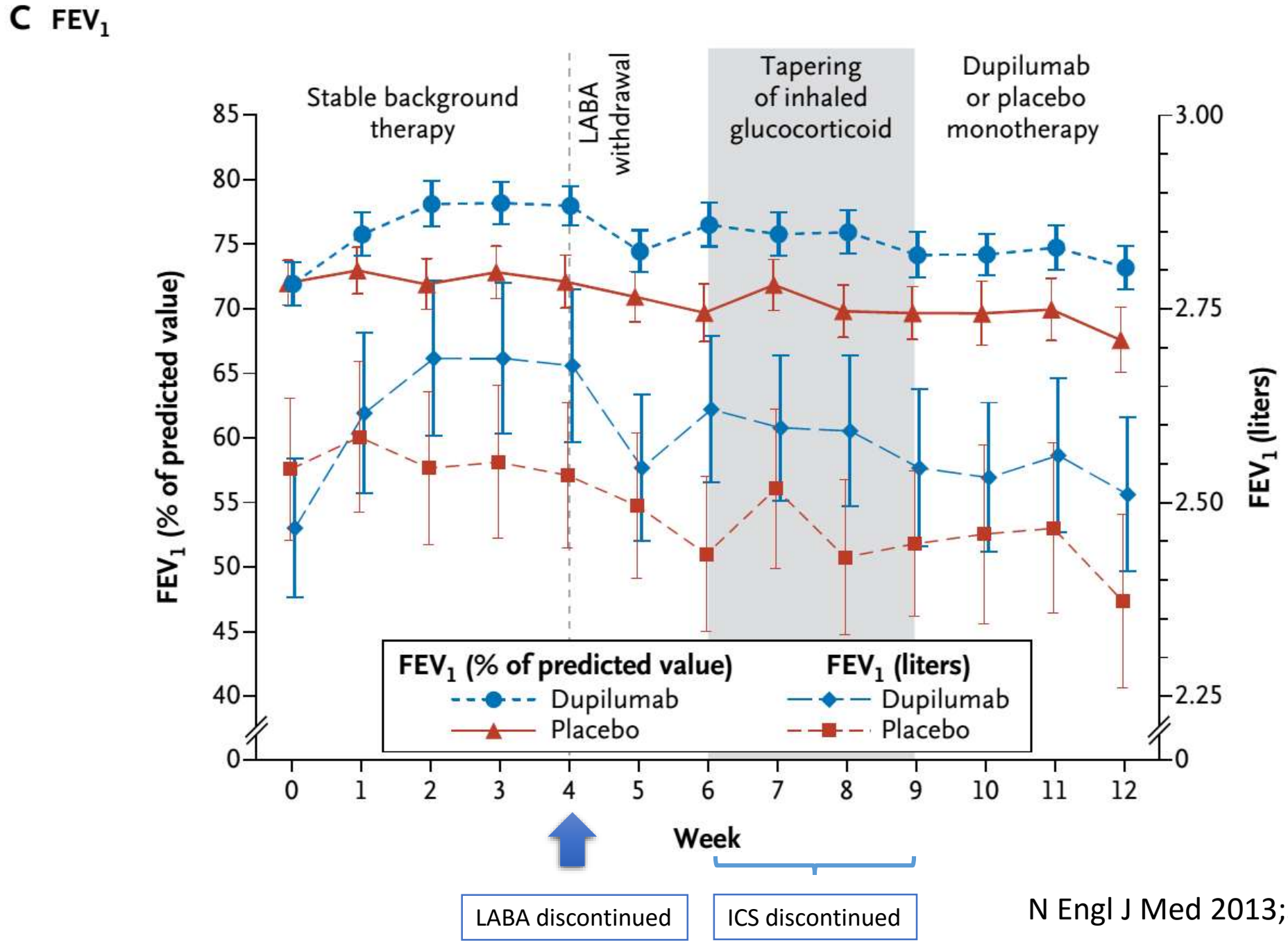


N Engl J Med 2013;368:2455-66

B **Time to Exacerbation**



N Engl J Med 2013;368:2455-66



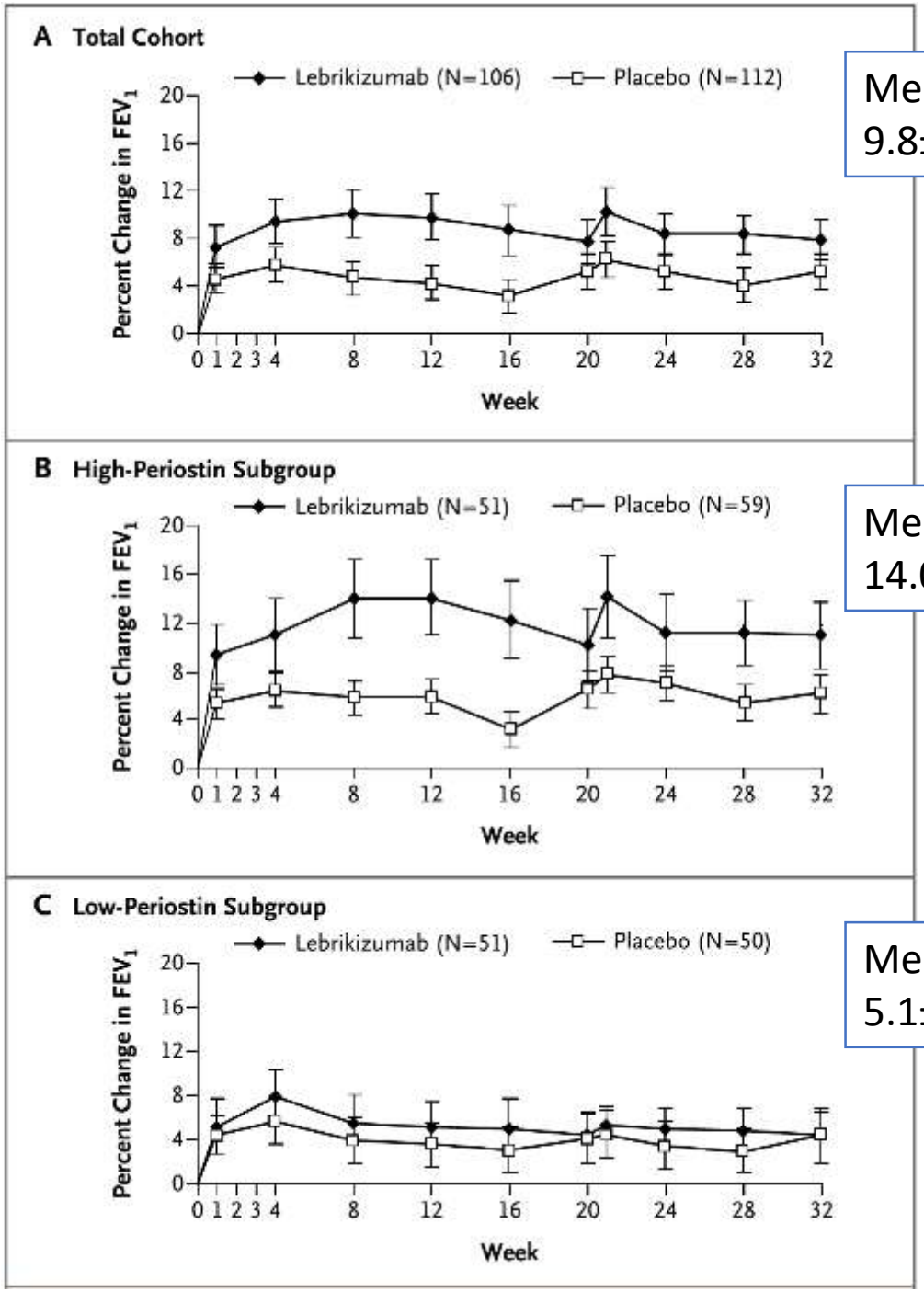
N Engl J Med 2013;368:2455-66

Lebrikizumab Treatment in Adults with Asthma

Jonathan Corren, M.D., Robert F. Lemanske, Jr., M.D., Nicola A. Hanania, M.D., Phillip E. Korenblat, M.D., Merdad V. Parsey, M.D., Ph.D., Joseph R. Arron, M.D., Ph.D., Jeffrey M. Harris, M.D., Ph.D., Heleen Scheerens, Ph.D., Lawren C. Wu, Ph.D., Zheng Su, Ph.D., Sofia Mosesova, Ph.D., Mark D. Eisner, M.D., M.P.H., Sean P. Bohen, M.D., Ph.D., and John G. Matthews, M.B., B.S., Ph.D.

- Lebrikizumab is a monoclonal antibody to interleukin-13
- Randomized, double-blind, placebo-controlled study of 219 adults who had asthma that was **inadequately controlled despite inhaled glucocorticoid therapy for 6M**
- Lebrikizumab 250 mg SC or placebo was given once a month for a total of 6 months
- Background Rx with ICS, LABA, LTRA unchanged

N Engl J Med 2011;365:1088-98



Mean change in FEV1 at 12 wks, 9.8±1.9% vs. 4.3±1.5%; P = 0.02

Mean change in FEV1 at 12 wks, 14.0±3.1% vs. 5.8±2.1%; P = 0.03

Mean change in FEV1 at 12wks, 5.1±2.4% vs. 3.5±2.1%; P = 0.61

IL-13 induces bronchial epithelial cells to secrete **periostin**, a matricellular protein which has a role in airway remodeling in asthma

N Engl J Med 2011;365:1088-98

Asthma: Anti-TNF

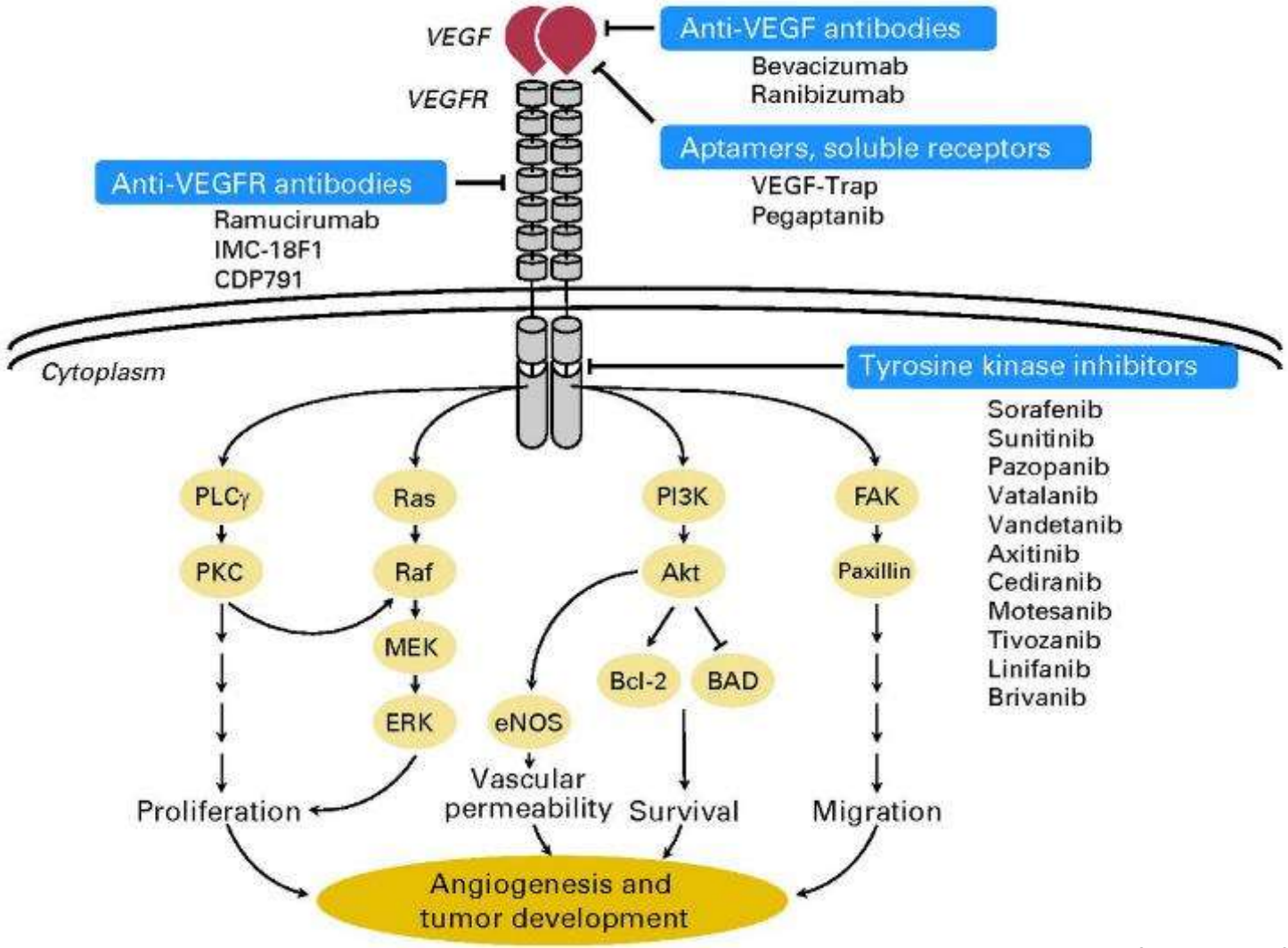
TNF antagonists

- Early studies in asthma involving selected patients with elevated TNF-α levels in BAL fluid or an increased expression of membrane-bound TNF-α demonstrated an improvement in asthma control and airway hyper-responsiveness.
- However, larger clinical trials involving patients with severe refractory asthma, but not elevated TNF-α levels in the airways, did not confirm these benefits and, in one study, was associated with an increased number of adverse effects including malignancy.

Thorax 2005;60:1012-18
N Engl J Med 2006;354:697-708
Am J Respir Crit Care Med 2009;179:549-58
Eur Respir J 2011;37:1352-59

Ca lung

Anti-VEGF



J Clin Oncol. 2012 Apr 1;30(10):1137-9

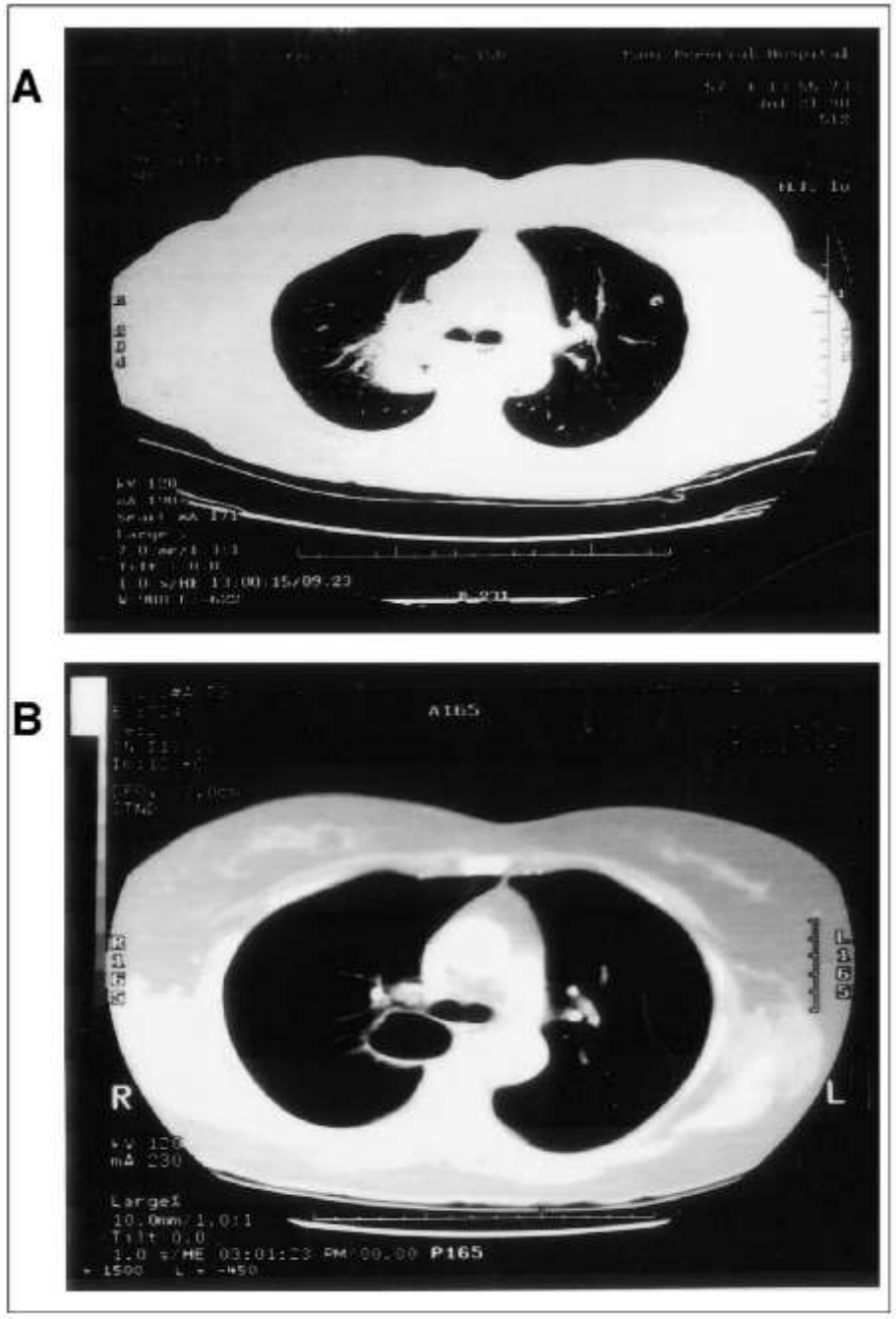


Fig 3. Area of tumor necrosis and cavitation following three cycles of treatment. (A) Tumor before treatment; (B) necrosis and cavitation.

Bevacizumab

- In the initial phase II trial comparing chemotherapy with or without bevacizumab, 6 patients developed life-threatening bleeding (4 fatal)
- Squamous 4/13; Adeno 2/54
- All patients had centrally located tumors in close proximity to major blood vessels; five patients had/developed cavitation or necrosis
- Subsequent trials evaluating the role of bevacizumab excluded patients with squamous histology

J Clin Oncol. 2012 Apr 1;30(10):1137-9
J Clin Oncol. 2004 Jun 1;22(11):2184-91

Annals of Oncology 24: 20–30, 2013
doi:10.1093/annonc/mds590
Published online 23 November 2012

Systematic review and meta-analysis of randomised, phase II/III trials adding bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer

J.-C. Soria[1], A. Mauguen[2], M. Reck[3], A. B. Sandler[4], N. Saijo[5], D. H. Johnson[6], D. Burcoveanu[2], M. Fukuoka[5], B. Besse[1], J.-P. Pignon[2] & on behalf of the meta-analysis of bevacizumab in advanced NSCLC collaborative group

[1]Department of Medicine, Institut Gustave Roussy, INSERM unit 981 and Paris University XI, Villejuif; [2]Meta-analysis Unit, Institut Gustave-Roussy, Villejuif, France; [3]Department of Thoracic Oncology, Hospital Grosshansdorf, Grosshansdorf, Germany; [4]Division of Hematology/Oncology, Department of Medicine, Oregon Health & Science University, Portland, USA; [5]Department of Medical Oncology, Kinki University Faculty of Medicine, Osaka, Japan; [6]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, USA

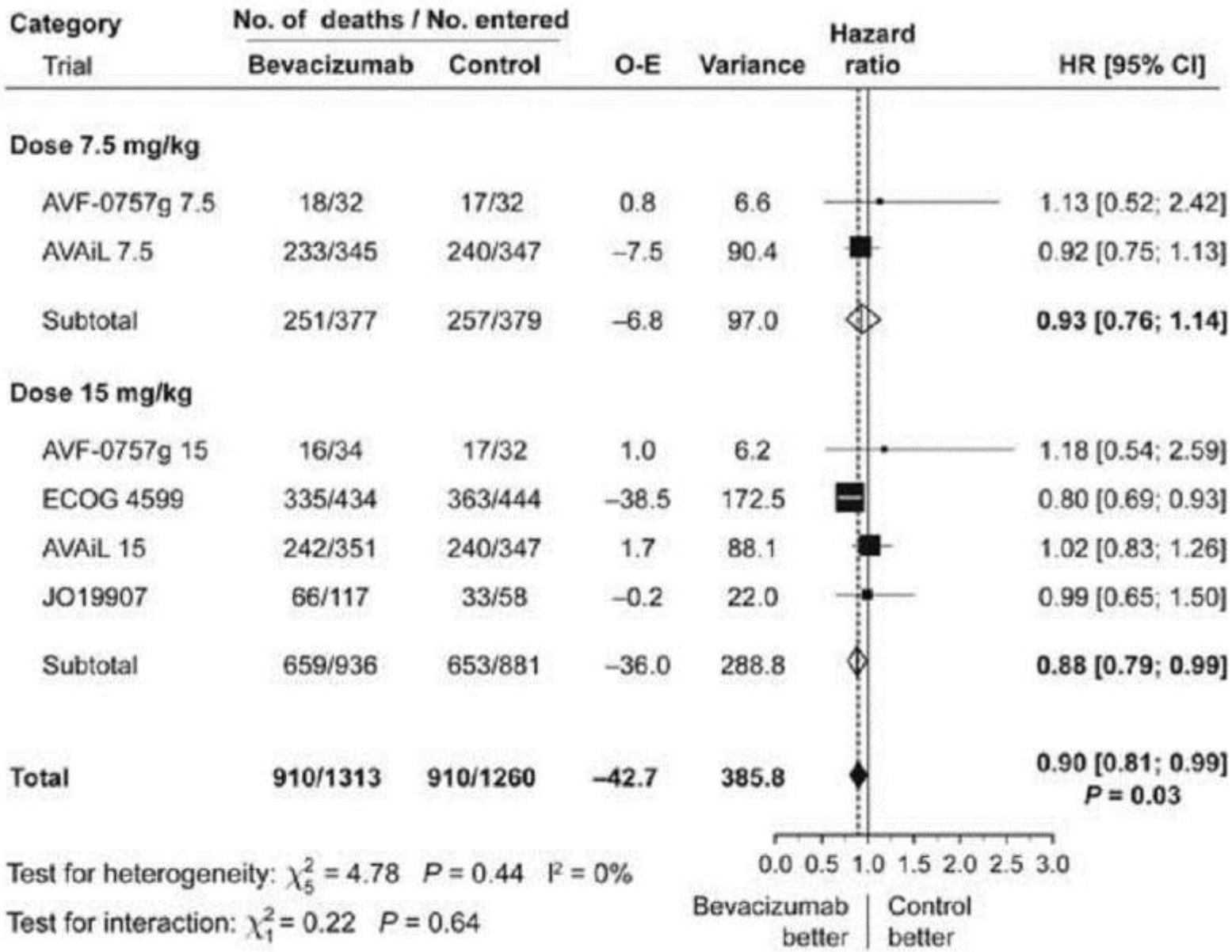
- Fourteen trials were screened for eligibility.
- Data of 2194 patients (1313 bevacizumab; 881 controls) from four phase II and III trials: AVF-0757g, JO19907, ECOG 4599 and AVAiL, were analysed.

Trial	Period of inclusion	Design, main inclusion/exclusion criteria, primary end point	Random-isation	Treatment arms[a]	*N* analysed /randomly assigned patients
AVF-0757g [24]	May 1998–Sep 1999	Design: open-label, parallel-group, multicentre, blinded assessment phase II Inclusion critera: histologically confirmed stage IIIB (with pleural effusion), stage IV or recurrent NSCLC; ECOG PS ≤2; life expectancy ≥3 months; no previous chemotherapy, biological therapy or radiotherapy. Exclusions included: CNS metastasis, therapeutic anticoagulation, uncontrolled hypertension Primary end point: PFS Tumour assessment: every three cycles (i.e. 9 weeks) for the first six cycles and every four cycles (12 weeks) thereafter	1:1:1	Bevacizumab 7.5 mg/kg + carboplatin + paclitaxel Bevacizumab 15 mg/kg + carboplatin + paclitaxel Carboplatin + paclitaxel	32/32 34/35 32/32
ECOG 4599 [21]	Jul 2001–Dec 2005	Design: open-label, parallel-group, multicentre, phase III Inclusion criteria: histologically or cytologically confirmed, predominantly non-squamous stage IIIB (with pleural effusion), stage IV or recurrent NSCLC; ECOG PS 0–1; no previous chemotherapy. Exclusions included: haemoptysis (≥2.5 ml per episode), tumours invading or abutting major blood vessels, CNS metastasis, therapeutic anticoagulation, uncontrolled hypertension Primary end point: OS Tumour assessment: every two cycles (i.e. every 6 weeks) for 24 weeks and then every three cycles thereafter	1:1	Bevacizumab 15 mg/kg + carboplatin + paclitaxel Carboplatin + paclitaxel	434/434 444/444
AVAiL [22]	Feb 2005–Aug 2006	Design: double-blind, parallel-group, multicentre, international, phase III Inclusion criteria: histologically or cytologically confirmed, stage IIIB (with supraventricular lymph node metastasis, or malignant pleural or pericardial effusion), stage IV or recurrent non-squamous NSCLC; ECOG PS 0–1; no previous chemotherapy. Exclusions included: haemoptysis (≥2·5 ml per episode), CNS metastasis, therapeutic anticoagulation, uncontrolled hypertension Primary end point: PFS Tumour assessment: every three cycles	1:1:1	Bevacizumab 7.5 mg/kg + cisplatin + gemcitabine Bevacizumab 15 mg/kg + cisplatin + gemcitabine Cisplatin + gemcitabine + placebo (low or high dose)	345/345 351/351 347/347
JO19907 [31]	Apr 2007– Mar 2008	Design: open-label, parallel-group, multicentre, phase II Inclusion criteria: previously untreated stage IIIB (with pleural and/or pericardial effusion and/or pleural dissemination), IV or recurrent non-squamous NSCLC; ECOG PS 0–1. Exclusions included haemoptysis and CNS metastasis, uncontrolled hypertension Primary end point: PFS Tumour assessment: every 6 weeks for the first 18 weeks and every 9 weeks thereafter	2[b]:1	Bevacizumab 15 mg/kg + carboplatin + paclitaxel Carboplatin + paclitaxel	117/121 58/59

[a]Doses: carboplatin, dosed to a target area under the curve of 6 mg/ml/min; paclitaxel, 200 mg/m^2; cisplatin, 80 mg/m^2; gemcitabine, 1250 mg/m^2. In all trials, treatment was administered in 3-week cycles for up to six cycles, or until disease progression or unacceptable toxicity. Patients who completed six cycles of bevacizumab-containing therapy in ECOG 4599, AVAiL and JO19907 then received bevacizumab monotherapy until disease progression or unacceptable toxicity. In AVF-0757g, non-progressing patients randomly assigned to bevacizumab could receive up to 18 doses of bevacizumab following the initial six cycles. Patients in the control arms were permitted to receive bevacizumab (15 mg/kg) on disease progression.

[b]Experimental arm.

Annals of Oncology 24: 20–30, 2013



Overall survival

Annals of Oncology 24: 20–30, 2013

Randomized Phase III Trial of Maintenance Bevacizumab With or Without Pemetrexed After First-Line Induction With Bevacizumab, Cisplatin, and Pemetrexed in Advanced Nonsquamous Non–Small-Cell Lung Cancer: AVAPERL (MO22089)

90% adeno

Fabrice Barlesi, Arnaud Scherpereel, Achim Rittmeyer, Antonio Pazzola, Neus Ferrer Tur, Joo-Hang Kim, Myung-Ju Ahn, Joachim G.J.V. Aerts, Vera Gorbunova, Anders Vikström, Elaine K. Wong, Pablo Perez-Moreno, Lada Mitchell, and Harry J.M. Groen

PFS was significantly improved in the bevacizumab plus pemetrexed arm (median, 3.7 v 7.4 months; HR, 0.48; 95% CI, 0.35 to 0.66; P < .001)
Median OS was 12.8 months (0 to 16 months) in the bevacizumab arm and was not yet reached (0.1 to 16.2 months) in the bevacizumab plus pemetrexed arm

J Clin Oncol 31:3004-3011

PointBreak: A Randomized Phase III Study of Pemetrexed Plus Carboplatin and Bevacizumab Followed by Maintenance Pemetrexed and Bevacizumab Versus Paclitaxel Plus Carboplatin and Bevacizumab Followed by Maintenance Bevacizumab in Patients With Stage IIIB or IV Nonsquamous Non–Small-Cell Lung Cancer

80% adeno

Jyoti D. Patel, Mark A. Socinski, Edward B. Garon, Craig H. Reynolds, David R. Spigel, Mark R. Olsen, Robert C. Hermann, Robert M. Jotte, Thaddeus Beck, Donald A. Richards, Susan C. Guba, Jingyi Liu, Bente Frimodt-Moller, William J. John, Coleman K. Obasaju, Eduardo J. Pennella, Philip Bonomi, and Ramaswamy Govindan

For PemCBev versus PacCBev, HR for OS was 1.00 (median OS, 12.6 v 13.4 months; P = 0.949); HR for PFS was 0.83 (median PFS, 6.0 v 5.6 months; P = 0.012)

J Clin Oncol 31:4349-4357

No trial comparing bevacizumab with pemetrexed based regimens available

Phase III Study Comparing Cisplatin Plus Gemcitabine With Cisplatin Plus Pemetrexed in Chemotherapy-Naive Patients With Advanced-Stage Non–Small-Cell Lung Cancer

Giorgio Vittorio Scagliotti, Purvish Parikh, Joachim von Pawel, Bonne Biesma, Johan Vansteenkiste, Christian Manegold, Piotr Serwatowski, Ulrich Gatzemeier, Raghunadharao Digumarti, Mauro Zukin, Jin S. Lee, Anders Mellemgaard, Keunchil Park, Shehkar Patil, Janusz Rolski, Tuncay Goksel, Filippo de Marinis, Lorinda Simms, Katherine P. Sugarman, and David Gandara

Overall survival was statistically superior for cisplatin/pemetrexed versus cisplatin/gemcitabine in patients with adenocarcinoma (n = 847; 12.6 v 10.9 months)

PARAMOUNT: Final Overall Survival Results of the Phase III Study of Maintenance Pemetrexed Versus Placebo Immediately After Induction Treatment With Pemetrexed Plus Cisplatin for Advanced Nonsquamous Non–Small-Cell Lung Cancer

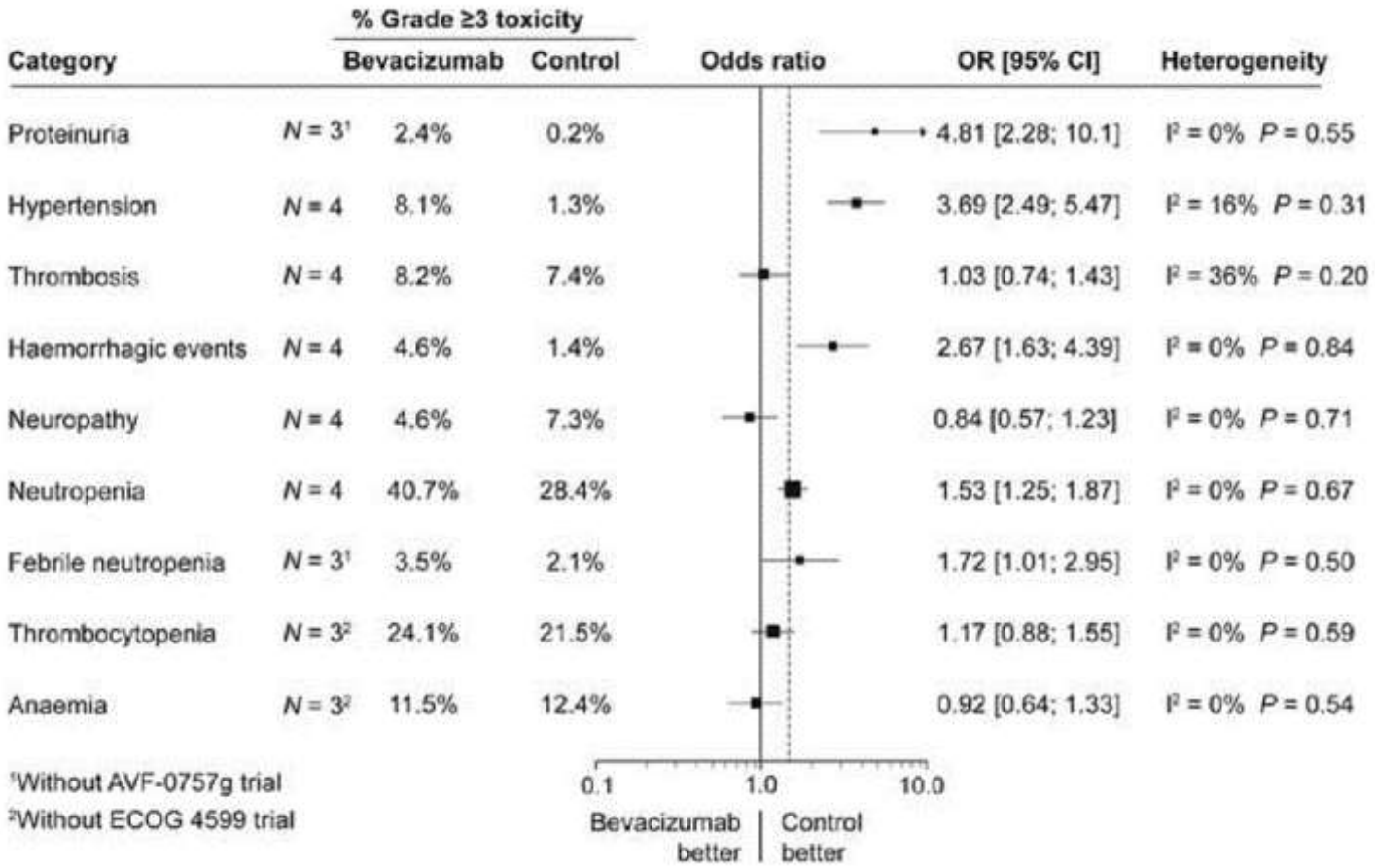
85% adeno

Luis G. Paz-Ares, Filippo de Marinis, Mircea Dediu, Michael Thomas, Jean-Louis Pujol, Paolo Bidoli, Olivier Molinier, Tarini Prasad Sahoo, Eckart Laack, Martin Reck, Jesús Corral, Symantha Melemed, William John, Nadia Chouaki, Annamaria H. Zimmermann, Carla Visseren-Grul, and Cesare Gridelli

Pemetrexed therapy resulted in a significant reduction in the risk of death (HR, 0.78; 95% CI, 0.64 to 0.96; P = 0.0195; median OS: 13.9 vs 11.0 months)

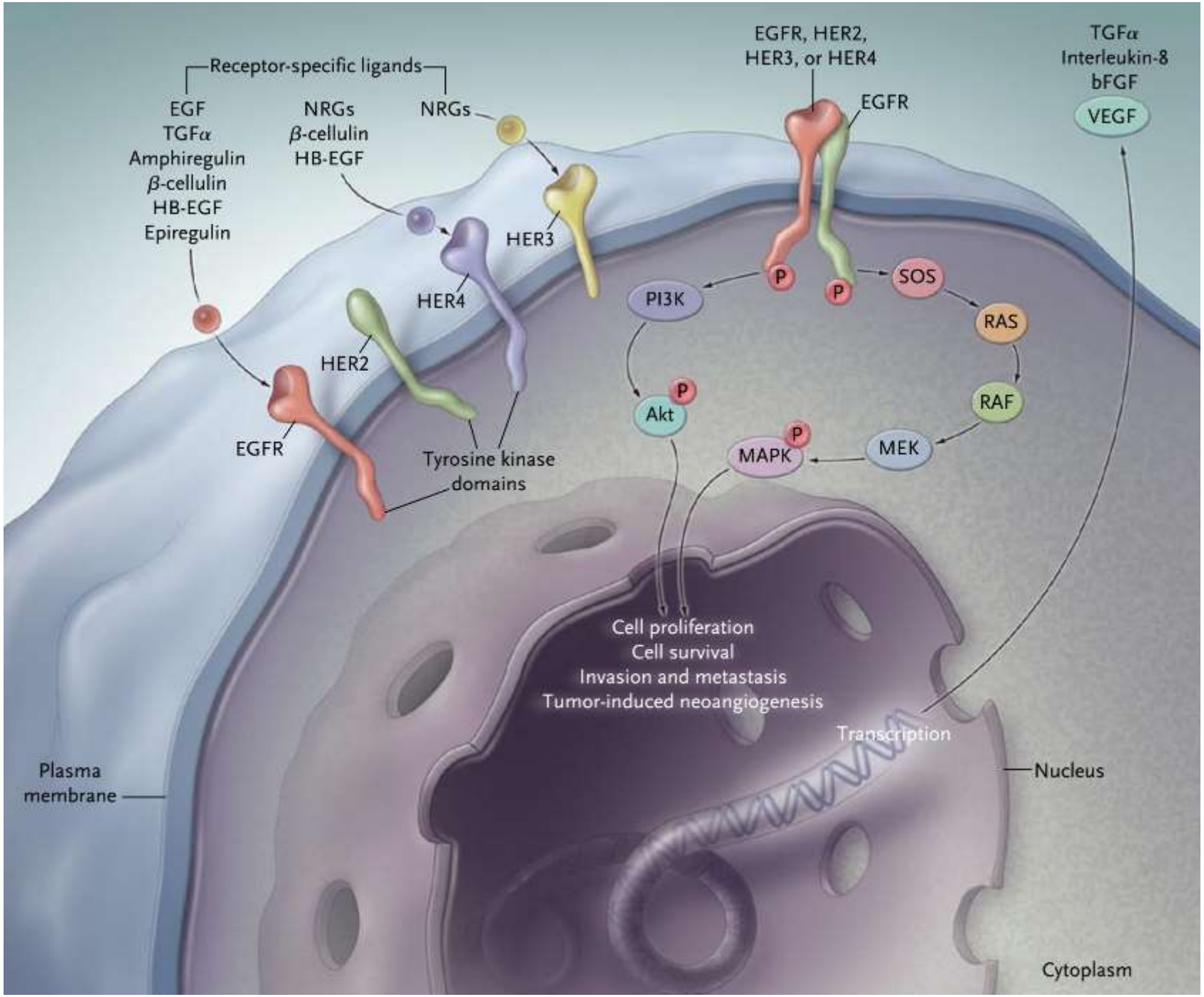
- No trial comparing bevacizumab with pemetrexed based regimens available.
- However, OS with Pemetrexed-Bevacizumab-platinum triplet appears to be similar to pemetrexed-platinum doublet with/without pemetrexed maintenance (approximately 13 months).
- Extra benefit of adding bevacizumab to pemetrexed-based regimen is unclear.

Bevacizumab: Adverse events



Bevacizumab significantly increased the risk of grade ≥3 proteinuria, hypertension, haemorrhagic events, neutropenia and febrile neutropenia

Annals of Oncology 24: 20–30, 2013



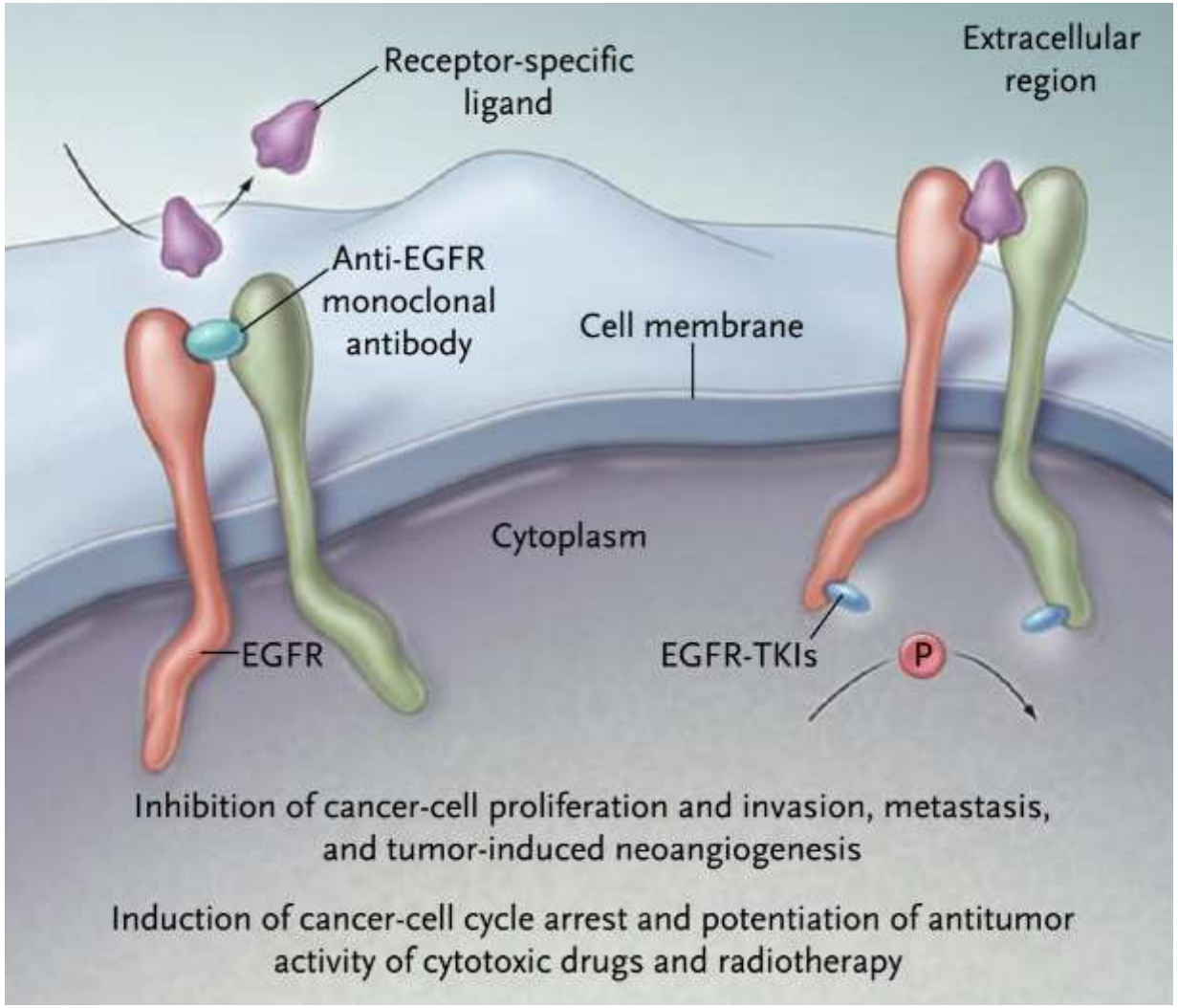
EGFR

- EGFR is a transmembrane receptor belonging to a family of four related proteins which includes:
  - HER1 (EGFR/erbB1)
  - HER2 (neu, erbB2)
  - HER3 (erbB3)
  - HER4 (erbB4)

- After a ligand binds to a single-chain EGFR, the receptor forms a dimer that signals within the cell by activating receptor autophosphorylation through tyrosine kinase activity

N Engl J Med 2008;358:1160-74

Anti-EGFR therapy



- **Anti-EGFR monoclonal antibodies** bind to the extracellular domain of EGFR and block ligand binding and receptor activation
- **Small-molecule EGFR tyrosine kinase inhibitors (TKIs)** compete with ATP to bind to the intracellular EGFR tyrosine kinase catalytic domain and thus block EGFR autophosphorylation and downstream signaling

N Engl J Med 2008;358:1160-74

Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial

*Robert Pirker, Jose R Pereira, Aleksandra Szczesna, Joachim von Pawel, Maciej Krzakowski, Rodryg Ramlau, Ihor Vynnychenko, Keunchil Park, Chih-Teng Yu, Valentyn Ganul, Jae-Kyung Roh, Emilio Bajetta, Kenneth O'Byrne, Filippo de Marinis, Wilfried Eberhardt, Thomas Goddemeier, Michael Emig, Ulrich Gatzemeier on behalf of the FLEX Study Team**

- Chemotherapy-naive patients with advanced **EGFR-expressing** advanced stage wet IIIB or stage IV NSCLC were randomly assigned in a 1:1 ratio to chemotherapy plus cetuximab or just chemotherapy **(Chemotherapy = Cisplatin + vinorelbine)**
- 1125 patients were randomly assigned to chemotherapy plus cetuximab (n=557) or chemotherapy alone (n=568)
- Patients given chemotherapy plus cetuximab survived longer than those in the chemotherapy-alone group (median 11·3 months vs 10·1 months; hazard ratio for death 0·871 [95% CI 0·762—0·996]; p=0·044).
- The main cetuximab-related adverse event was **acne-like rash** (57 [10%] of 548, grade 3)

Lancet 2009; 373: 1525–31

EGFR expression as a predictor of survival for first-line chemotherapy plus cetuximab in patients with advanced non-small-cell lung cancer: analysis of data from the phase 3 FLEX study

Robert Pirker, Jose R Pereira, Joachim von Pawel, Maciej Krzakowski, Rodryg Ramlau, Keunchil Park, Filippo de Marinis, Wilfried E E Eberhardt, Luis Paz-Ares, Stephan Störkel, Karl-Maria Schumacher, Anja von Heydebreck, Ilhan Celik, Kenneth J O'Byrne

- Tumour EGFR expression data was used to generate an **immunohistochemistry score** for FLEX study patients on a continuous scale of 0—300 (using 4 levels of staining intensity and fraction of cells staining at each intensity)
- **For patients in the high EGFR expression group (score >200), overall survival was longer** in the chemotherapy plus cetuximab group than in the chemotherapy alone group (median 12·0 months [95% CI 10·2—15·2] vs 9·6 months [7·6—10·6]; HR 0·73, 0·58—0·93; p=0·011), with no meaningful increase in side-effects

Lancet Oncol 2012; 13: 33–42

Cetuximab and First-Line Taxane/Carboplatin Chemotherapy in Advanced Non–Small-Cell Lung Cancer: Results of the Randomized Multicenter Phase III Trial BMS099

Thomas J. Lynch, Taral Patel, Luke Dreisbach, Michael McCleod, William J. Heim, Robert C. Hermann, Eugene Paschold, Nicholas O. Iannotti, Shaker Dakhil, Steven Gorton, Virginie Pautret, Martin R. Weber, and Donald Woytowitz

- 676 chemotherapy-naïve patients with stage IIIB (pleural effusion) or IV NSCLC, **without restrictions by histology or EGFR expression**
- Adeno 50%
- Median PFS was 4.40 months with cetuximab/TC versus 4.24 months with TC (P = 0.236)
- Median OS was 9.69 months with cetuximab/TC versus 8.38 months with TC (P = 0.169)

J Clin Oncol 28:911-917

Docetaxel or pemetrexed with or without cetuximab in recurrent or progressive non-small-cell lung cancer after platinum-based therapy: a phase 3, open-label, randomised trial

Edward S Kim, Marcus Neubauer, Allen Cohn, Lee Schwartzberg, Lawrence Garbo, John Caton, Francisco Robert, Craig Reynolds, Terry Katz, Sreeni Chittoor, Lorinda Simms, Scott Saxman

- 605 received pemetrexed (301 with cetuximab and 304 alone) and 333 received docetaxel (167 with cetuximab and 166 alone) [Adeno ≈ 50%]
- Primary analysis was changed to compare PFS with cetuximab plus pemetrexed versus pemetrexed due to change in standard of care
- Median PFS with cetuximab plus pemetrexed was 2·9 months vs 2·8 months with pemetrexed (p=0·76)
- **EGFR expression in tumour tissue was not required for study eligibility**; however, tissue was collected and analysed for EGFR expression by immunohistochemistry
- Prespecified efficacy **subgroup analyses by EGFR and histology were not different** to the overall findings

Lancet Oncol 2013; 14: 1326–36

Pulmonary Vasculitis

RAVE trial

Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

John H. Stone, M.D., M.P.H., Peter A. Merkel, M.D., M.P.H., Robert Spiera, M.D., Philip Seo, M.D., M.H.S., Carol A. Langford, M.D., M.H.S., Gary S. Hoffman, M.D., Cees G.M. Kallenberg, M.D., Ph.D., E. William St. Clair, M.D., Anthony Turkiewicz, M.D., Nadia K. Tchao, M.D., Lisa Webber, R.N., Linna Ding, M.D., Ph.D., Lourdes P. Sejismundo, R.N., B.S.N., Kathleen Mieras, C.C.R.P., David Weitzenkamp, Ph.D., David Ikle, Ph.D., Vicki Seyfert-Margolis, Ph.D., Mark Mueller, B.S., C.C.R.P., Paul Brunetta, M.D., Nancy B. Allen, M.D., Fernando C. Fervenza, M.D., Ph.D., Duvuru Geetha, M.D., Karina A. Keogh, M.D., Eugene Y. Kissin, M.D., Paul A. Monach, M.D., Ph.D., Tobias Peikert, M.D., Coen Stegeman, M.D., Ph.D., Steven R. Ytterberg, M.D., and Ulrich Specks, M.D., for the RAVE–ITN Research Group*

Initial results (6M)

Efficacy of Remission-Induction Regimens for ANCA-Associated Vasculitis

Ulrich Specks, M.D., Peter A. Merkel, M.D., M.P.H., Philip Seo, M.D., Robert Spiera, M.D., Carol A. Langford, M.D., M.H.S., Gary S. Hoffman, M.D., Cees G.M. Kallenberg, M.D., Ph.D., E. William St. Clair, M.D., Barri J. Fessler, M.D., Linna Ding, M.D., Ph.D., Lisa Viviano, R.N., Nadia K. Tchao, M.D., Deborah J. Phippard, Ph.D., Adam L. Asare, Ph.D., Noha Lim, Ph.D., David Ikle, Ph.D., Brett Jepson, M.S., Paul Brunetta, M.D., Nancy B. Allen, M.D., Fernando C. Fervenza, M.D., Ph.D., Duvuru Geetha, M.D., Karina Keogh, M.B., B.Ch., Eugene Y. Kissin, M.D., Paul A. Monach, M.D., Ph.D., Tobias Peikert, M.D., Coen Stegeman, M.D., Ph.D., Steven R. Ytterberg, M.D., Mark Mueller, B.S., C.C.R.P., Lourdes P. Sejismundo, R.N., Kathleen Mieras, C.C.R.P., and John H. Stone, M.D., M.P.H., for the RAVE-ITN Research Group*

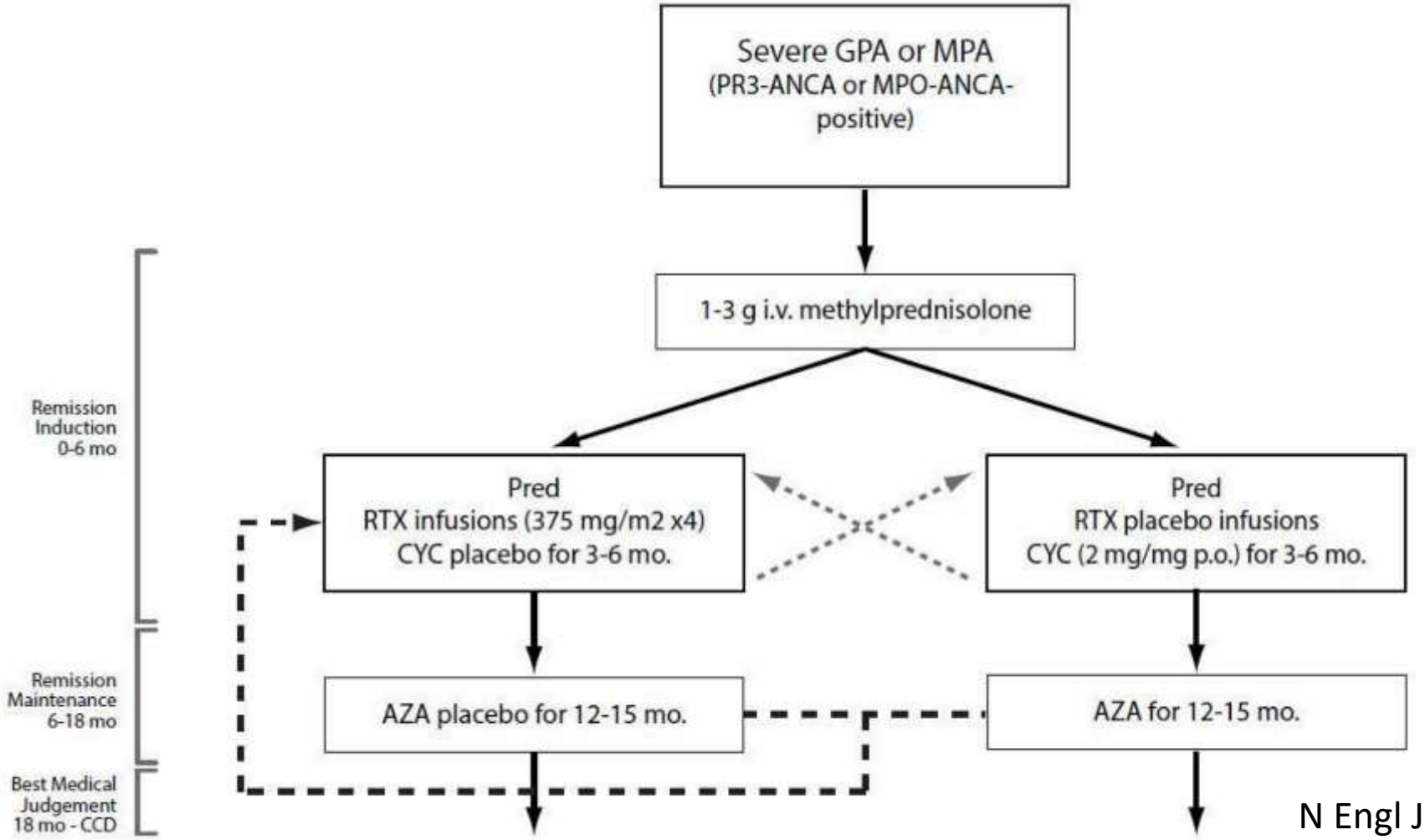
Long-term follow-up results (18M)

N Engl J Med 2010;363:221-32
N Engl J Med 2013;369:417-27

RAVE: Methodology

- Multicenter, randomized, double-blind, double-dummy, noninferiority trial of rituximab
- 197 patients with ANCA-associated vasculitis were enrolled (99 were assigned to the rituximab group, and 98 patients to the control group)
- 48 patients (24%) had microscopic polyangiitis, and 148 (75%) had Wegener's granulomatosis, 1 indeterminate.
- Approximately 49% of patients in both groups had a new diagnosis.
- Approximately 54% had pulmonary involvement and 66% had renal involvement at baseline.

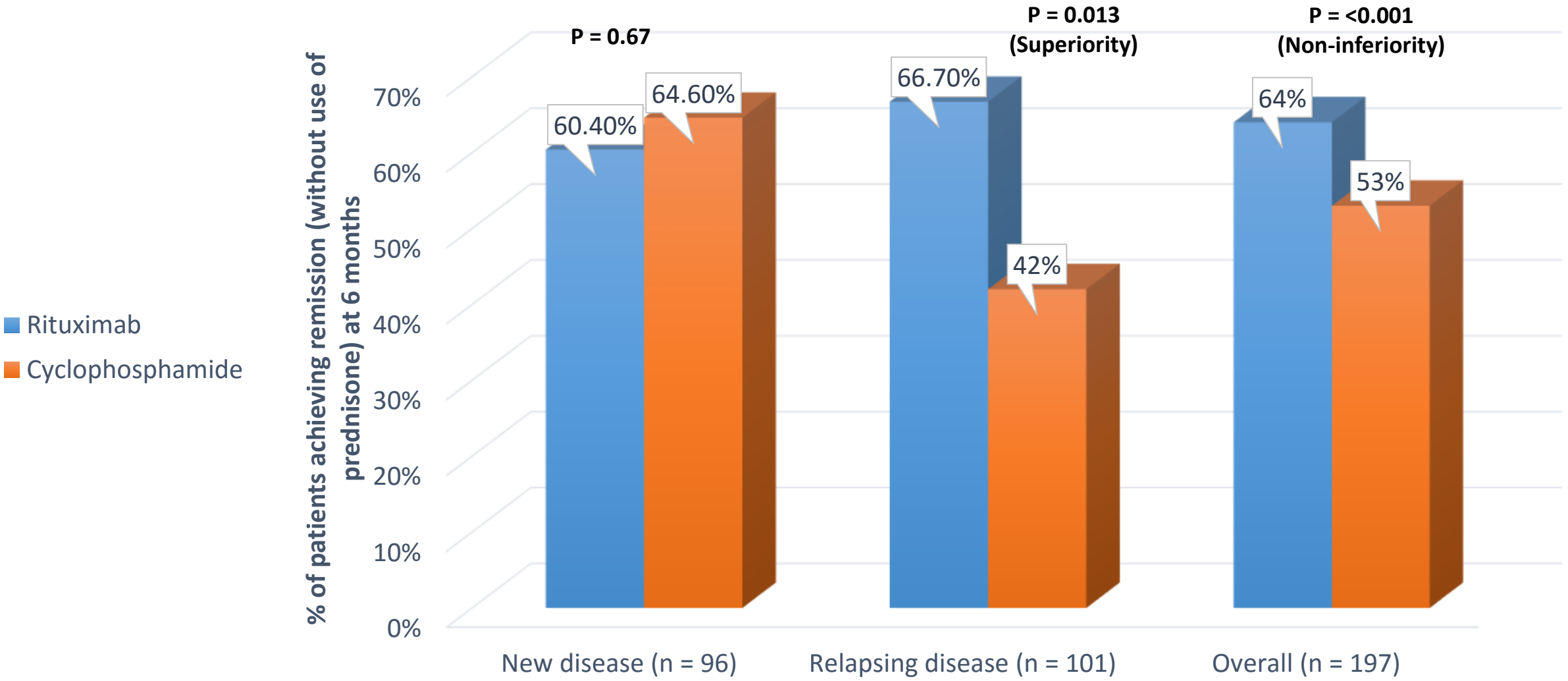
N Engl J Med 2010;363:221-32
N Engl J Med 2013;369:417-27



N Engl J Med 2013;369:417-27

- Patients who experienced a limited disease relapse were treated with an increased dose of prednisone. These patients remained in the originally assigned treatment group unless their disease progressed to a severe relapse.
- Patients who experienced a severe flare between 1-6M were eligible for blinded cross-over to the opposite Rx arm.
- Patients who experienced a severe flare between 6-18M were eligible for Rx with rituximab remission induction regimen (open-label)
- Patients who completed 18M were subsequently treated according to best medical judgment and followed for safety until the common close-out date (CCD). The CCD was the date the last enrolled patient completed 18 months of study therapy.

RAVE: Primary end point (at 6 months)



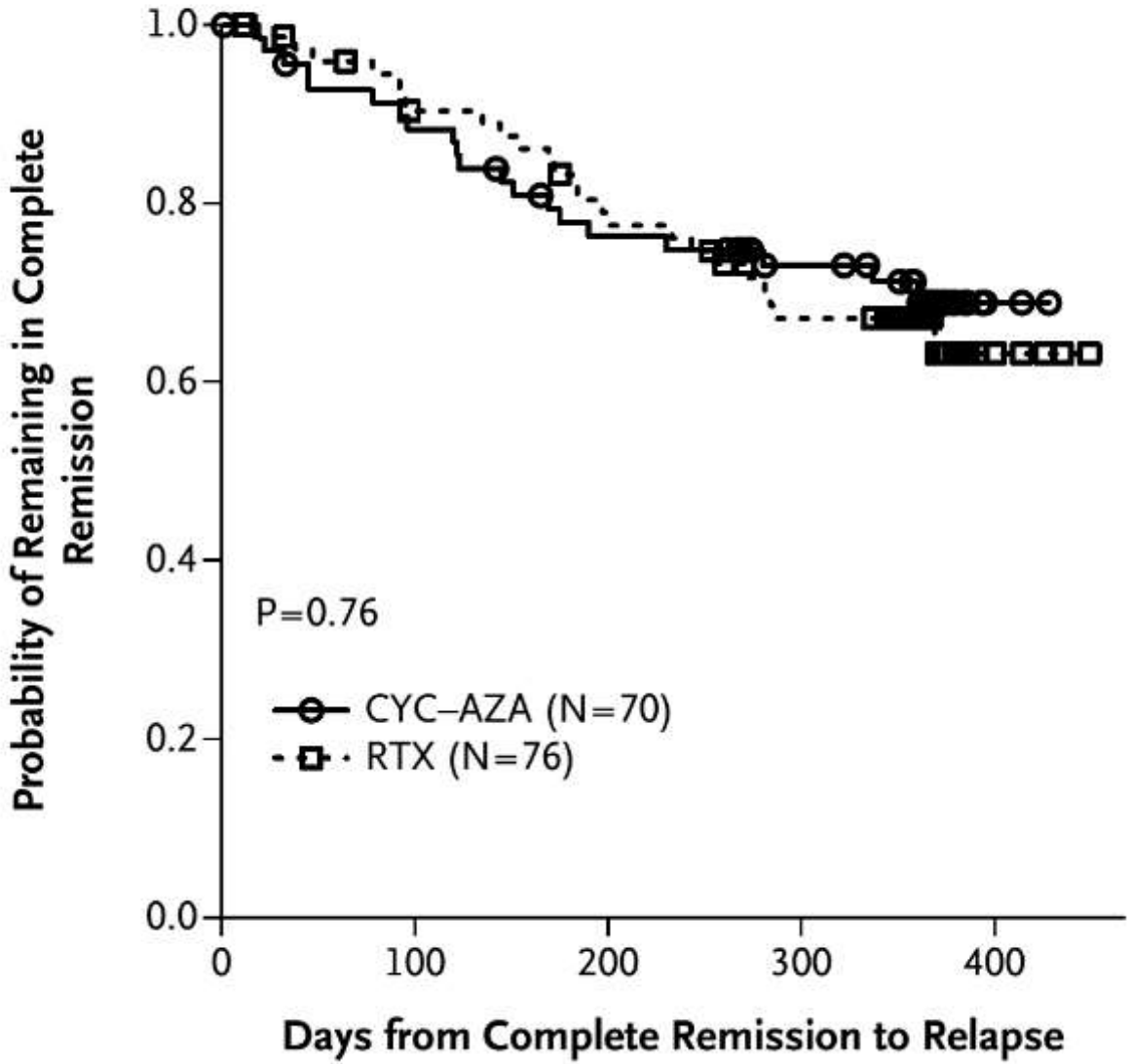
N Engl J Med 2010;363:221-32

Efficacy Measure	Rituximab (N=99)	Cyclophosphamide–Azathioprine (N=98)	Difference	P Value
	number (percent)		*percentage points (95% CI)*	
Complete remission				
6 mo	63 (64)	52 (53)	11 (–3 to 24)	0.13
12 mo	47 (47)	38 (39)	9 (–5 to 22)	0.22
18 mo	39 (39)	32 (33)	7 (–7 to 20)	0.32
Remission and <10 mg/day of prednisone				
6 mo	70 (71)	60 (61)	10 (–4 to 23)	0.16
12 mo	59 (60)	60 (61)	–2 (–15 to 12)	0.82
18 mo	54 (55)	52 (53)	2 (–12 to 15)	0.84
Complete remission at any time†	76 (77)	70 (71)		0.15
Remission and <10 mg/day of prednisone at any time‡	82 (83)	84 (86)		0.91
Remission at any time‡	89 (90)	89 (91)		0.50
Complete remission in patients with relapsing disease at baseline†				
6 mo	34/51 (67)	21/50 (42)	25 (6 to 44)	0.01
12 mo	25/51 (49)	12/50 (24)	25 (7 to 43)	0.009
18 mo	19/51 (37)	10/50 (20)	17 (0 to 34)	0.06
	milliliters per minute			

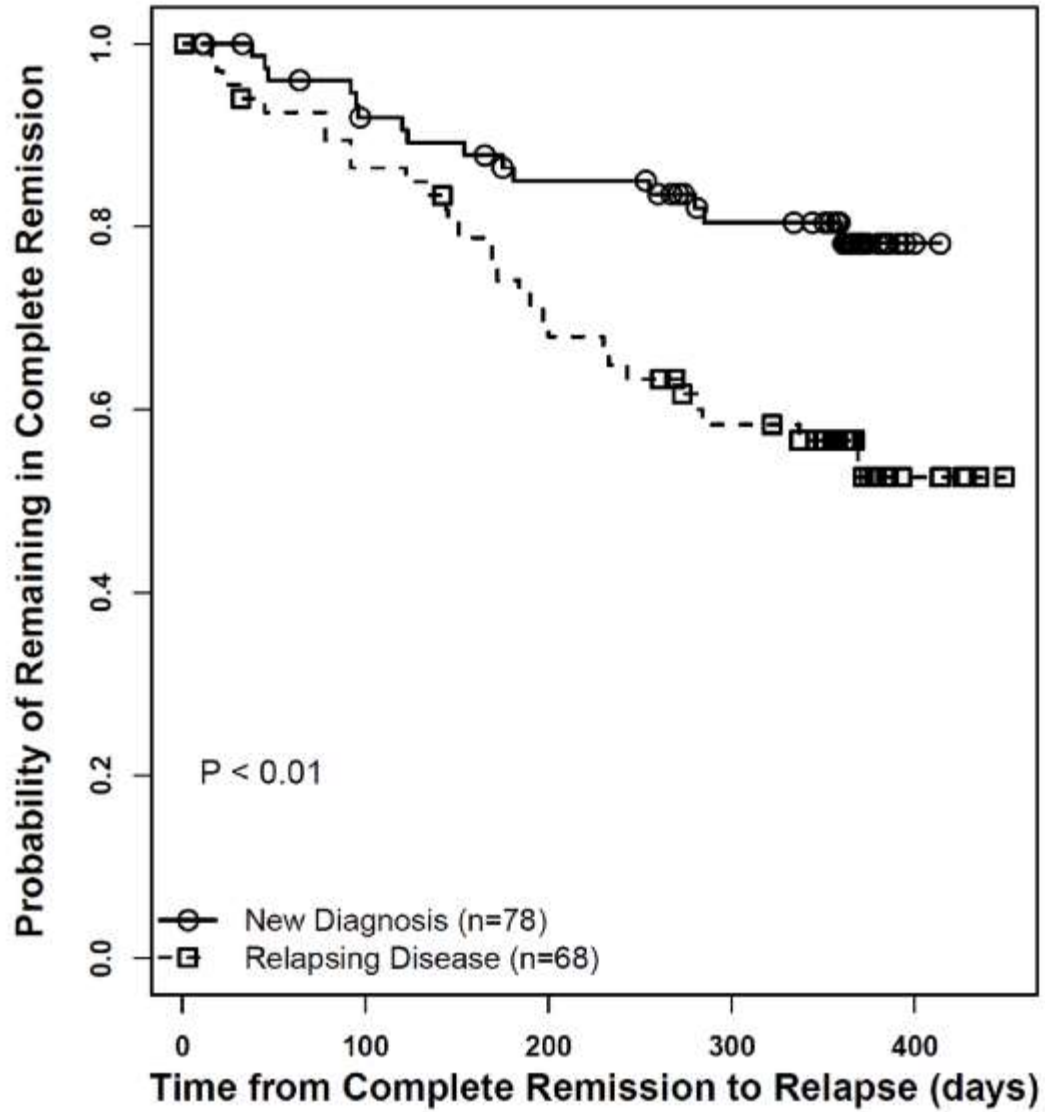
18M follow-up

N Engl J Med 2013;369:417-27

Time to First Relapse after Complete Remission, According to Treatment

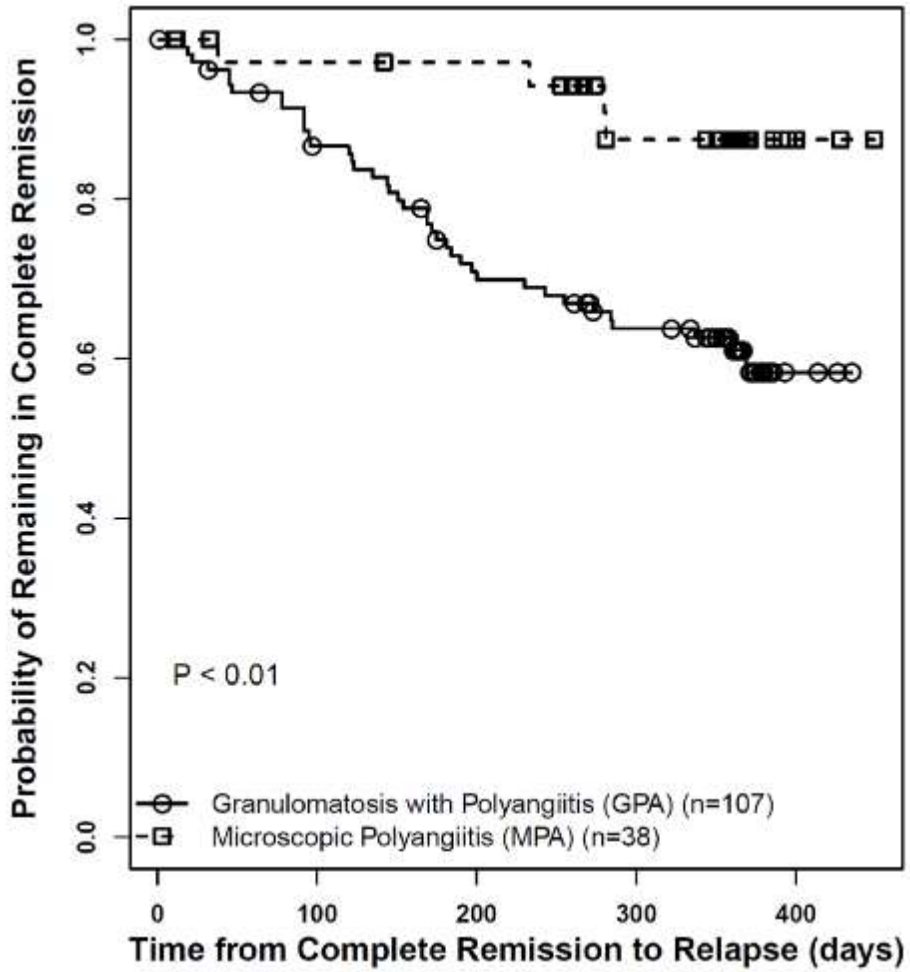


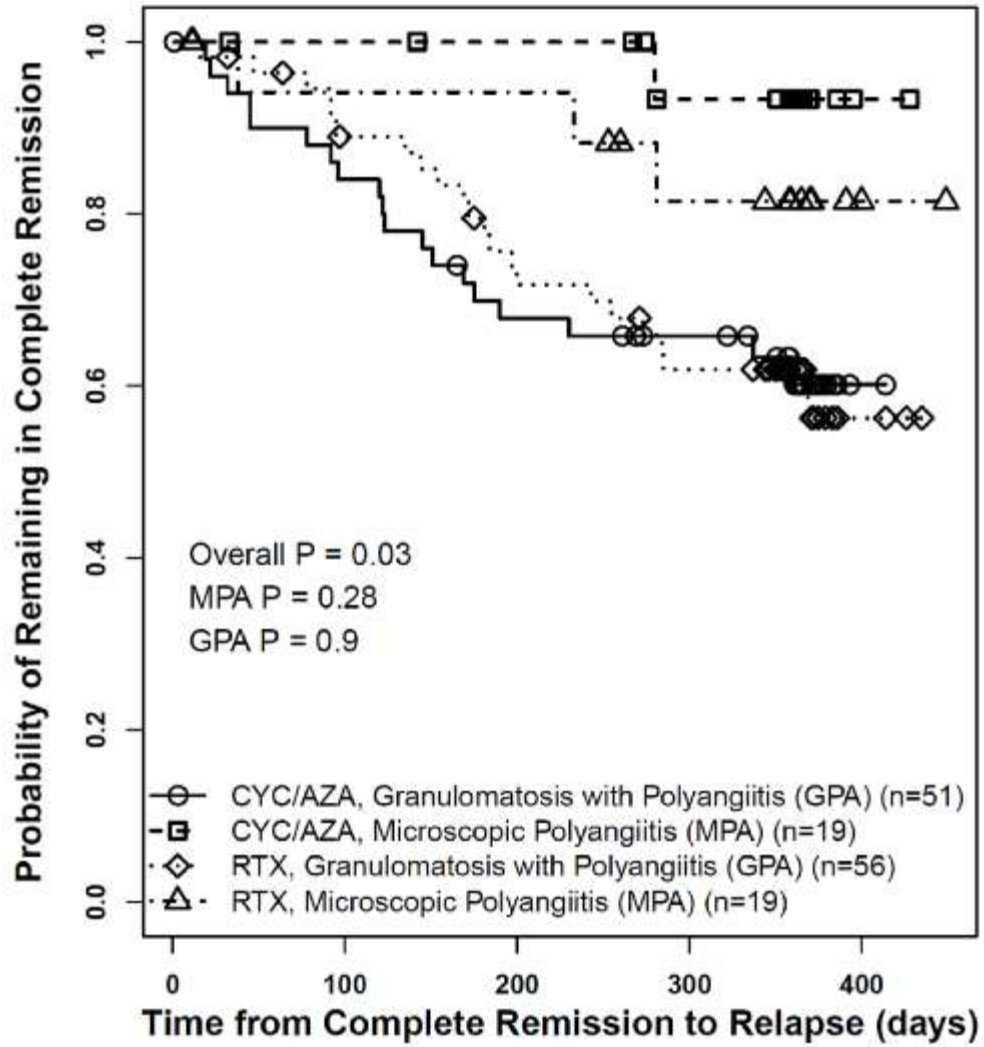
N Engl J Med 2013;369:417-27



N Engl J Med 2013;369:417-27

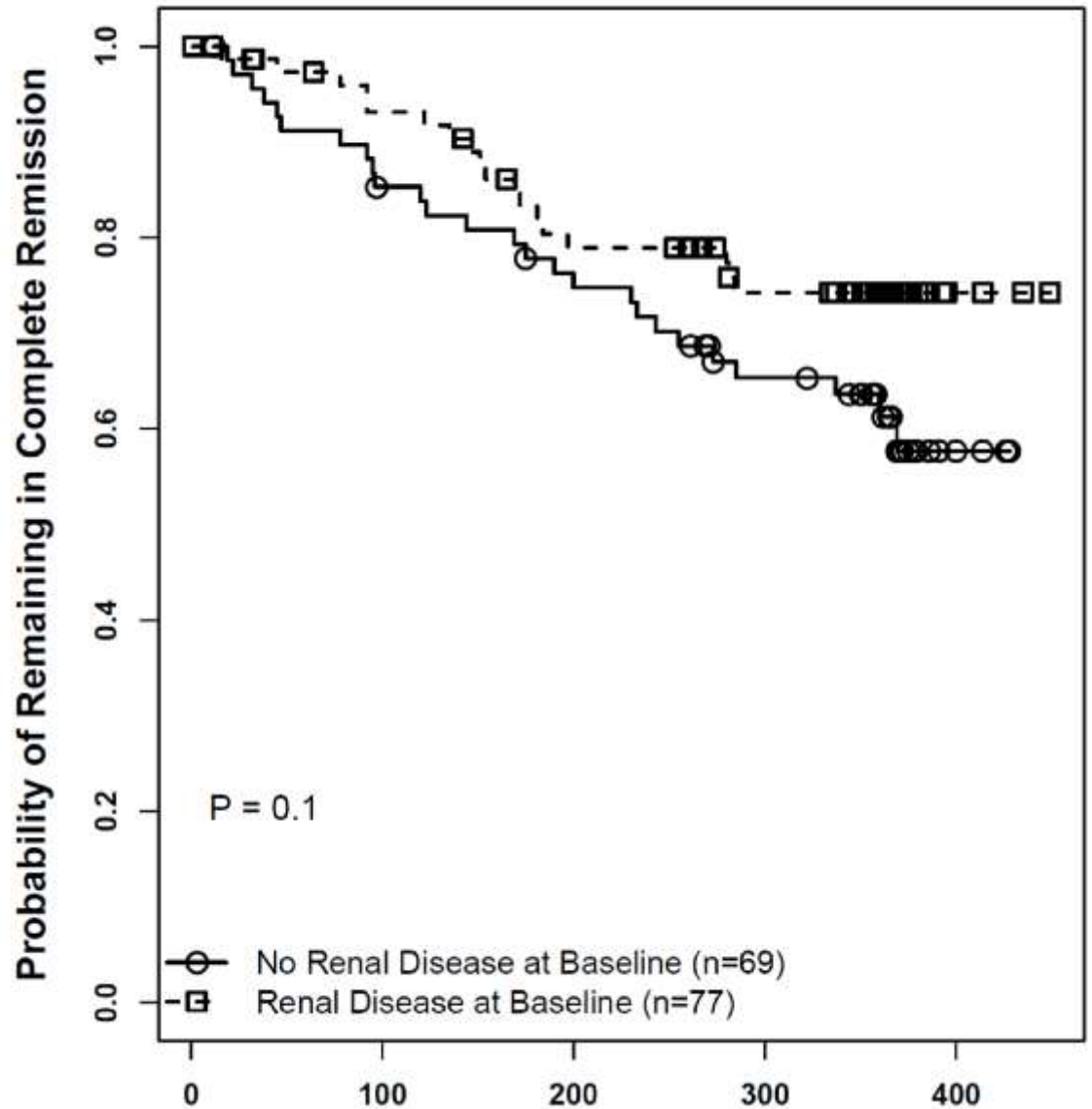
Patients who entered the trial with relapsing disease were more likely to have a relapse than were those with newly diagnosed disease





Patients with GPA were more likely to have a relapse than were those with MPA (regardless of the Rx arm)

N Engl J Med 2013;369:417-27



N Engl J Med 2013;369:417-27

No difference in relapse rates between patients with and without renal disease at baseline

Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

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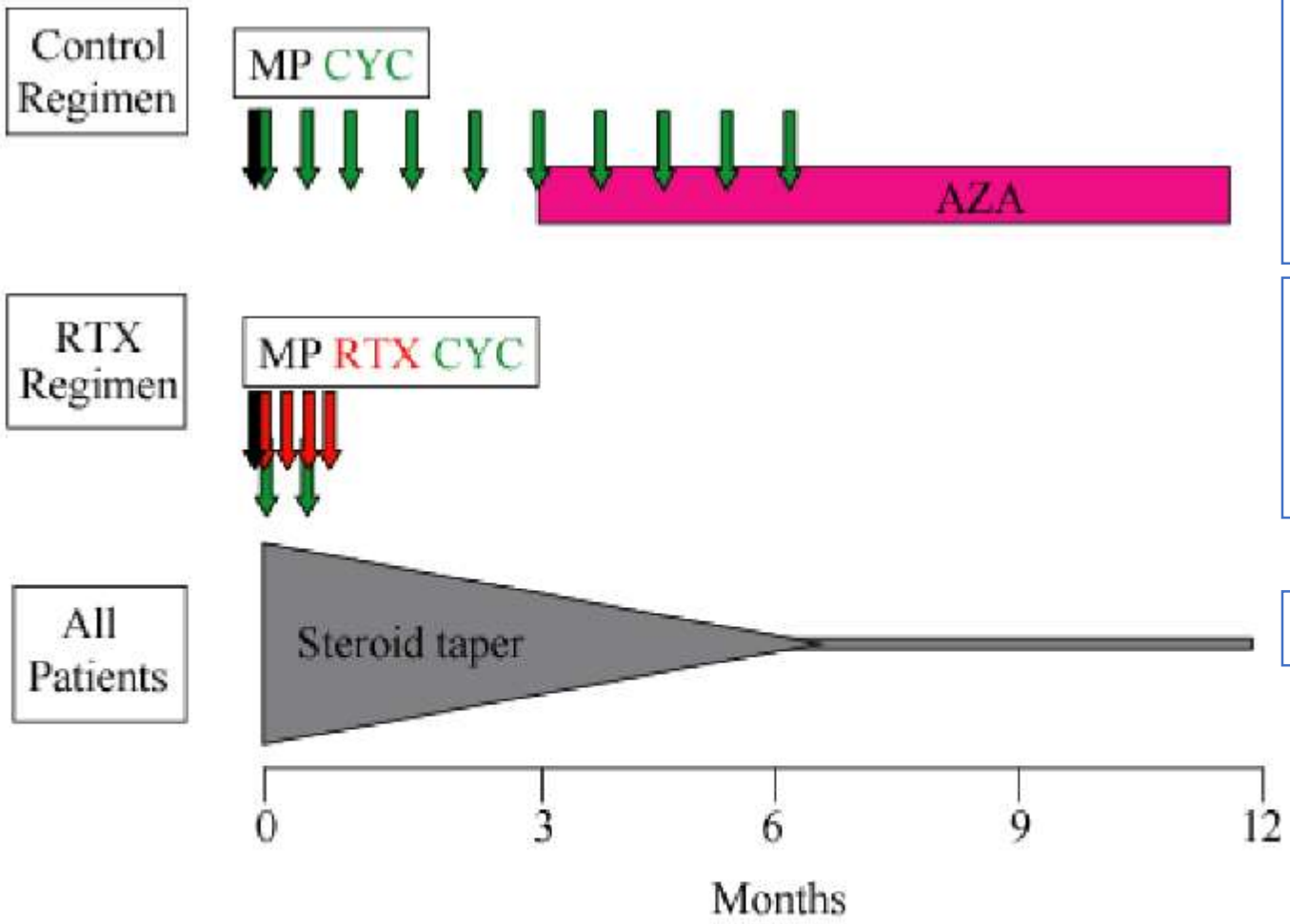
RITUXVAS trial

- Open-label, two-group, parallel design, randomized trial involving 44 patients from eight centers in Europe and Australia
- Newly diagnosed AAV with renal involvement, as evidenced by necrotizing glomerulonephritis on biopsy or red cell casts or hematuria (≥30 RBCs/HPF)

N Engl J Med 2010;363:211-20



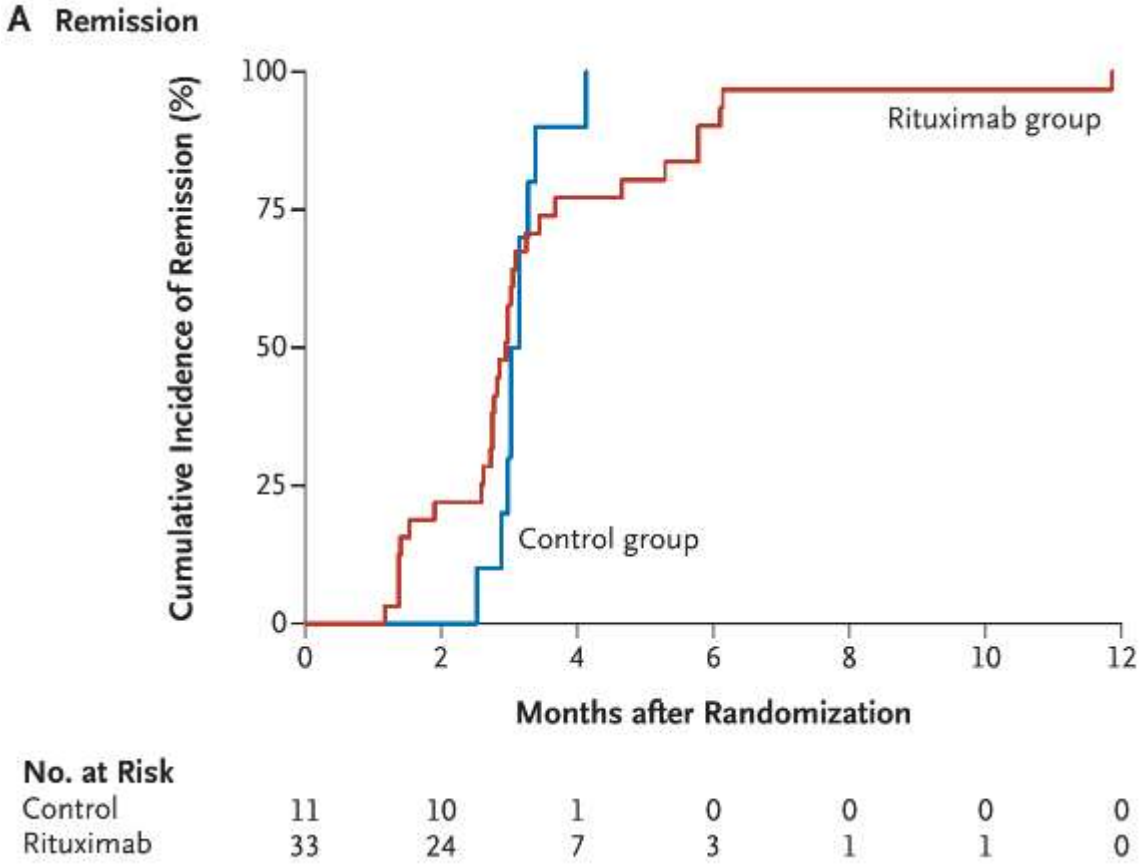
- CYC every 2 weeks for the first three doses, then every three weeks thereafter until stable remission was achieved (minimum 6, maximum 10 doses)
- AZA for remission maintenance after CYC withdrawal

- Rituximab weekly for four consecutive weeks, and CYC, with the first and third rituximab infusions
- Did not receive azathioprine for remission maintenance

- Steroid 1mg/kg/d initially, reduced to 5mg/d by 6M

Black arrows indicate intravenous methylprednisolone (MP), 1 gram. Red arrows indicate intravenous rituximab (RTX), 375mg/m^2. Green arrows indicate intravenous cyclophosphamide (CYC), 15mg/kg with dose adjustments for age and renal function. AZA=azathioprine.

N Engl J Med 2010;363:211-20

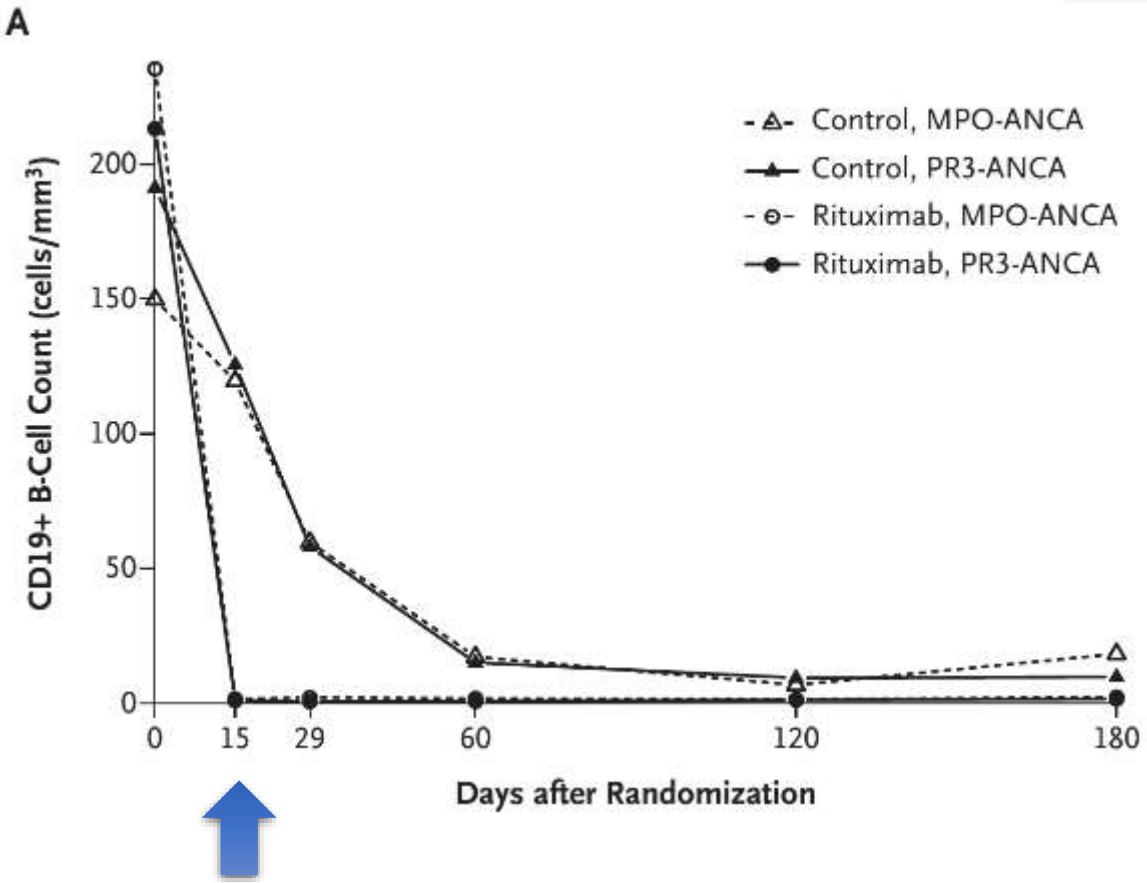


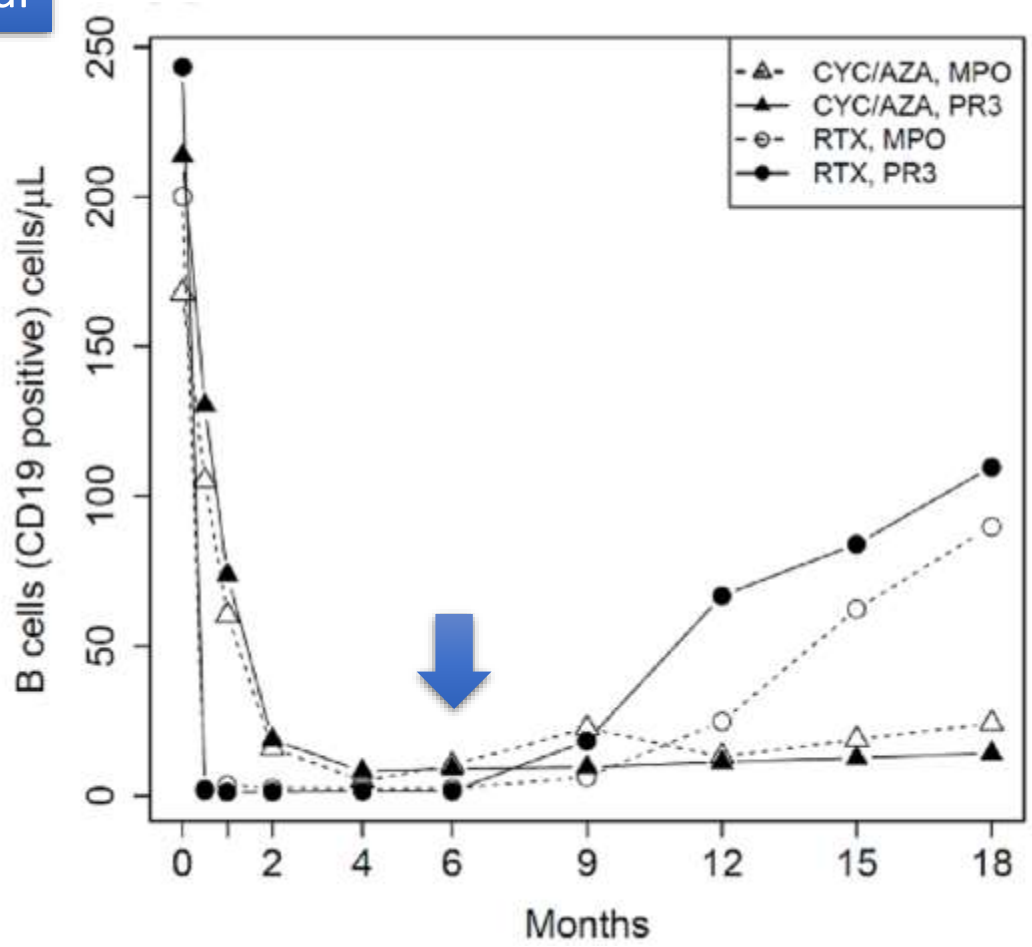
- Rituximab-based regimen was not superior to standard IV cyclophosphamide. 25 patients in the rituximab group (76%) and 9 patients in the control group (82%) had a sustained remission (P = 0.68).
- Median time to remission was 90 days (IQR, 79 to 112) in the rituximab group and 94 days (IQR, 91 to 100) in the control group (P = 0.87).
- Rituximab-based regimen was not associated with reductions in early severe adverse events.

N Engl J Med 2010;363:211-20

Role of rituximab in remission maintenance?

RAVE trial





- B-cell count in rituximab group decreased to <10/mm^3 after two infusions in 96% of cases and remained so until 6M. Most rituximab-treated patients fully reconstituted their B-cells between 9 and 12M.
- 87.5% of the relapses in Rituximab group (incl. all severe relapses) occurred after B-cells became re-detectable.
- However, 2/3rd of the rituximab-treated patients who had reconstituted their B-cells did not have a relapse.
- Relationship between relapse risk and B-cells in control arm was less clear.

N Engl J Med 2010;363:221-32
N Engl J Med 2013;369:417-27

Rituximab for Remission Maintenance in Relapsing Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

Rona M. Smith,[1] Rachel B. Jones,[1] Mary-Jane Guerry,[1] Simona Laurino,[1] Fausta Catapano,[1] Afzal Chaudhry,[1] Kenneth G. C. Smith,[2] and David R. W. Jayne[1]

- Retrospective analysis of 73 patients sequential patients receiving rituximab for refractory or relapsing AAV at a single center
- Patients given rituximab as first-line therapy were excluded, as were those with <6 months of follow-up

Arthritis Rheum. 2012 Nov;64(11):3760-9

Group A (n = 28)	• Rituximab induction therapy (4 infusions of 375 mg/m2 or 2 infusions 1 g) and further rituximab at the time of subsequent relapse
Group B (n = 45)	• Routine rituximab re-treatment for 2 years: 2 doses of 1 gm each for remission induction, then 1 g every 6 months (total of 6 g)
Group C (n = 19)	• Patients in group A who subsequently relapsed and began routine re-treatment for 2 years

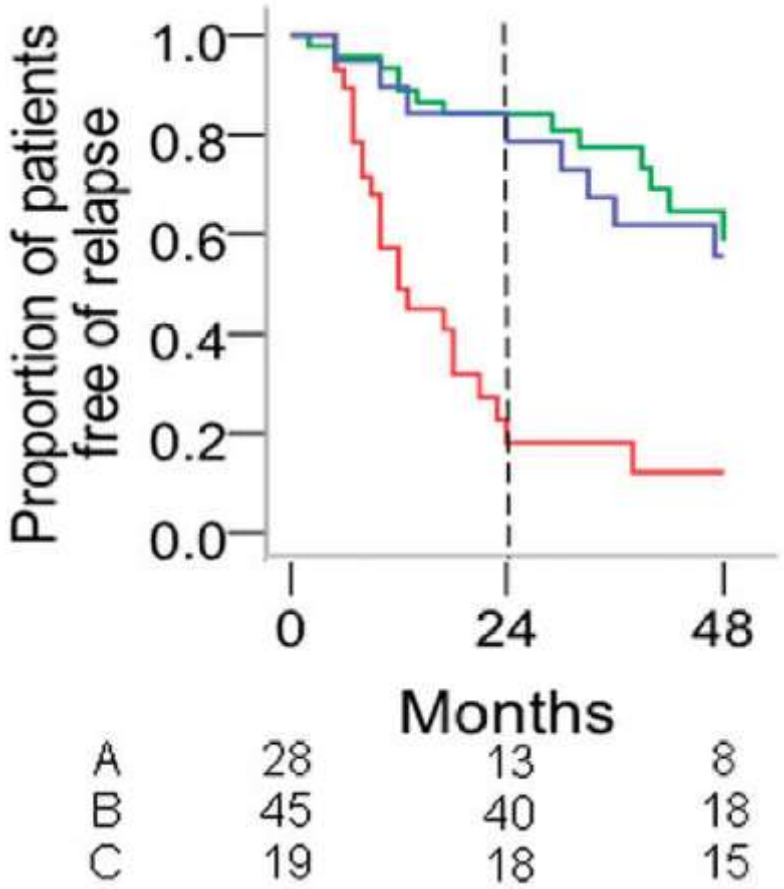
Arthritis Rheum. 2012 Nov;64(11):3760-9

	Group A (n = 28)	Group B (n = 45)	Group C (n = 19)	Groups A and B (n = 73)
Age at first RTX dose, median (range) years	53 (16–71)	51 (16–77)	61 (34–74)	52 (16–77)
No. (%) male	12 (43)	18 (40)	7 (37)	30 (41)
Diagnosis, no. (%)				
GPA	20 (71)	41 (91)	15 (79)	61 (84)
MPA	8 (29)	4 (9)	4 (21)	12 (16)
Disease duration, median (range) months	87 (6–360)	43 (8–220)	114 (37–399)	57 (6–360)
Prior CYC therapy				
No. (%) of patients	27 (96)	41 (91)	18 (95)	68 (93)
Cumulative dose, median (range) gm	29.0 (0–150)	14.9 (0–130)	30.0 (0–77.5)	19.5 (0–150)
Prior therapies, no. (%)				
Alemtuzumab	5 (18)	2 (4)	5 (26)	7 (10)
Anti-TNF	8 (29)	5 (11)	6 (31)	13 (18)
Azathioprine	21 (75)	33 (73)	14 (74)	54 (74)
Gusperimus	4 (14)	9 (20)	3 (16)	13 (18)
IVIG	5 (18)	12 (27)	3 (16)	17 (23)
MMF	22 (79)	34 (76)	14 (74)	56 (77)
Methotrexate	10 (36)	15 (33)	7 (37)	25 (34)
Plasma exchange	3 (11)	7 (16)	1 (5)	10 (14)
Other†	1 (4)	3 (7)	1 (6)	4 (5)
No. of prior immunosuppressive agents (excluding corticosteroids), median (range)	4 (2–8)	3 (1–8)	4 (2–7)	4 (1–8)

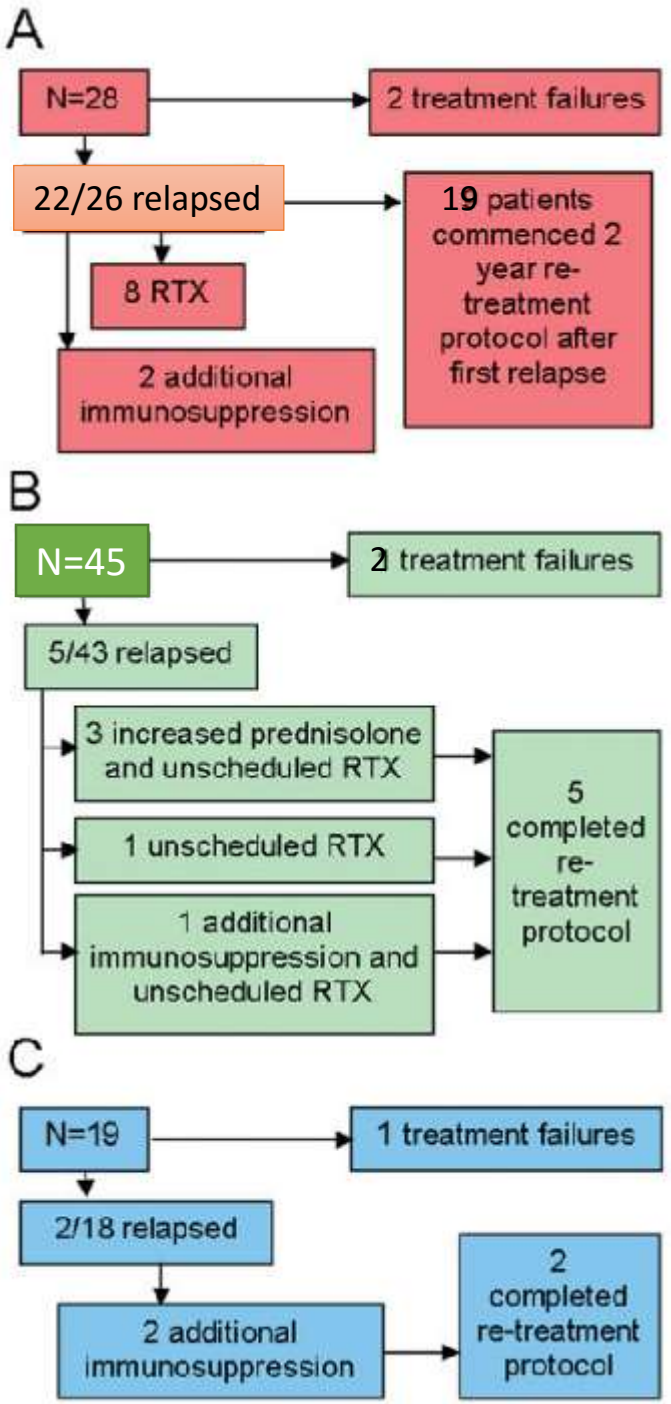
Arthritis Rheum. 2012 Nov;64(11):3760-9

	Group A	Group B	Group C
Initial response	93%	96%	95%
Relapse (2Y)	73%	12% (P < 0.001)	11% (P < 0.001)
Relapse at last FU (Median 44M)	85%	26% (P < 0.001)	56% (P = 0.001)

Arthritis Rheum. 2012 Nov;64(11):3760-9



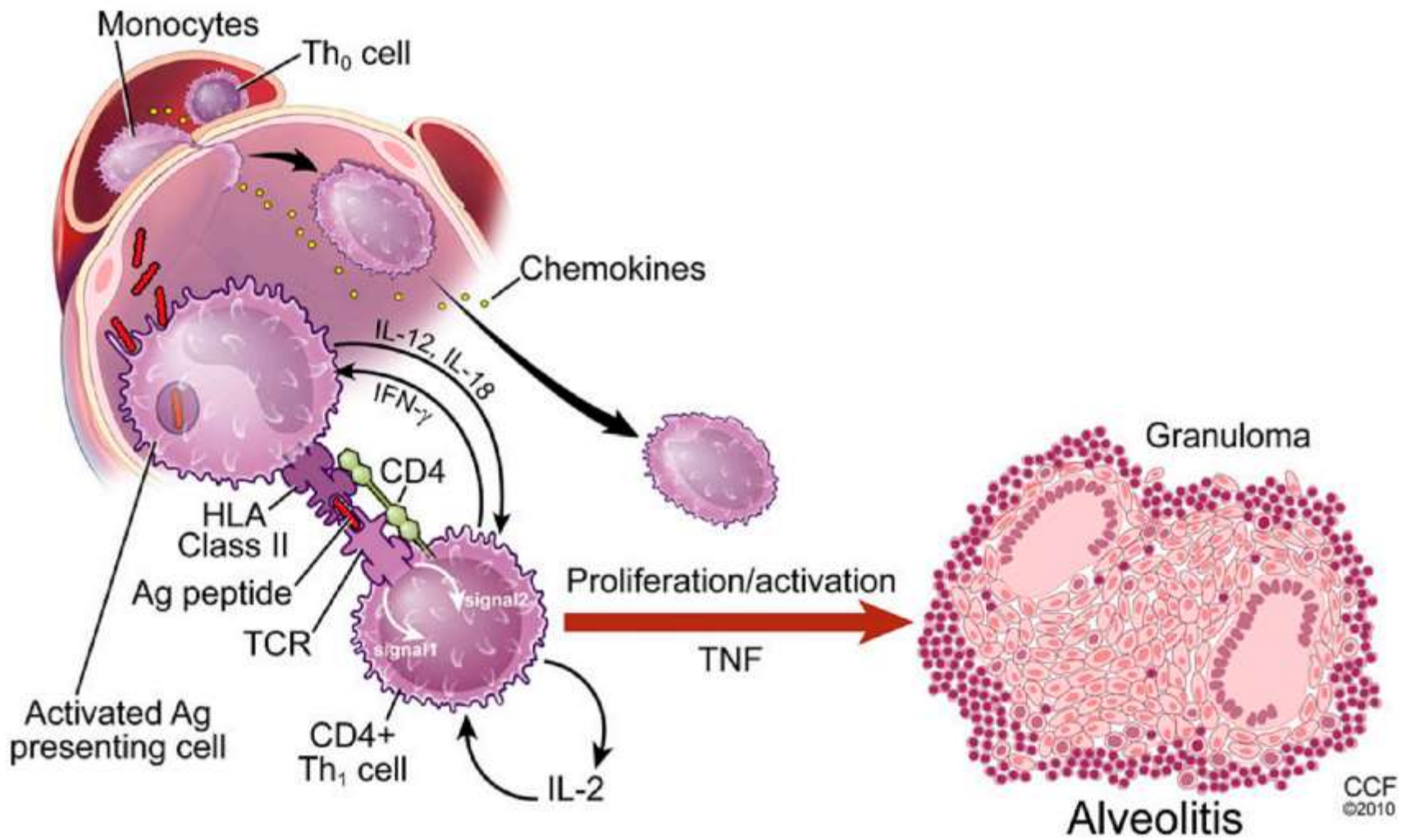
Red lines = Group A
Green lines = Group B
Blue lines = Group C



Management of first relapse within initial 24M

Arthritis Rheum. 2012 Nov;64(11):3760-9

Sarcoidosis



Am J Respir Crit Care Med Vol 183. pp 573–581, 2011

TNF antagonists

Drug	Dose	Route of administration	Adverse effects (common for all anti-TNF)
Infliximab	3–5 mg/kg	Infusion intravenously every four to eight weeks	Local erythema Increased risk of infections
Etanercept	25 mg	Subcutaneous injection, twice weekly	Increased risk of tuberculosis reactivation
Etanercept	50 mg	Subcutaneous injection, weekly	Congestive heart failure Desmyelinating diseases
Adalimumab	40 mg	Subcutaneous injection every two weeks	Neoplasm

Therapeutics and Clinical Risk Management 2008:4(6) 1305–1313

	Agent	Patients	Result
Utz, 2003 (Phase 2 trial)	Etanercept 25mg SC twice weekly (as sole Rx)	Stage II or III progressive pulmonary sarcoidosis who had not used any other immunosuppressive agent in the preceding 3 months	Study terminated after the enrollment of 17 patients due to excessive treatment failures (11/17)
Baughman, 2006 (RCT)	Infliximab IV (3 or 5 mg/kg) or placebo at Weeks 0, 2, 6, 12, 18, 24 and were followed through Week 52 (Bacground Rx continued)	138 patients with chronic pulmonary sarcoidosis treated with at least 10 mg/d of prednisone or equivalent or one or more immunosuppressants for at least 3 months	Patients in the infliximab groups had a mean increase of 2.5% from baseline to Week 24 in % predicted FVC, compared with no change in placebo-treated patients (p=0.038)
Rossman 2006 (RCT)	Infliximab 5mg/kg (group I) or placebo (group II) at weeks 0 and 2 and open-label infliximab 5mg/kg for all subjects at weeks 6 and 14.	Stage II, III, and IV active pulmonary sarcoidosis despite corticosteroids or previous intolerance to corticosteroids	At 6 weeks the mean +/- SD relative change in VC compared to baseline was 15.22 +/- 9.91% for group I (n=13) and 8.39 +/- 3.33% for group II (n=6) (p=0.65).
Kamphuis, 2010 (Case series)	Adalimumab SC (160, 80, and 40 mg at Weeks 0, 2, and 4, thereafter biweekly 40mg for at least 1 year)	5 patients with chronic sarcoidosis (both pulmonary & extrapulmonary)	Radiological response noted in all patients

Chest. 2003;124(1):177-185
Am J Respir Crit Care Med Vol 174. pp 795–802, 2006
Sarcoidosis Vasc Diffuse Lung Dis. 2006 Oct;23(3):201-8
Am J Respir Crit Care Med. 2011 Nov 15;184(10):1214-6

Infliximab Therapy in Patients with Chronic Sarcoidosis and Pulmonary Involvement

Robert P. Baughman, Marjolein Drent, Mani Kavuru, Marc A. Judson, Ulrich Costabel, Roland du Bois, Carlo Albera, Martin Brutsche, Gerald Davis, James F. Donohue, Joachim Müller-Quernheim, Rozsa Schlenker-Herceg, Susan Flavin, Kim Hung Lo, Barry Oemar, and Elliot S. Barnathan, on behalf of the Sarcoidosis Investigators

- Phase 2, multicenter, randomized, double-blind, placebo controlled study conducted in 138 patients with chronic pulmonary sarcoidosis.
- Patients must have been treated with at least 10 mg/d of prednisone or equivalent or one or more immunosuppressants for at least 3 months before screening.
- Patients were randomized to receive intravenous infusions of infliximab (3 or 5 mg/kg) or placebo at Weeks 0, 2, 6,12, 18, and 24 and were followed through Week 52.
- During the study, background medication regimen and doses remained stable.
- The primary endpoint was the change from baseline to Week 24 in percent of predicted FVC.

Am J Respir Crit Care Med Vol 174. pp 795–802, 2006

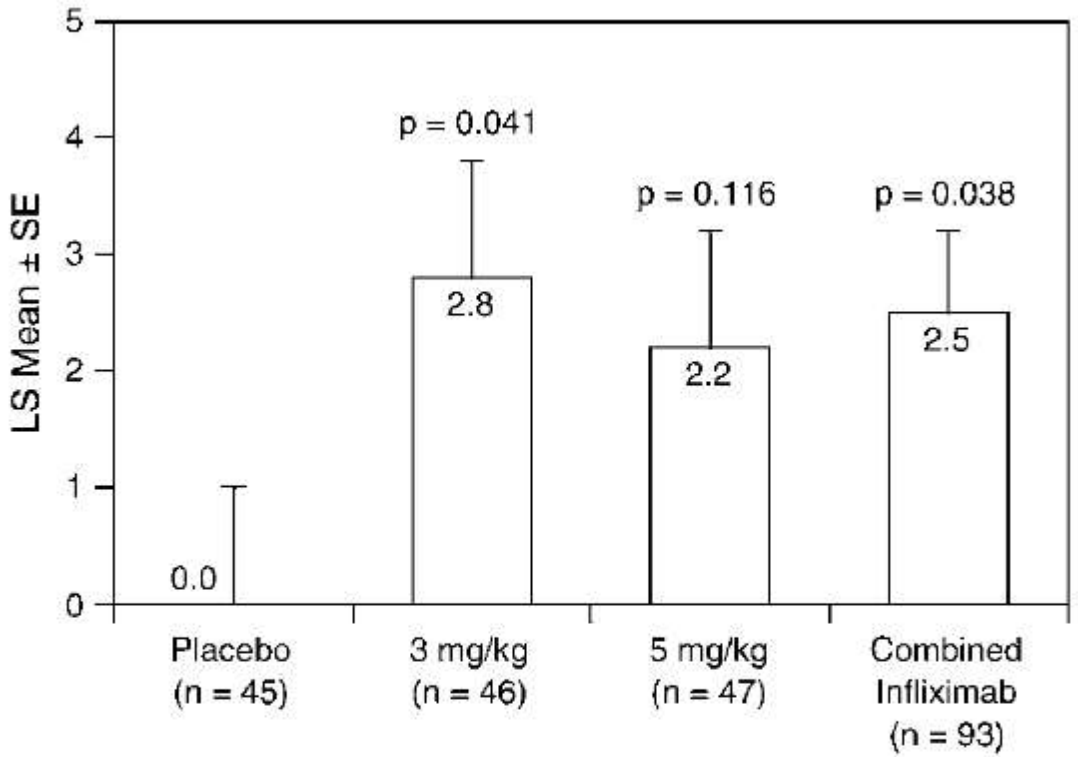


Figure 2. Summary of change from baseline to Week 24 in percent of predicted FVC with last observation carried forward. LS mean = least square mean.

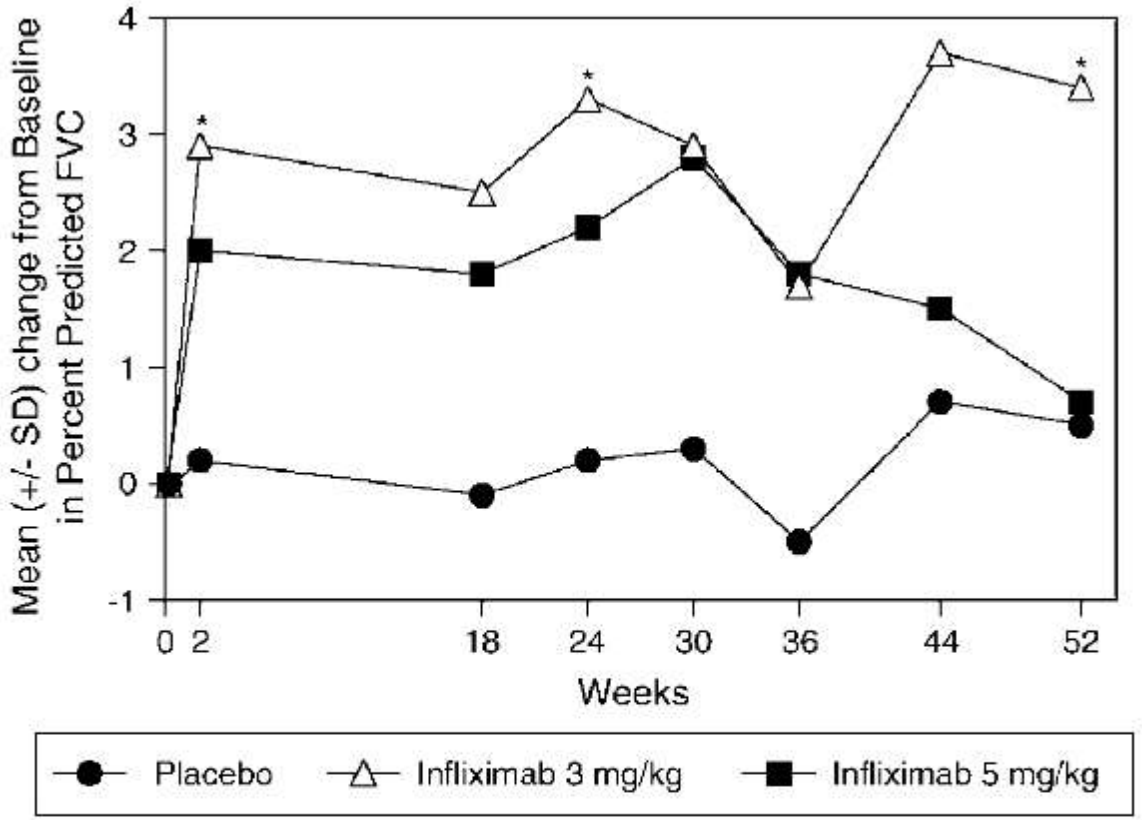


Figure 3. Mean (± SD) changes from baseline in percentage of predicted FVC through Week 52 (randomized patients, no imputation for missing data). *p < 0.05 versus placebo group.

Am J Respir Crit Care Med Vol 174. pp 795–802, 2006

Pulmonary Disorders Induced by Monoclonal Antibodies

Pulmonary Disorders Induced by Monoclonal Antibodies in Patients with Rheumatologic Autoimmune Diseases

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Analysis of case reports, case series, post-marketing studies and controlled studies (when available) was done to identify pulmonary disorders induced by monoclonal antibodies

The American Journal of Medicine (2011) 124, 386-394

Table 1 Classification of Pulmonary Involvement Induced by Monoclonal Antibodies in Patients with Rheumatologic Autoimmune Disorders

Interstitial pneumonia	
Usual interstitial pneumonia	118 cases
Nonspecific interstitial pneumonia	
Organizing pneumonia	
Diffuse alveolar damage	
Lymphoid interstitial pneumonia	
Sarcoid-like disorder	
Pulmonary infiltrates	40 cases
Hilar adenopathies	
Mediastinal adenopathies	
Granulomatous pleural involvement	
Pulmonary vasculitis	
Antineutrophil cytoplasmic antibody (ANCA) + alveolar hemorrhage	3 cases
Necrotizing pulmonary nodules	
Pulmonary lymphocytic vasculitis	
Other respiratory processes	
Rhinitis, sinusitis, and self-limited cough	
Severe bronchospasm	
Hypersensitivity pneumonitis	
Acute respiratory distress syndrome	

- 97% of cases are associated with agents blocking tumor necrosis factor (TNF)
- Drug-induced interstitial pneumonia has a poor prognosis, with an overall mortality rate of around one-third, rising to two-thirds in patients with pre-existing interstitial disease.
- Sarcoid-like disease has a better prognosis, with resolution or improvement in 90% of cases.

The American Journal of Medicine (2011) 124, 386-394

Summary

- Omalizumab has been proven to be a useful adjunct to steroids in subjects with moderate to severe asthma and may allow tapering/discontinuation of ICS.
- Anti-IL mAbs may be useful in specific subsets of moderate to severe asthma.
- Bevacizumab improves OS when added to paclitaxel based doublet in advanced non-squamous NSCLC, however additional benefit over pemetrexed based regimens is not clear.
- Cetuximab may improve OS when used with chemotherapy in patients with EGFR positive advanced NSCLC.
- Rituximab is a valuable alternative to cyclophosphamide for remission induction in AAV. It may also have a role in maintenance of remission.
- TNF-antagonists may have a role in the Rx of chronic pulmonary sarcoidosis. However, further studies are needed to substantiate their role.
- Use of monoclonal antibodies (esp. TNF antagonists) may be associated with pulmonary disorders like ILDs and sarcoidosis.