

# PREDICTORS OF RESPONSE TO ANTI-TNF $\alpha$ TREATMENT IN CROHN'S DISEASE



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# Background

- Infliximab (monoclonal IgG1 antibody against TNF- $\alpha$ ) is effective in refractory and fistulizing Crohn's disease
- Placebo-controlled double-blind randomised trials
  - Targan et al, *NEJM* 1997
  - Present et al, *NEJM* 1999
- Efficacy of re-treatment trials
  - Rutgeerts et al, *Gastroenterology* 1999
  - Hanauer et al, *Lancet* 2002 (ACCENT I)
  - Sands BE et al, *NEJM* in press (ACCENT II)

Overall response rates of 70-75%  
Therapy refractoriness in  $\pm$  30% of patients

# Importance of predictive factors

- Allows clear selection of patients likely to benefit from the drug and can prevent patients from undergoing unnecessary treatment
- Identification of modifiable factors associated with response leads to
  - optimization of response rates
  - optimization of duration of response
- Optimal cost-effectiveness: avoidance of unnecessary expensive infusions
- Identification of predictors of response to infliximab in Crohn's disease may also lead to direct implications in other diseases where infliximab is being used (rheumatoid arthritis, psoriasis, spondylarthropathy)

# Predictive factors for response to infliximab

1. Clinical predictors
2. Genetic predictors
3. Serological predictors

# Study population

- Patients followed at the IBD-unit of the University Hospital Gasthuisberg (Leuven, Belgium) and treated with infliximab for therapy-resistant luminal or fistulizing disease
- Demographic and clinical data available through clinical workstation (= electronic patients chart containing all visits, biochemistry, X-rays, endoscopy, biopsy results)
- Response to infliximab determined by changes in Crohn's Disease Activity Index (luminal) or drainage assessment index (fistulising)
- Group of 200 healthy individuals used for control of allele frequencies in genetic studies

# Predictive factors for response to infliximab

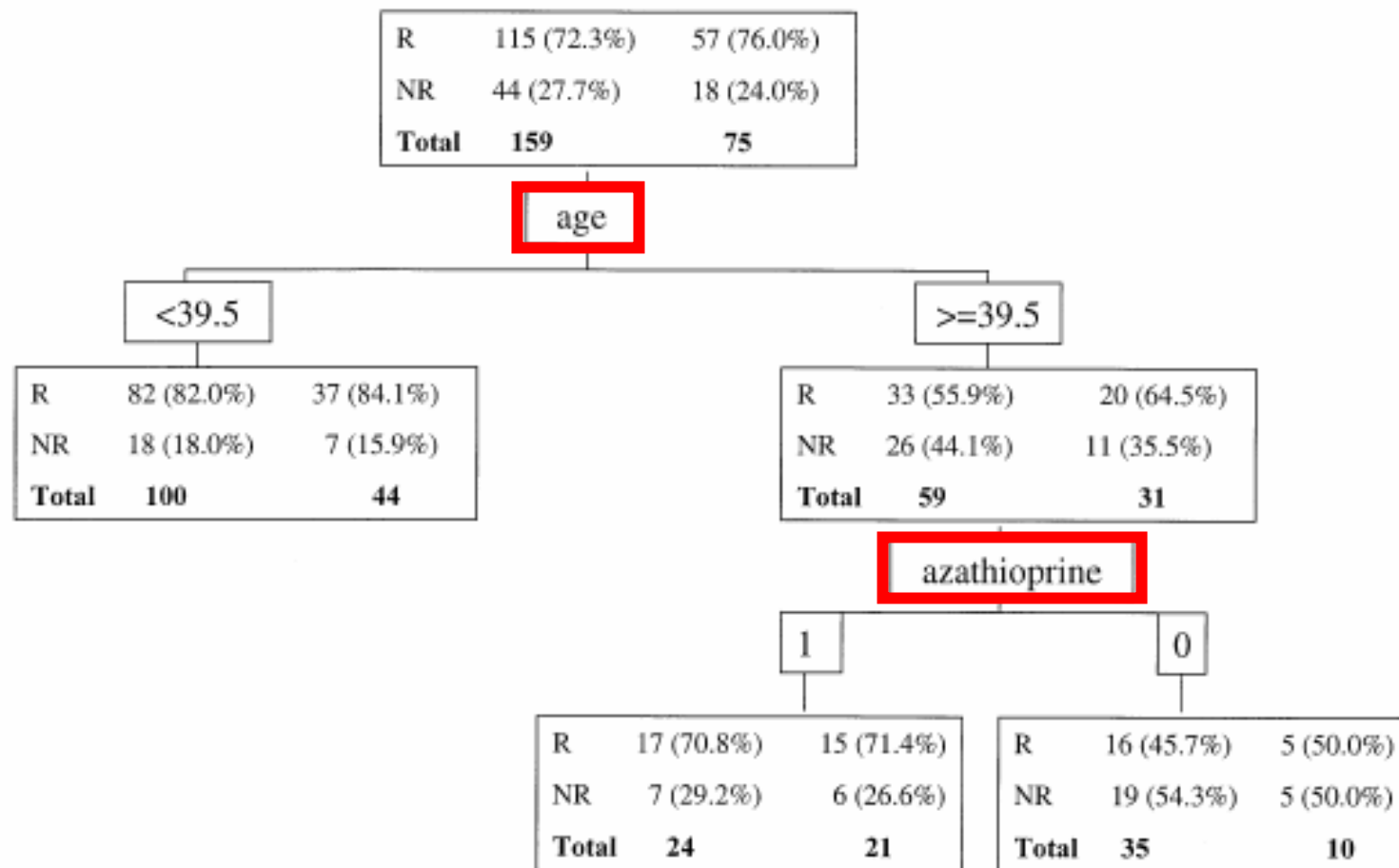
1. Clinical predictors

2. Genetic predictors

3. Serological predictors

**Table 1.** Demographic and Baseline Clinical Characteristics of the Study Population (*N* = 240)

	Refractory CD (n = 137)	Fistulizing CD (n = 103)	All Patients (N = 240)
Mean baseline CDAI (range)	294 (72–609)	200 (51–526)	261 (51–609)
Mean baseline CRP (mg/L)	24.5	24.9	24.7
Median age (yr) (IQR)	34 (28–44)	37 (30–46)	36 (28–44.75)
Female/male (%)	84/53 (61.3/38.7)	69/34 (67.0/33.0)	153/87 (63.8/36.2)
Smoking (%)	68 (49.6)	39 (37.8)	107 (44.6)
Mean disease duration (yr)	10.7	13.0	11.7
Involved intestinal area			
Ileitis (%)	23 (16.8)	17 (16.5)	40 (16.7)
Ileocolitis (%)	70 (51.1)	35 (34.0)	105 (43.8)
Colitis (%)	43 (31.4)	46 (44.7)	89 (37.1)
Localization of fistulas			
Perianal		69	
Rectovaginal		23	
Enterocutaneous		19	
Into bladder		1	
Enterocolic		1	
Concomitant treatment			
Aminosalicylates (%)	59 (43.1)	47 (45.6)	106 (44.2)
Steroids (%)	75 (54.7)	33 (32.0)	108 (45.0)
6-MP/AZA/MTX (%)	76 (55.5)	64 (62.1)	140 (57.9)
Oral contraceptives	31 (22.6)	21 (20.4)	52 (21.7)
NSAIDs	8 (5.8)	5 (4.9)	13 (5.4)
Previous abdominal surgery	51 (37.2)	31 (30.1)	82 (34.2)



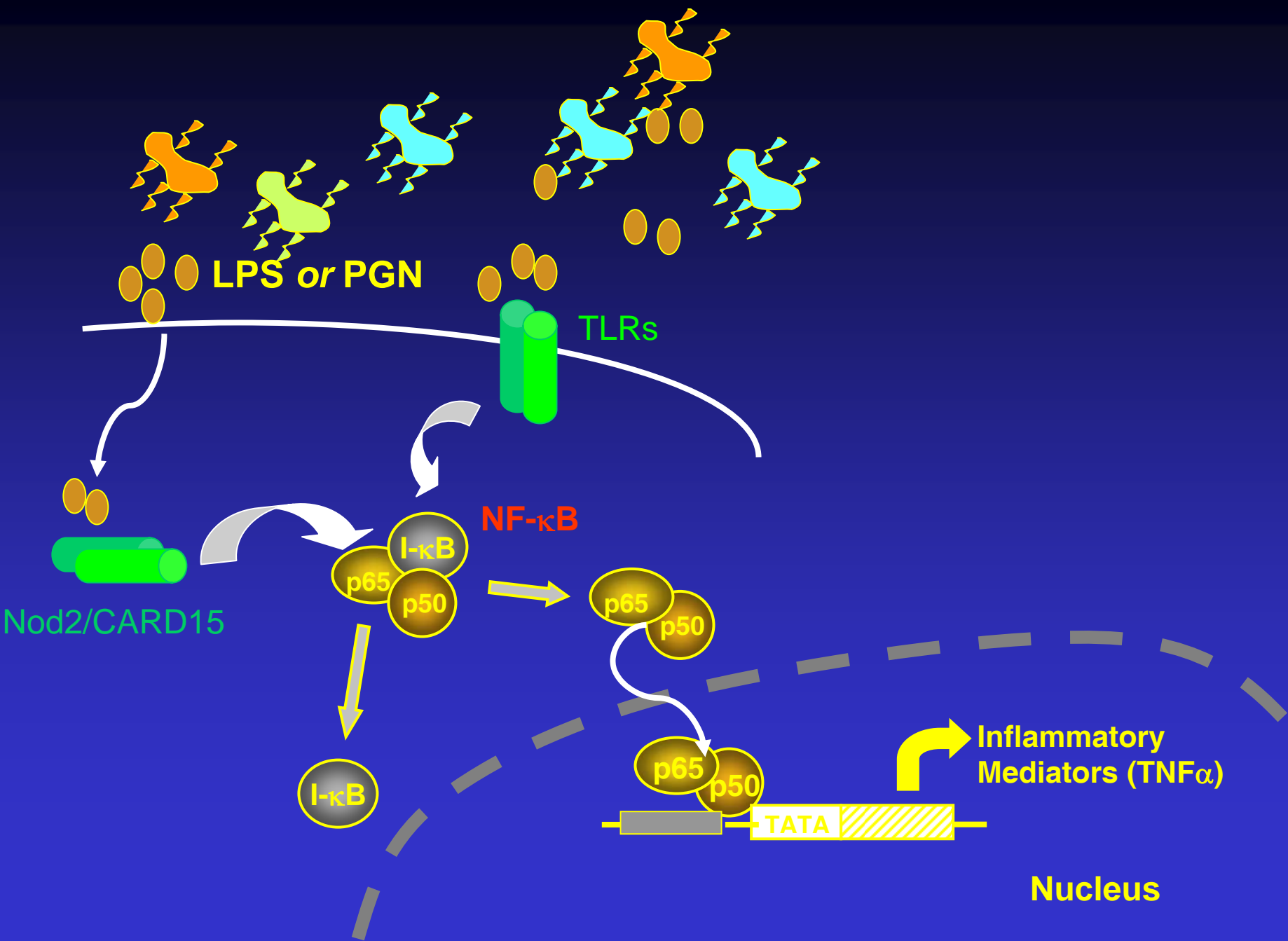
**Figure 1.** Decision tree analysis (using SAS enterprise Miner; see text) on the total study population (n = 240). Absolute numbers as well as percentage of response (R) and nonresponse (NR) for the training data set (left column) and validation data set (right column) are given. Age was selected as the first splitting variable to predict the target, whereas use of azathioprine was selected as second splitting variable in the group of patients >39.5 yr.

# Predictive factors for response to infliximab

1. Clinical predictors

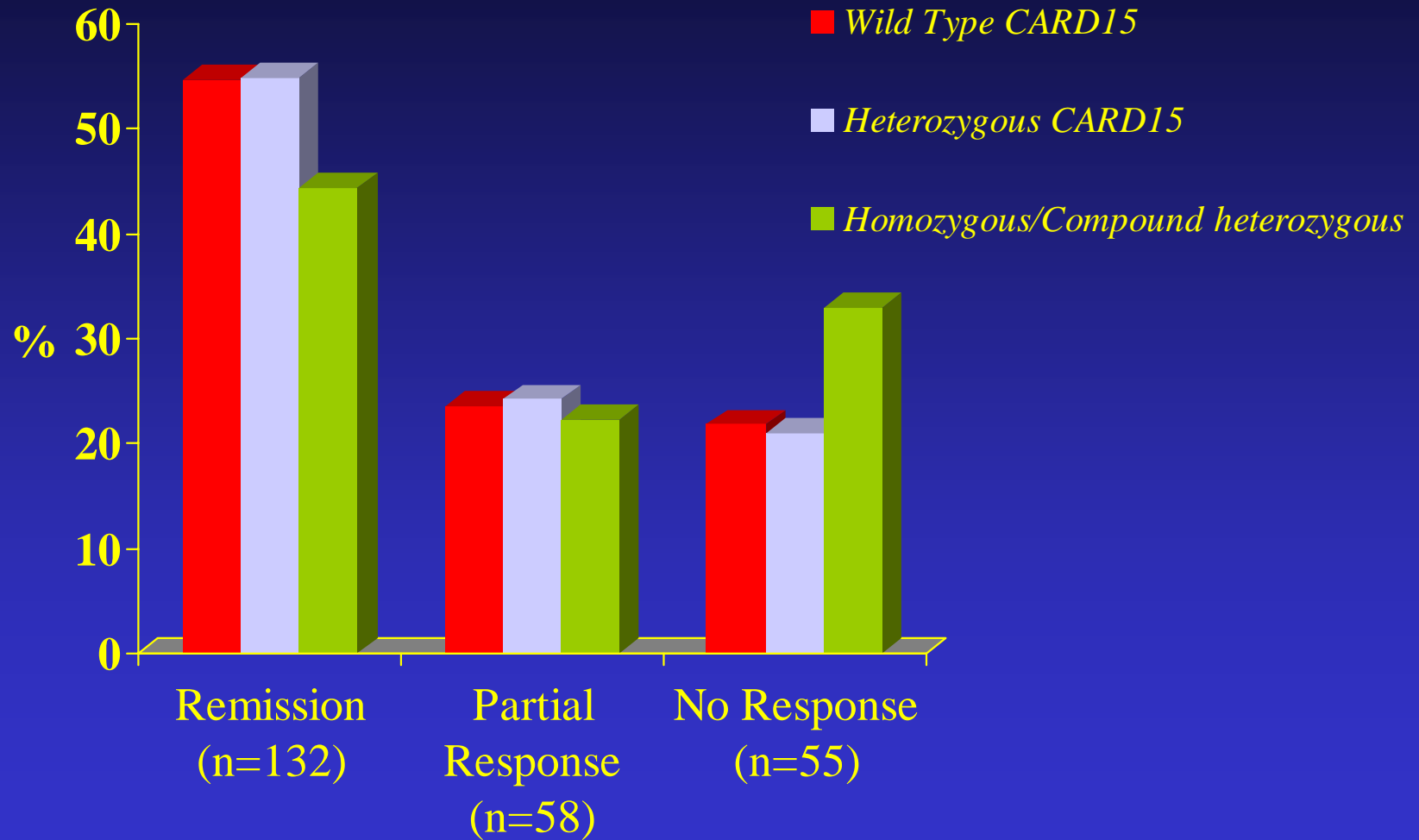
2. Genetic predictors

3. Serological predictors



N=245

# NOD2/CARD15



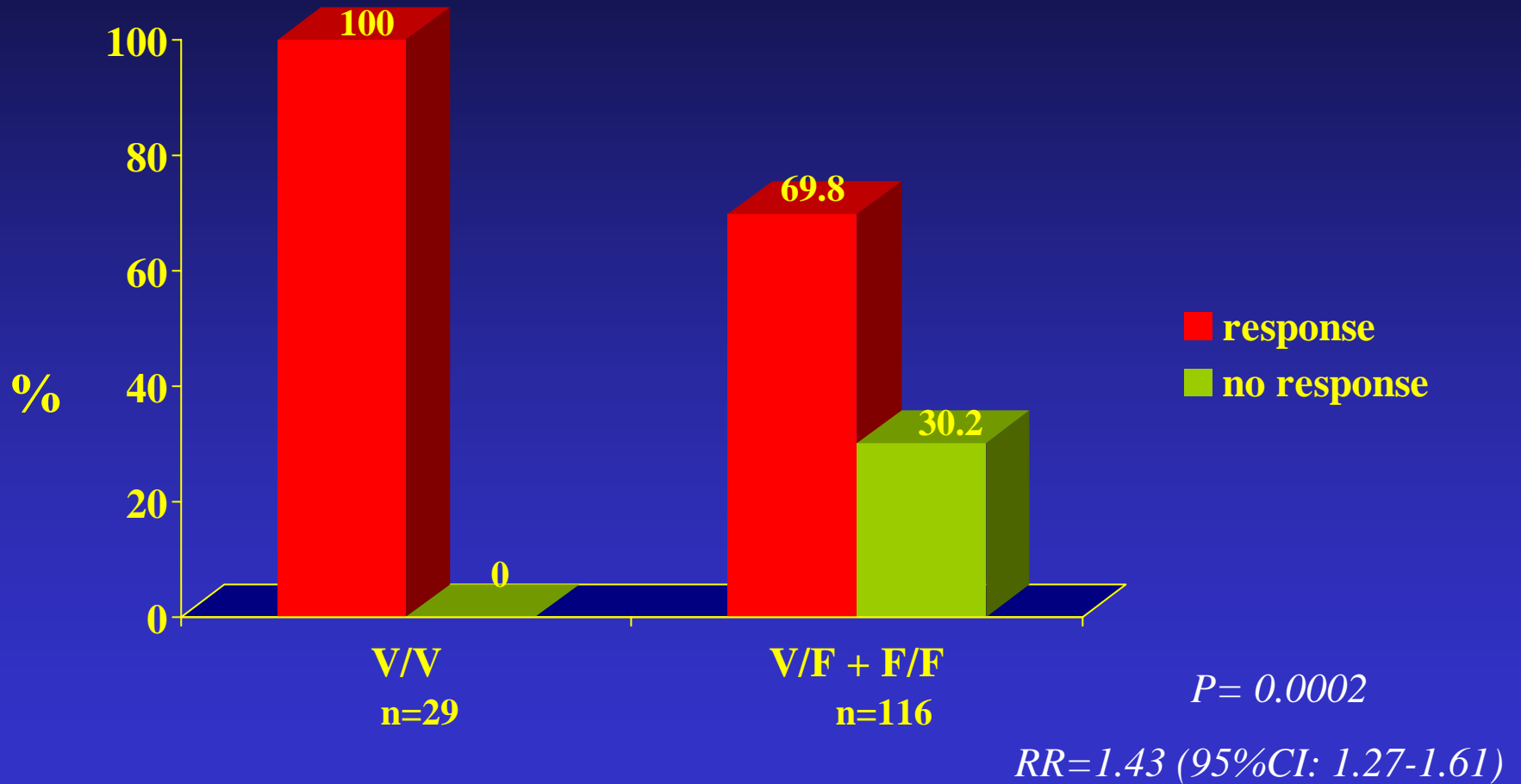
# Infliximab and ADCC

- Infliximab binds mTNF $\alpha$  leading to complement activation and ADCC in vivo (*Scallon et al cytokine 1995*)
- ADCC important effector mechanism in eradication of intracellular pathogens and tumor cells and requires leukocyte receptors for IgG Fc
- FcGR3a, the gene coding for Fc $\gamma$ R3a expressed on macrophages and NK cells carries functional polymorphism at aa position -158
- FcGR3a-158 valine allotype higher affinity for IgG1 than Fc $\gamma$ R3a-158 phenylalanine allotype
- More affinity for IgG1 = more potent ADCC
- FcGR3a associated with response to rituximab in non-Hodgkin's lymphoma (*Cartron G et al Blood 2002*)

N=145

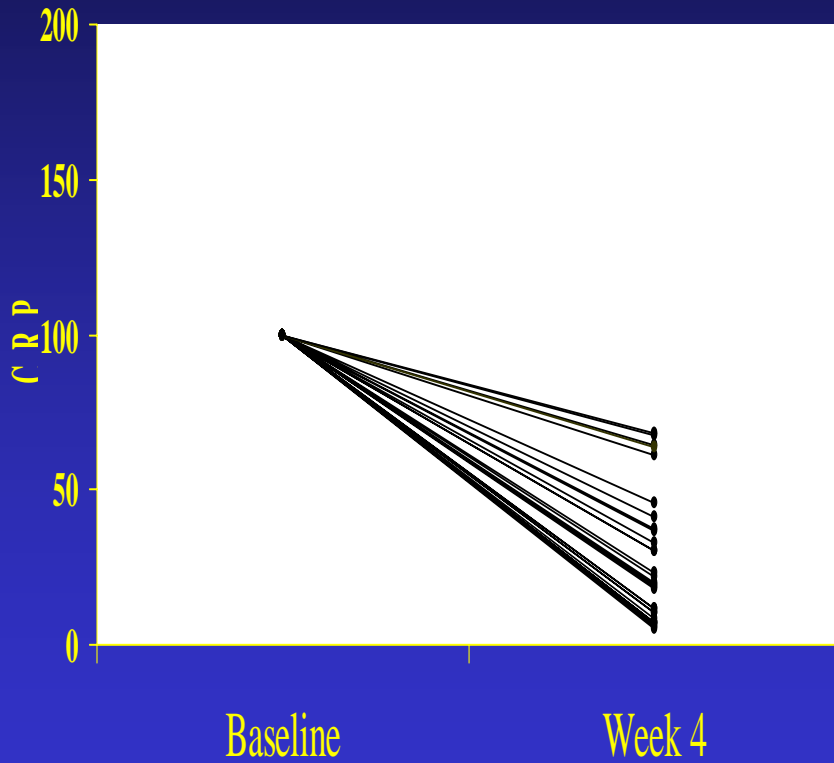
(all CRP>5mg/L)

# FcGR3a-158



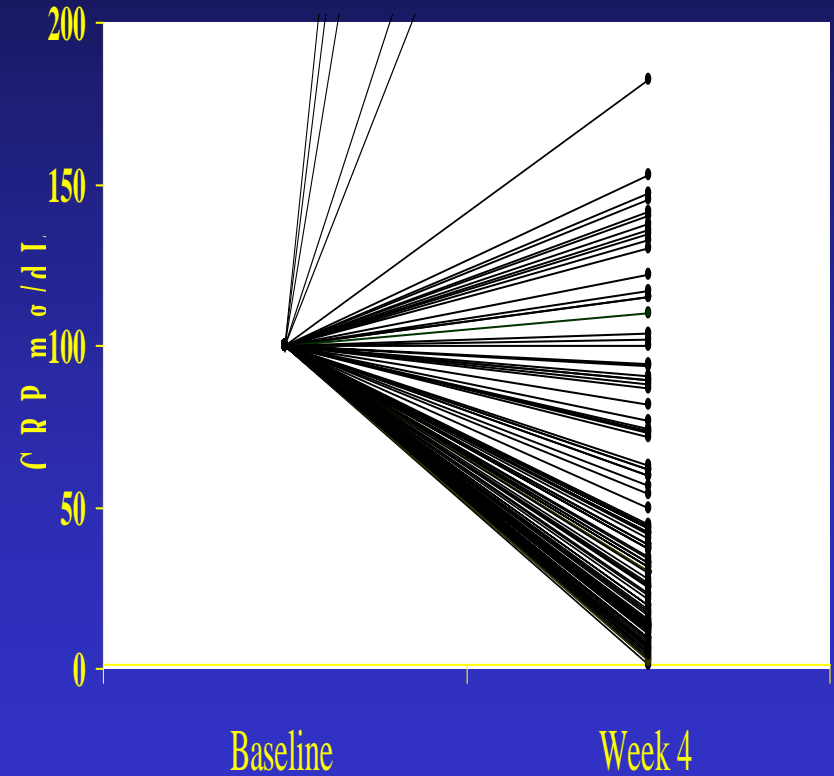
### V/V patients

Median variation -80.1%  
range: -31.0% - -94.8%



### V/F and F/F patients

median variation -63.2%  
range: +1100% - -98.1%

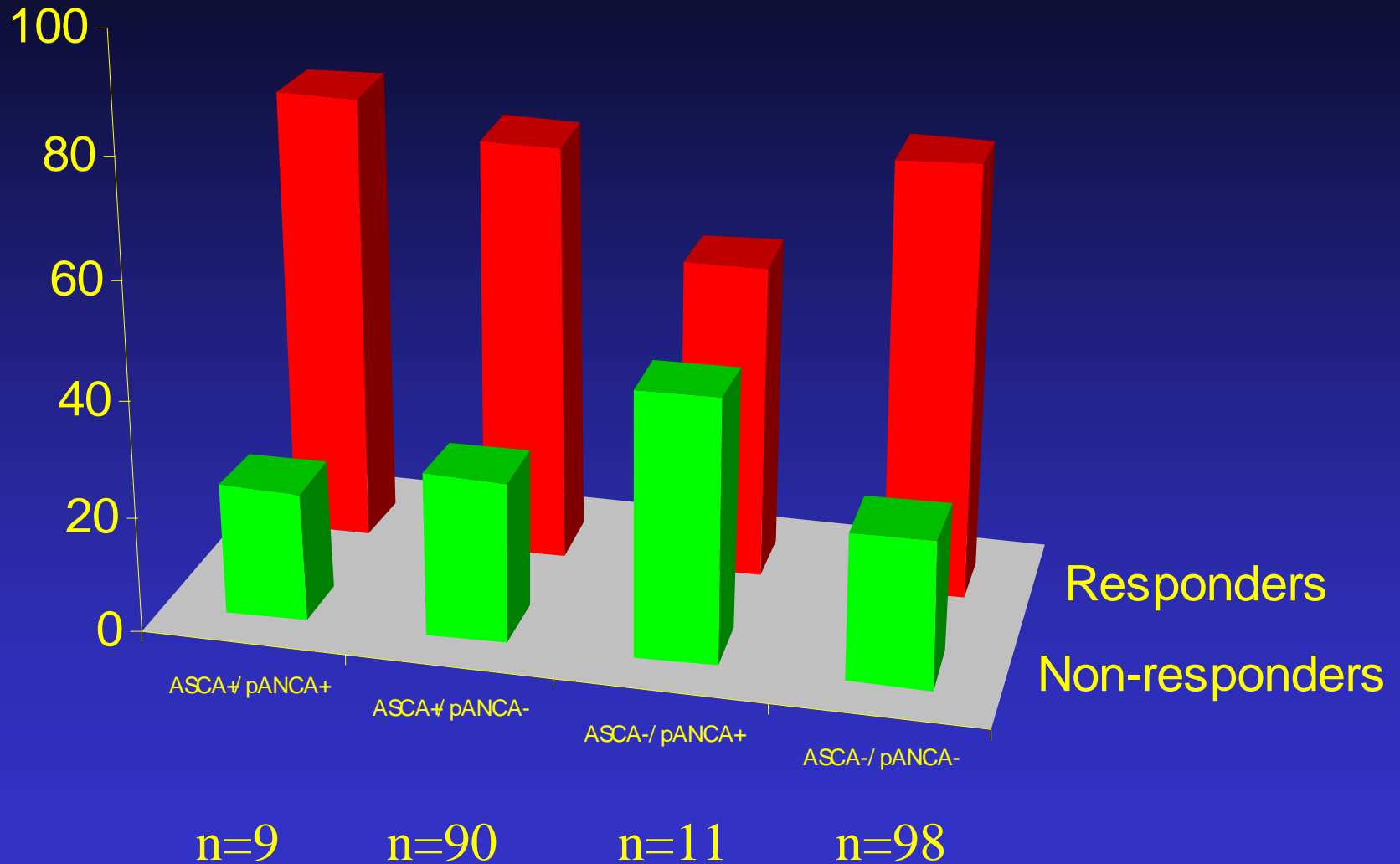


$P = 0.0078$

# Predictive factors for response to infliximab

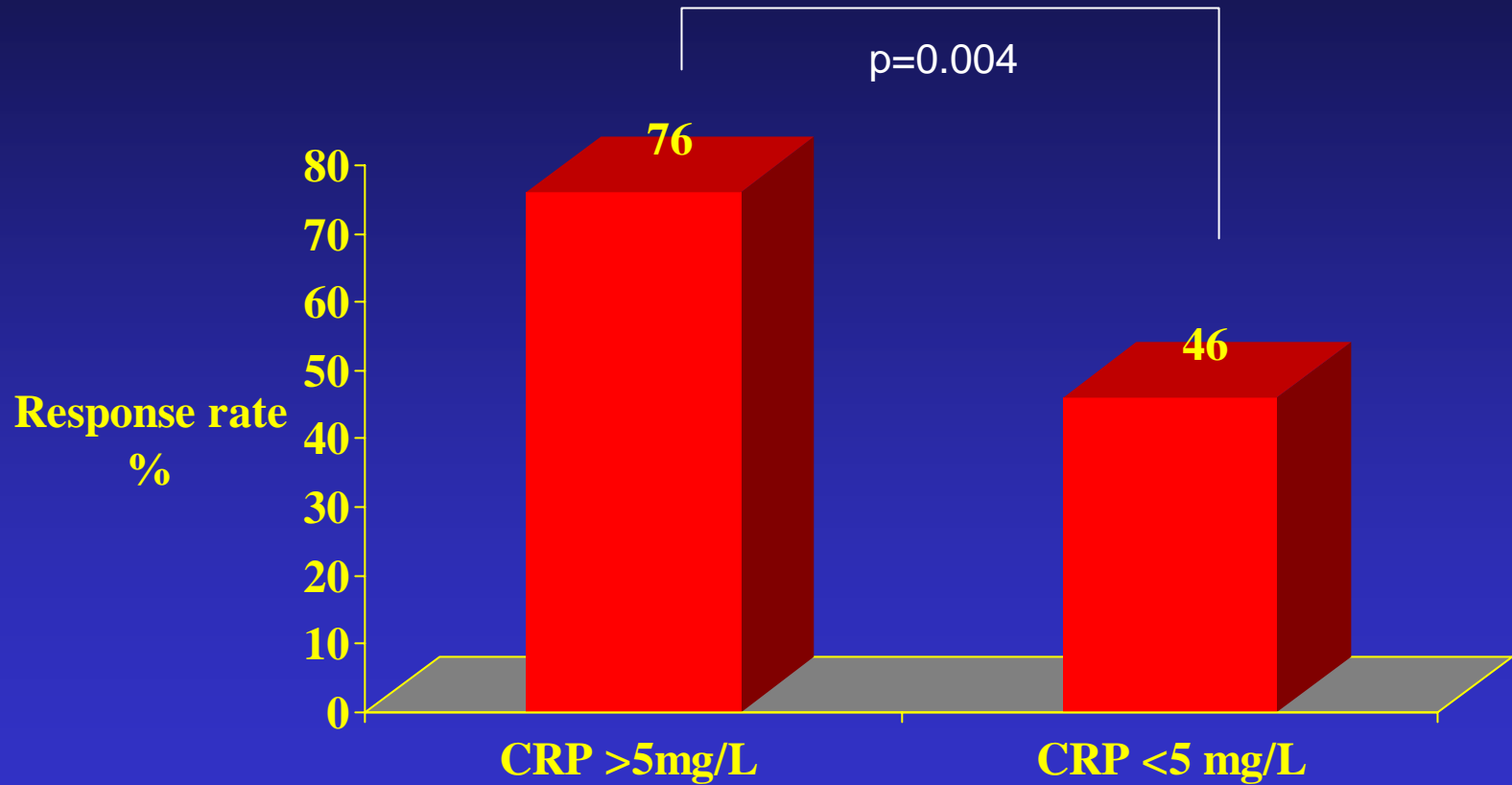
1. Clinical predictors
2. Genetic predictors
3. Serological predictors

**N= 183**



N=226

# C-Reactive Protein



# Conclusion:

## Predictive factors for response to infliximab

### 1. Clinical predictors of response

- Young age
- Concomitant immunosuppression
- Non-smoking
- Crohn's colitis

### 2. Genetic predictors

- LTA NcoI-TNFC-aa13L-aa26 haplotype: non response
- FcGR11a-158 Valine allotype: response

### 3. Serological predictors

- ASCA-/pANCA+: non response
- High baseline CRP

# Acknowledgements

- IBD patients
- Broad Medical Research Program:
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  - Prof Dr Daniel Hollander
  - Mrs Marciana Poland