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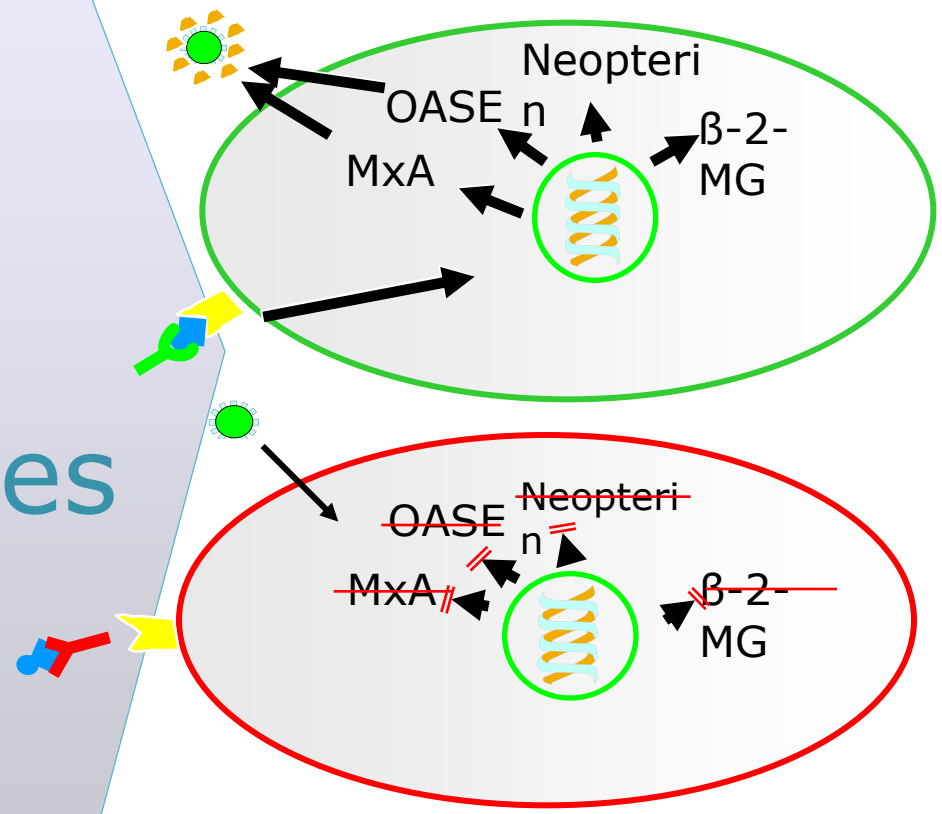
Clinical relevance of IFNb Nab in Multiple Sclerosis

Neutralizing

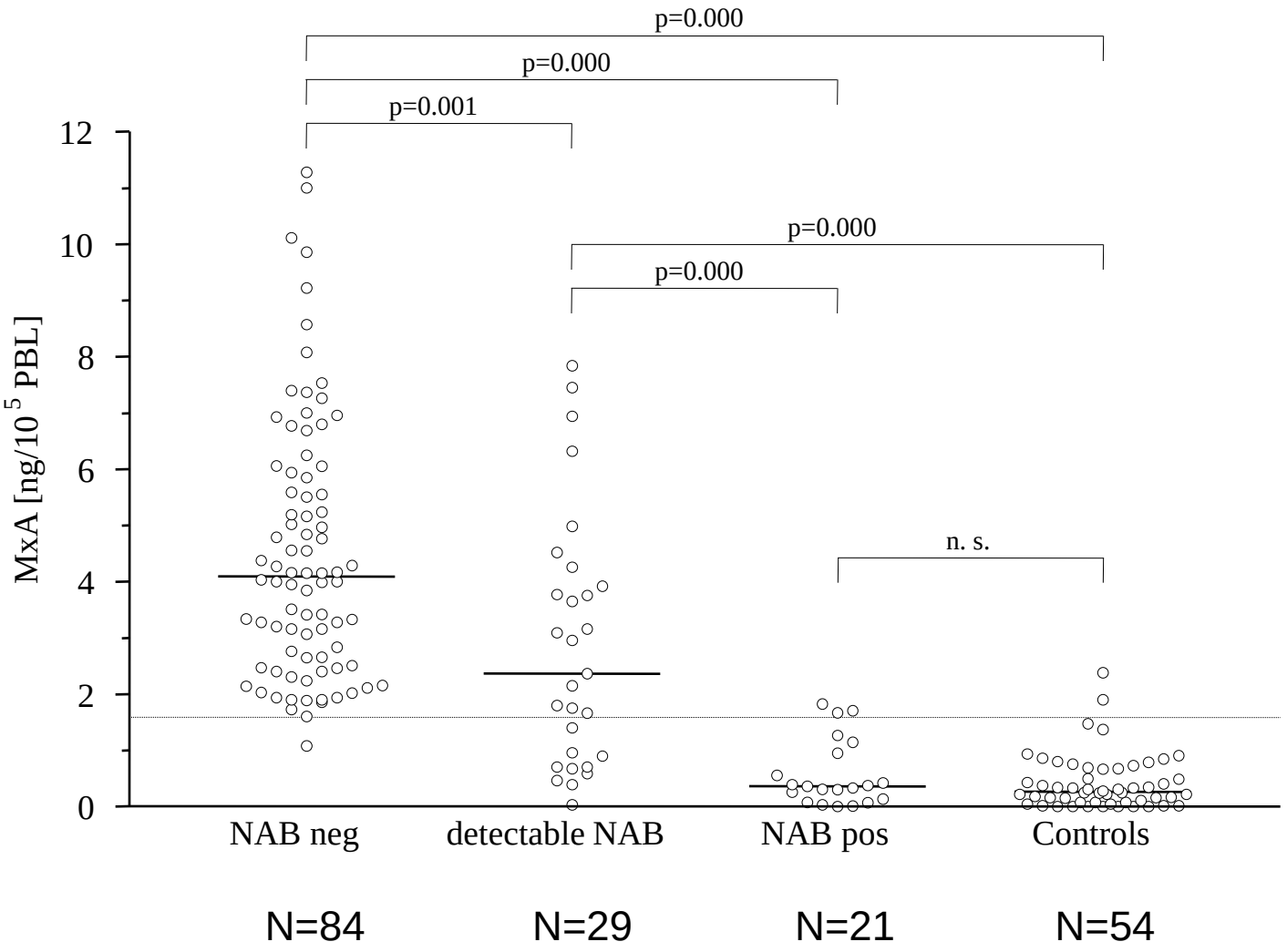
Bioassays

Antibodies

Binding assays

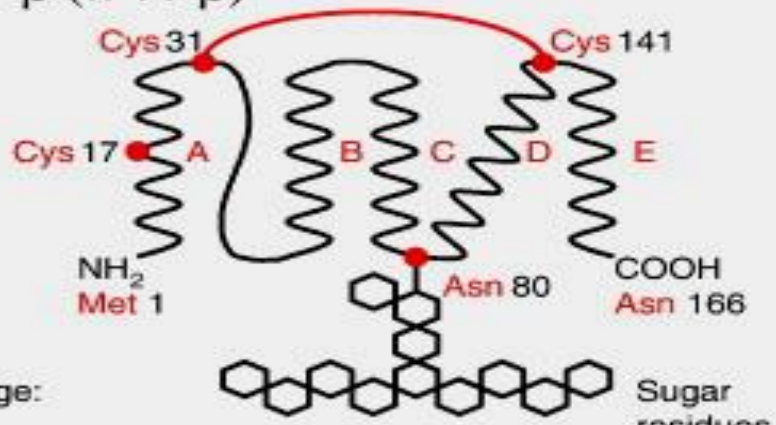


Bioactivity of IFN in NAB+ and NAB- patients



Interferon-β (IFN-β)

IFN-β1a
22.5 kDa

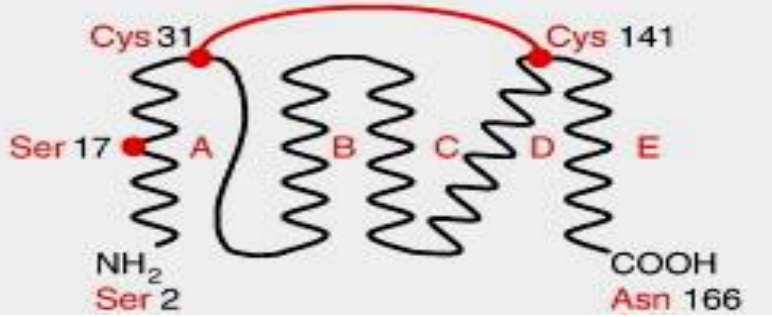


Disulphide bridge:
Cys 31-141

IFN-β1a: (glycosylated at Asn 80)

1 Met-Ser-Tyr-Asn-Leu-Leu-Gly-Phe-Leu-Gln
11 Arg-Ser-Ser-Asn-Phe-Gln-Cys-Gln-Lys-Leu
21 Leu-Trp-Gln-Leu-Asn-Gly-Arg-Leu-Glu-Tyr
31 Cys-Leu-Lys-Asp-Arg-Met-Asn-Phe-Asp-Ile
41 Pro-Glu-Glu-Ile-Lys-Gln-Leu-Gln-Gln-Phe
51 Gln-Lys-Glu-Asp-Ala-Ala-Leu-Thr-Ile-Tyr
61 Glu-Met-Leu-Gln-Asn-Ile-Phe-Ala-Ile-Phe
71 Arg-Gln-Asp-Ser-Ser-Ser-Thr-Gly-Trp-Asn
81 Glu-Thr-Ile-Val-Glu-Asn-Leu-Leu-Ala-Asn
91 Val-Tyr-His-Gln-Ile-Asn-His-Leu-Lys-Thr
101 Val-Leu-Glu-Glu-Lys-Leu-Glu-Lys-Glu-Asp
111 Phe-Thr-Arg-Gly-Lys-Leu-Met-Ser-Ser-Leu
121 His-Leu-Lys-Arg-Tyr-Tyr-Gly-Arg-Ile-Leu
131 His-Tyr-Leu-Lys-Ala-Lys-Glu-Tyr-Ser-His
141 Cys-Ala-Trp-Thr-Ile-Val-Arg-Val-Glu-Ile
151 Leu-Arg-Asn-Phe-Tyr-Phe-Ile-Asn-Arg-Leu
161 Thr-Gly-Tyr-Leu-Arg-Asn

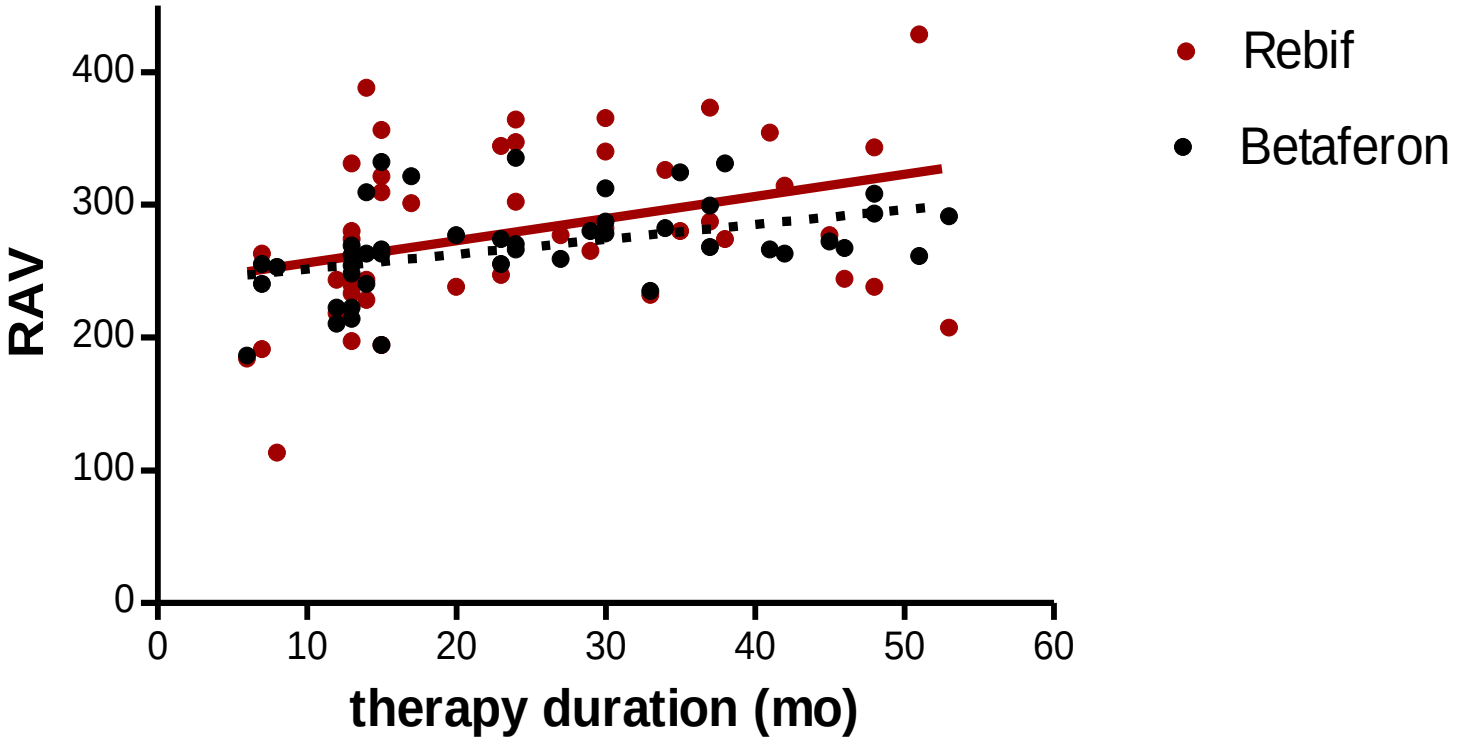
IFN-β1b
18.5 kDa



IFN-β1b:

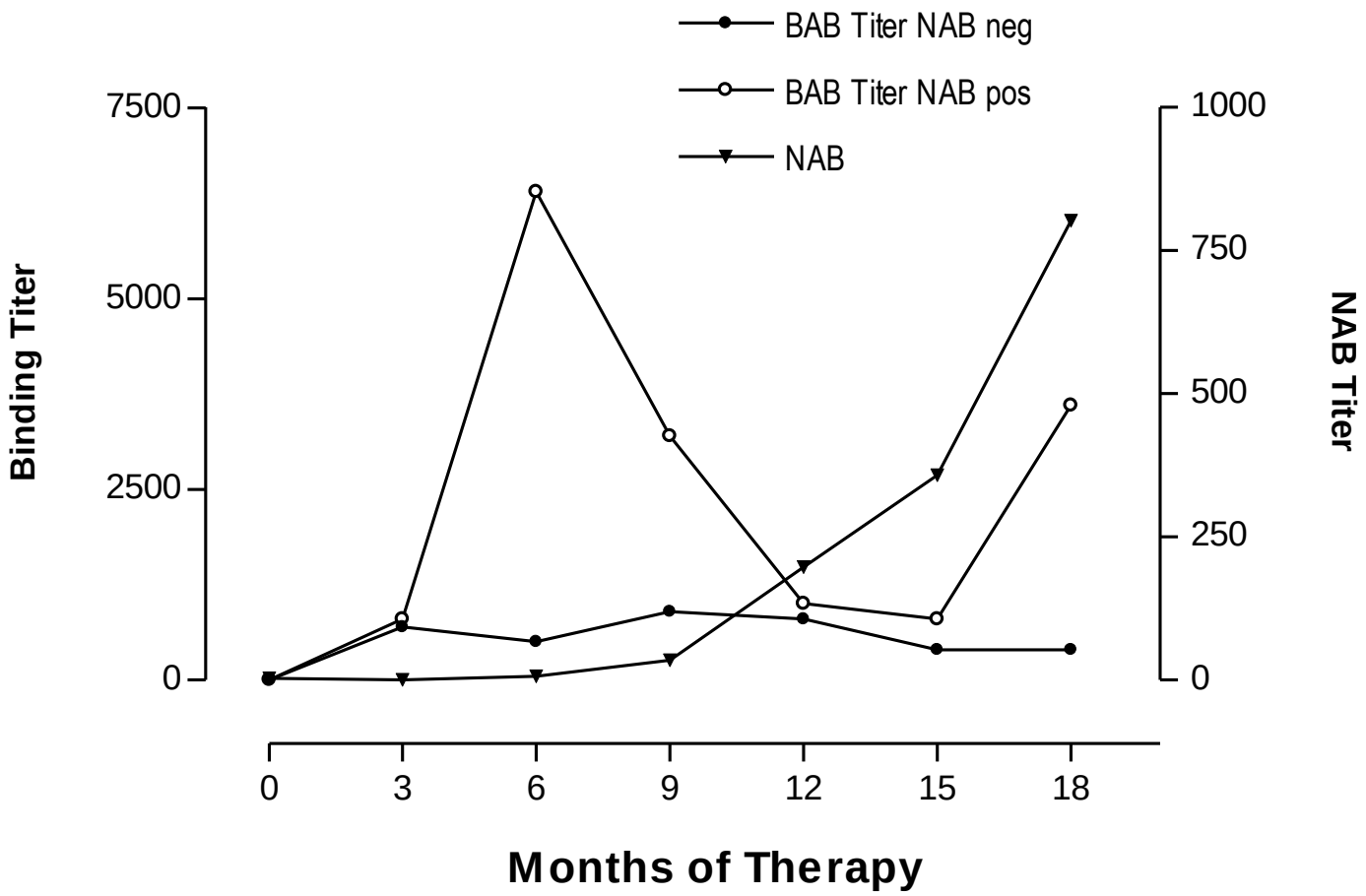
- Not glycosylated
- Met 1 lacking
- Cys 17 replaced by Ser 17

Affinity maturation
IFNb 1a vs 1b



Gneiss et al. J Neuroimmunol 174 (2006) 174–179

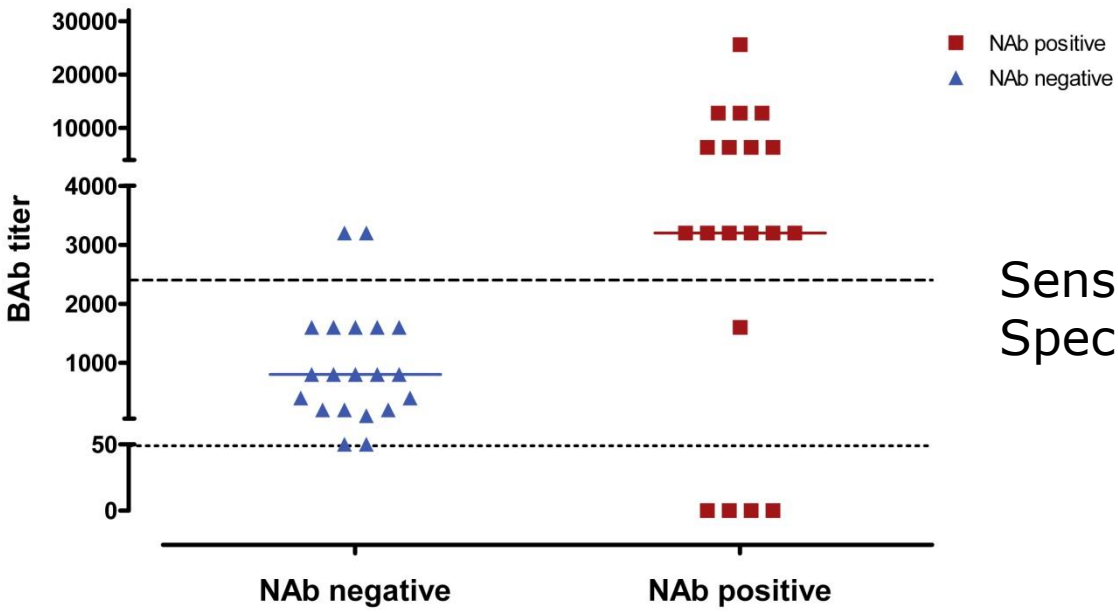
Binding titers in NAB+ and NAB- patients



Eur J Neurol. 2003;10:462-4

Predictiveness of BAB for NAB+

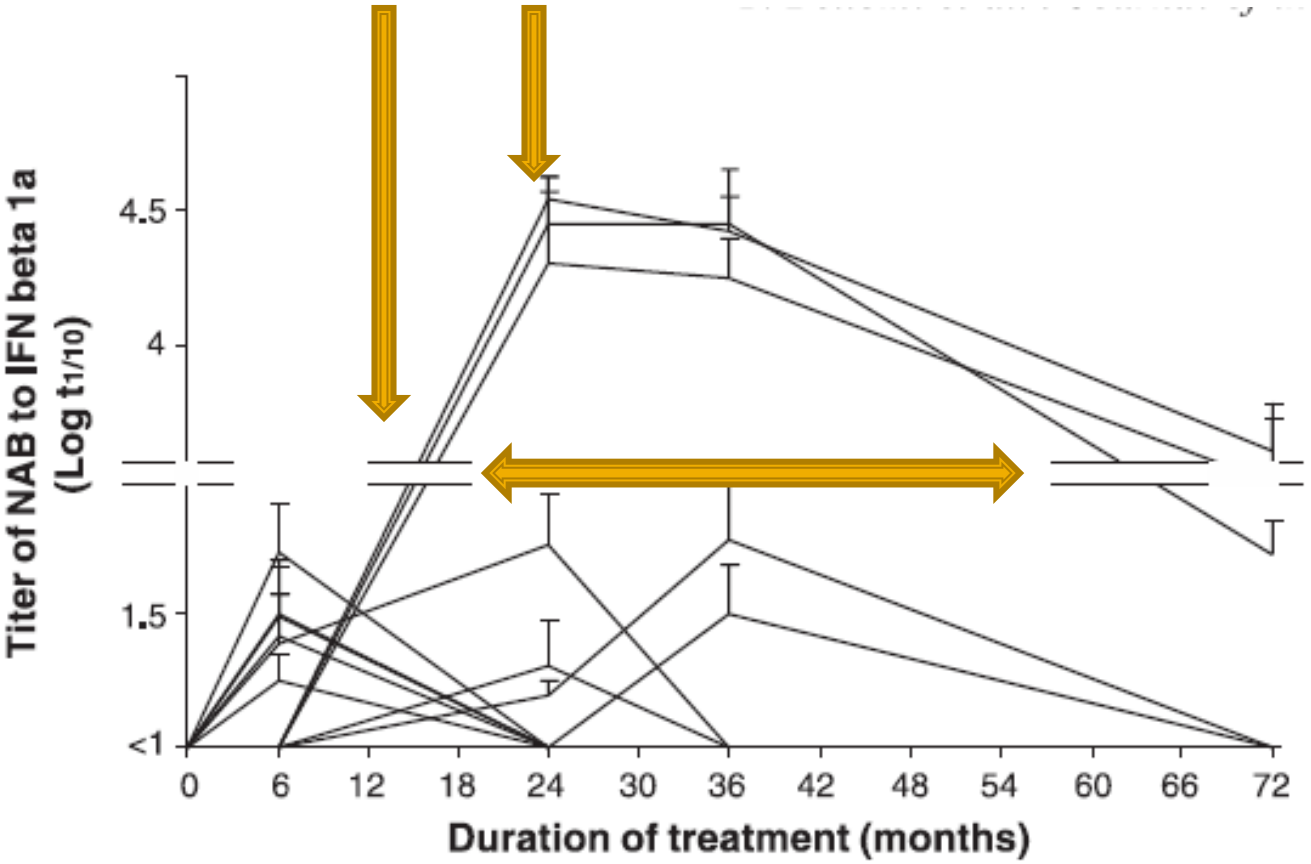
3 of 22 NAB+ @ mo 3



Sensitivity 73.7%
Specificity 98.5%

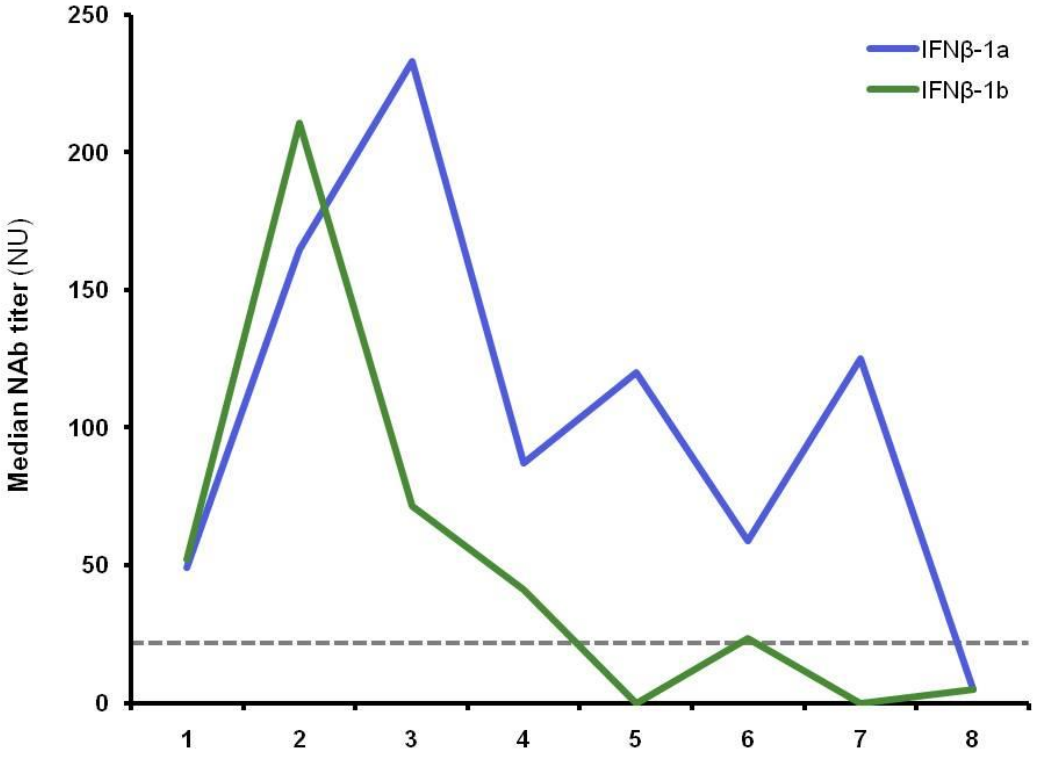
Mult Scler. 2014 Apr;20(5):577-87 -This work was supported by the European Union (grant number LSHB-CT-2005-018926)

NAB persistency depends on titer



Journal of the Neurological Sciences 215 (2003) 3 – 8

Long-term development of NAbs

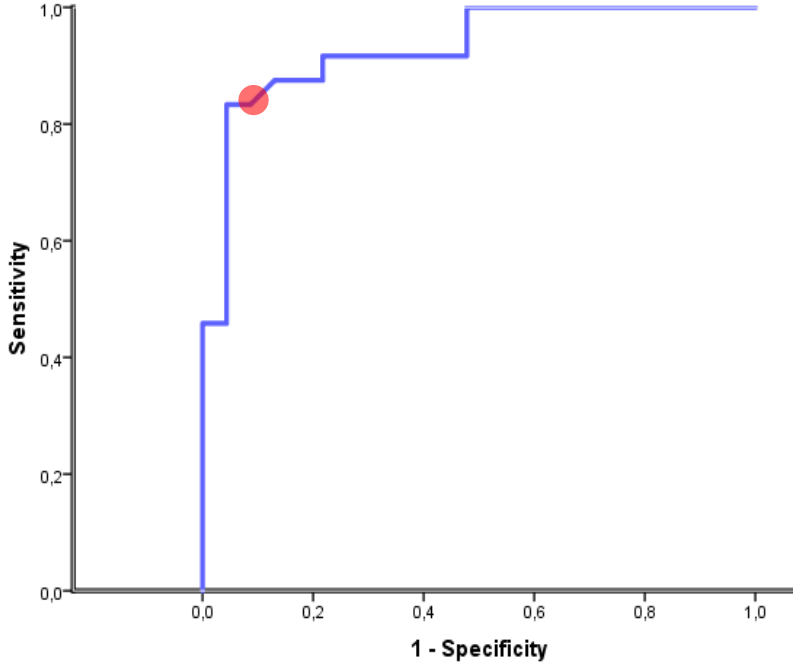


No. of patients								
IFNβ-1a	11	14	23	14	17	10	4	4
IFNβ-1b	15	16	18	14	17	10	7	2

Hegen et al. submitted

Predictive NAb cut-off titers

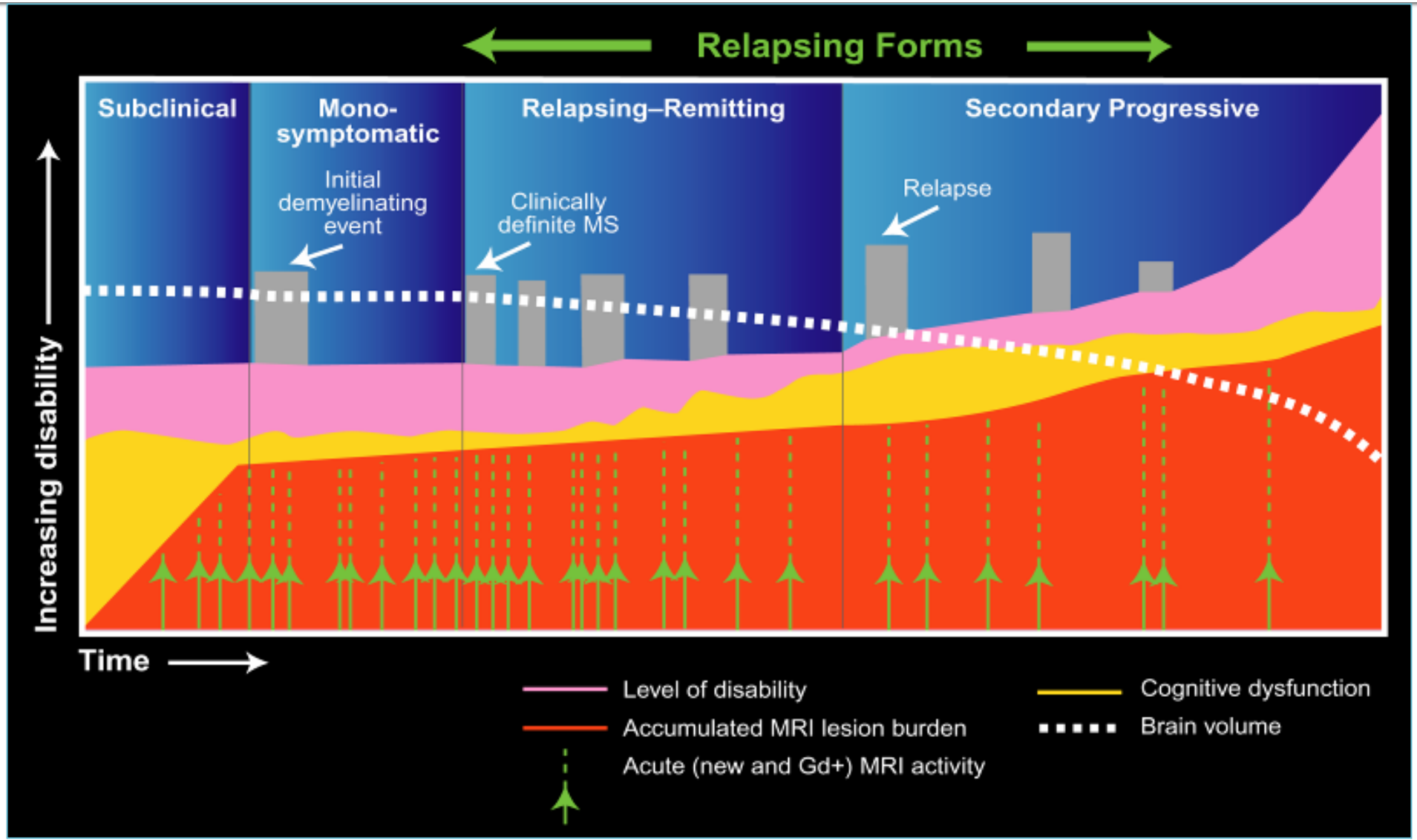
	All IFNβ	IFNβ-1a	IFNβ-1b
Sensitivity (%)	83.3	81.3	100
Specificity (%)	91.3	90.9	91.7
Cut-off NAb titer (TRU)	> 344	> 258	> 460

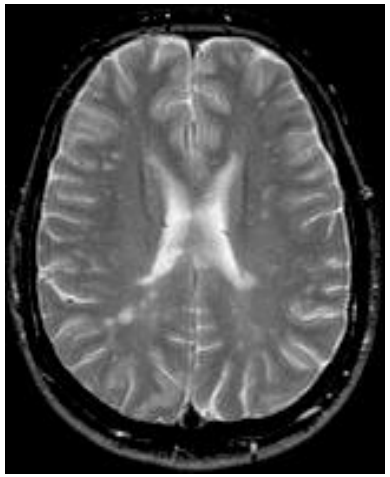


Hegen et al. submitted

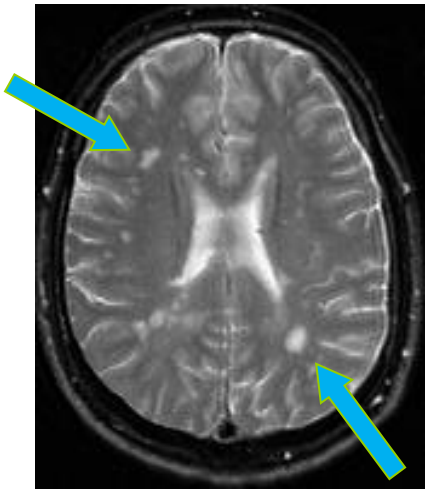
Clinical data

The natural course of MS....





New lesion formation (enlarging lesions)

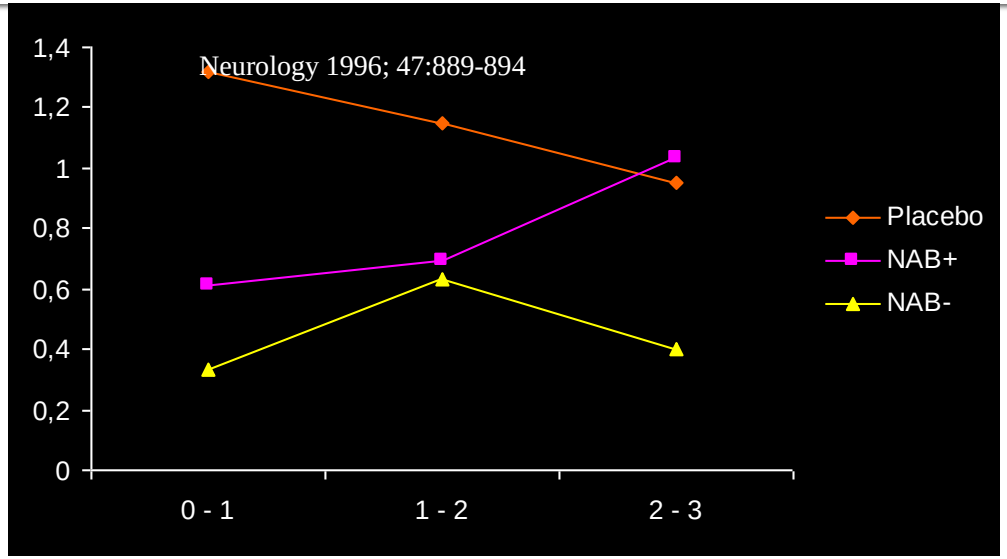


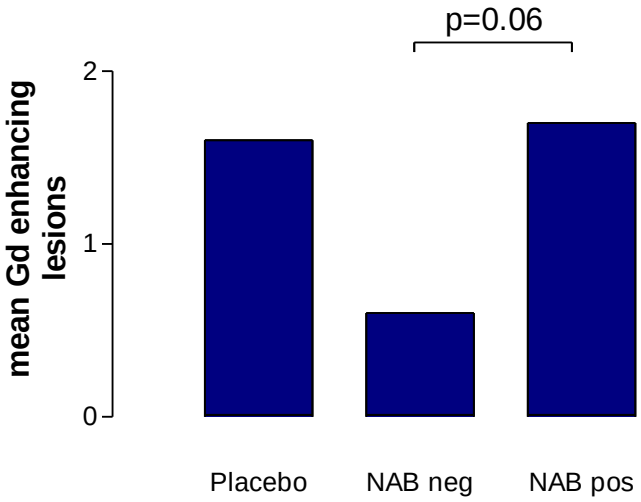
- Occurrence of new (focal) T2 lesions is consistent with new areas of MS related tissue damage
- Modifications by
  - Imaging parameters (sequence, slice thickness, etc.)
- Outcome variables
  - Number of new T2 lesions
  - Number of enlarging T2 lesions

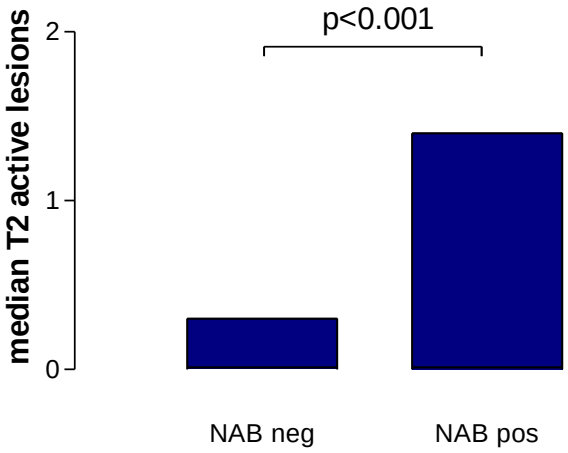
Number of newly active lesions
(new and enlarging T2 and new contrast enhancing lesions)

Number of new MRI lesions

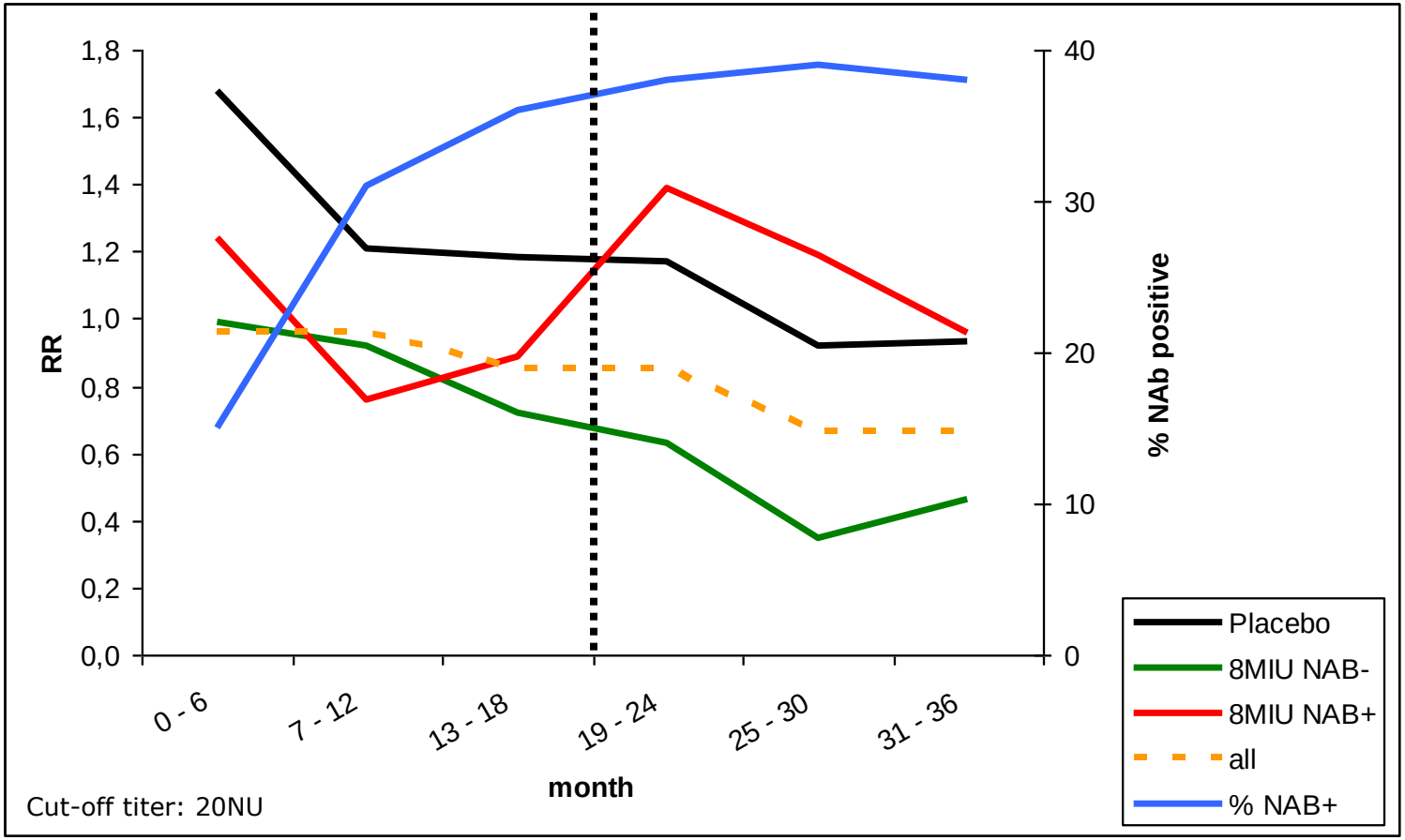
Betaferon trial 8MIU, Avonex trial, PRISMS-4





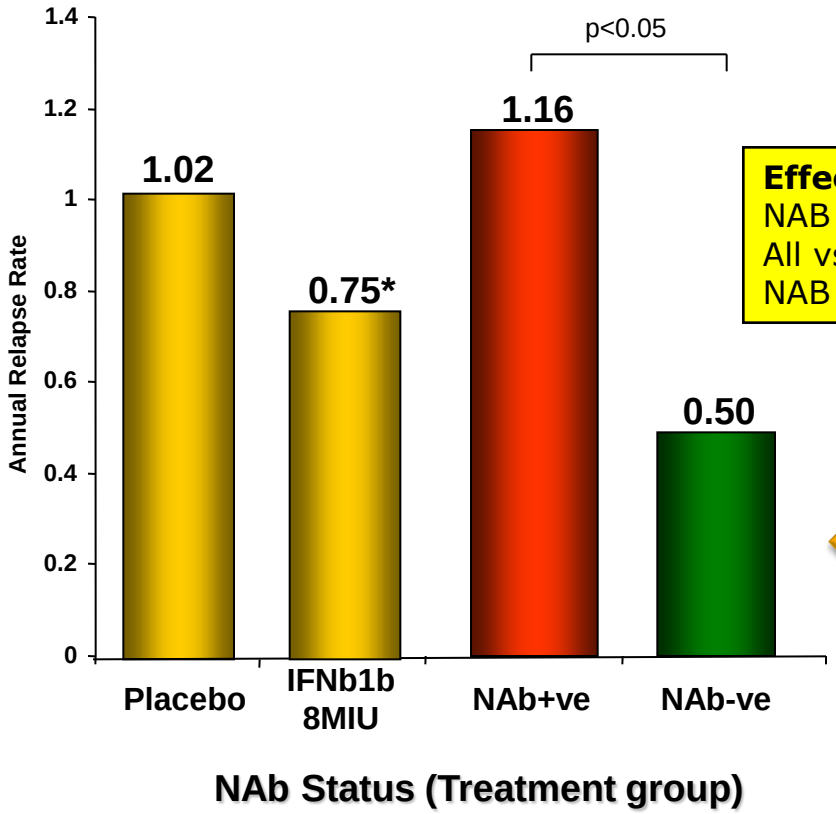


NAB timeline (Betaferon trial)



IFNB study group
Neurology 1996;47:889-894

IFNβ - Clinical Impact



Effect size year 3	RR
NAB pos vs Pl	+17%
All vs Pl	- 28%
NAB neg vs Pl	- 57%

Enriched patient population

*Neurology 1996;47:889-894; *approximately*

PRISMS-4: NABs and relapse rates

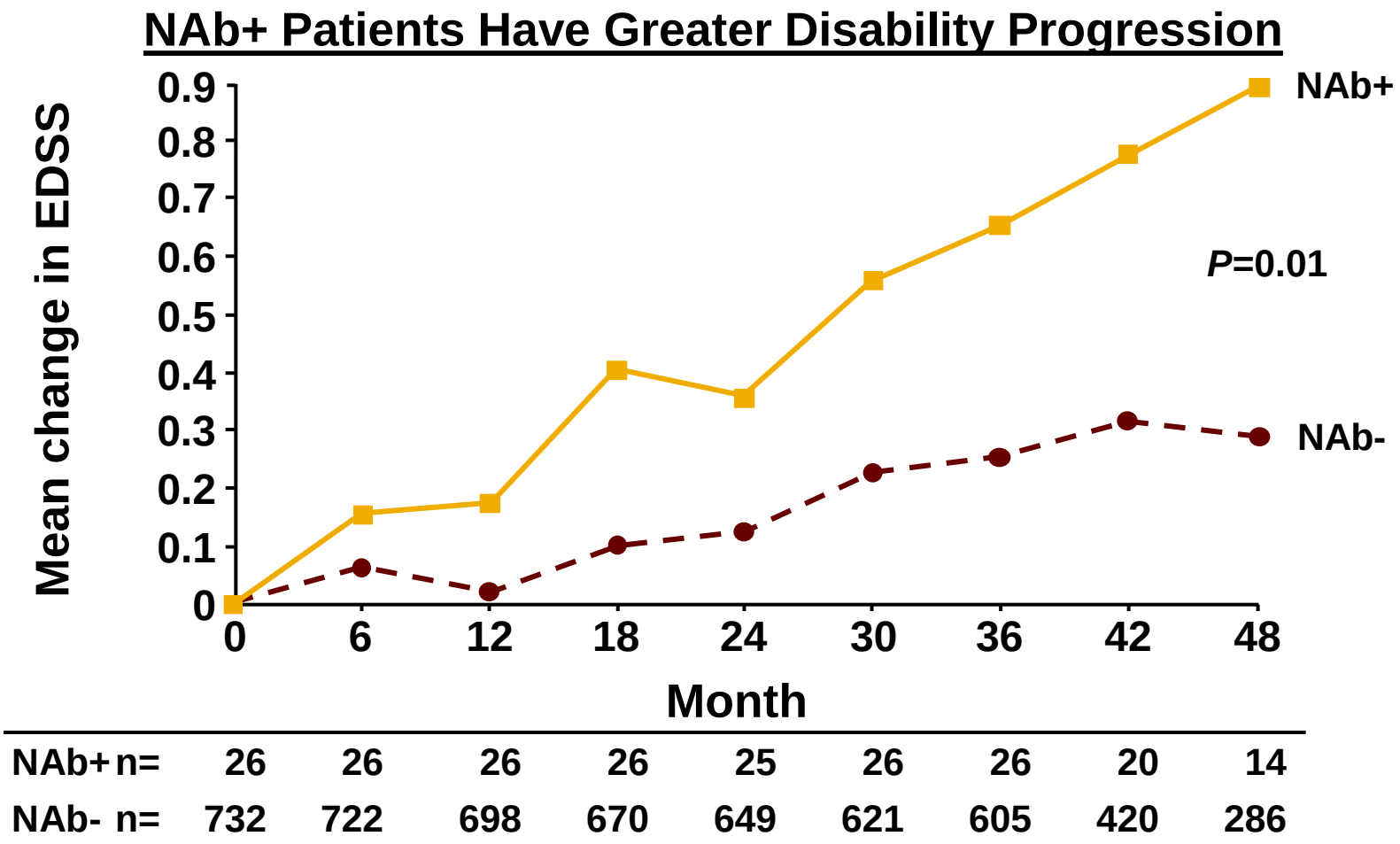
Table 2 *Relapse rate based on NAb status: PRISMS 4-year data*

Time	Mean annualized relapse rate		Adjusted relapse rate ratio NAb+/NAb− (95% CI)	*p* Value
	NAb− (22 and 44 μg) n = 278	NAb+ (22 and 44 μg) n = 90		
"Anytime positive" method*				
Years 1–4	0.74	0.82	1.00 (0.82–1.22)	0.98
Years 1–2	0.94	0.83	0.81 (0.65–1.01)	0.06
Years 3–4	0.51	0.82	1.41 (1.12–1.78)	0.004
"Interval positive" method†				
Years 1–4	0.74	0.86	1.21 (1.03–1.43)	0.02
Years 1–2	0.92	0.88	1.04 (0.84–1.28)	0.73
Years 3–4	0.52	0.85	1.60 (1.29–1.97)	<0.001

* Patients remain in same category throughout, regardless of when Ab first detected.
† Patients may change category if Ab status changes.

NEUROLOGY 2005;65:48–55

Effect of NAbs on Disability



Kappos et al. *Neurology.* 2005;65:40.

Titre-dependency of clincal effects

Table 4 *Percentage increase in relapse rates for eventually NAB+ subgroups in low- and high-NAB+ periods relative to NAB− periods**

	Increase in relapse rate					
	Low NAB+, cutoff titer 20			High NAB+		
Cutoff titer	% Increase	95% CI	*p* Value	% Increase	95% CI	*p* Value
"Once positive, always positive"						
100, n = 57	48	10, 98	0.01	39	0, 94	0.05
200, n = 45	41	5, 90	0.02	70	21, 140	0.002
400, n = 33	41	6, 89	0.02	115	54, 200	<0.001
"All switches considered"						
100, n = 57	29	−5, 75	0.10	21	−10, 62	>0.20
200, n = 45	23	−9, 65	0.17	46	7, 99	0.02
400, n = 33	22	−8, 62	0.17	82	37, 140	<0.001

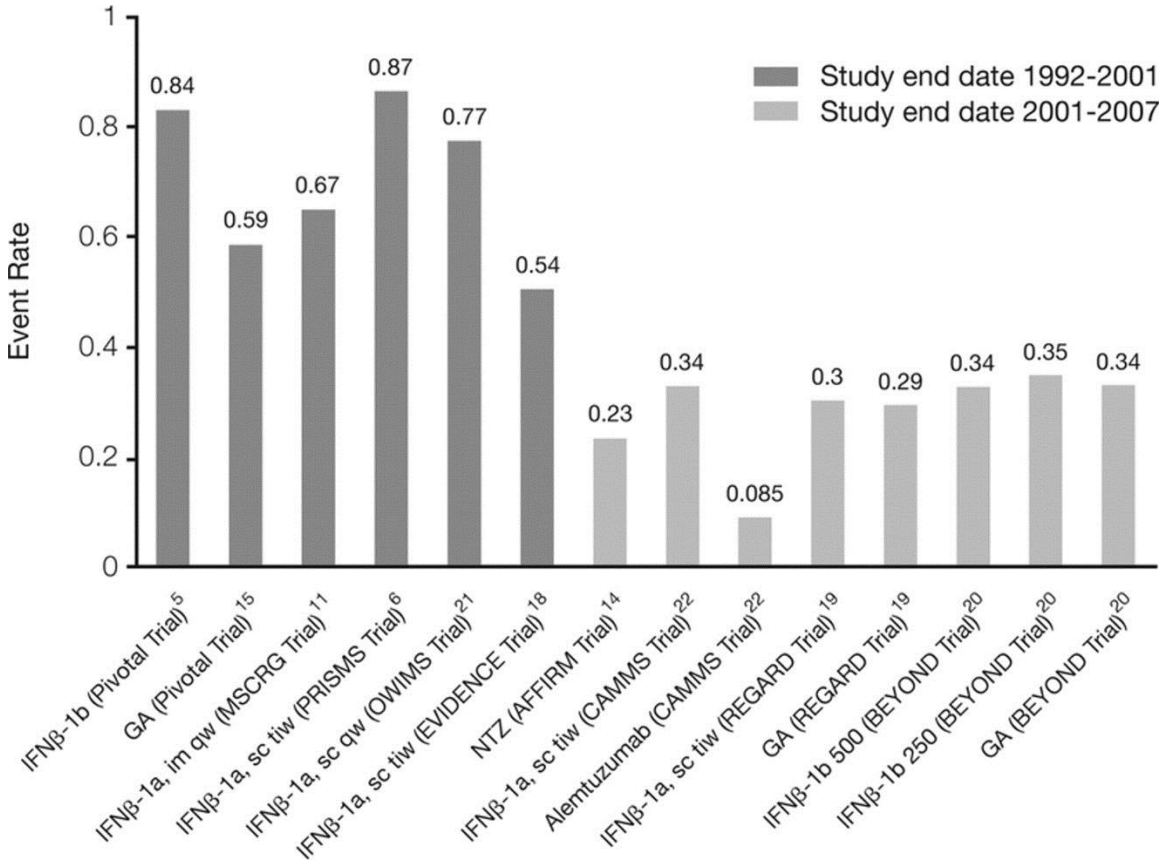
Patient counts refer to patients with high-NAB+ status, which differ from counts in eventually NAB+ subgroups for respective cutoff titers as no confirmation was required.

* Definition of low-NAB+ periods (confirmation required) refers to cutoff titer of 20. Definition of high-NAB+ periods (no confirmation required) refers to respective cutoffs.

NAB = neutralizing antibodies.

Neurology 2003;60:37-43.

Relapse rates in RCTs



Goodin, D. S. Neurology 2008;71:S8-S13

IFNb dose dependency

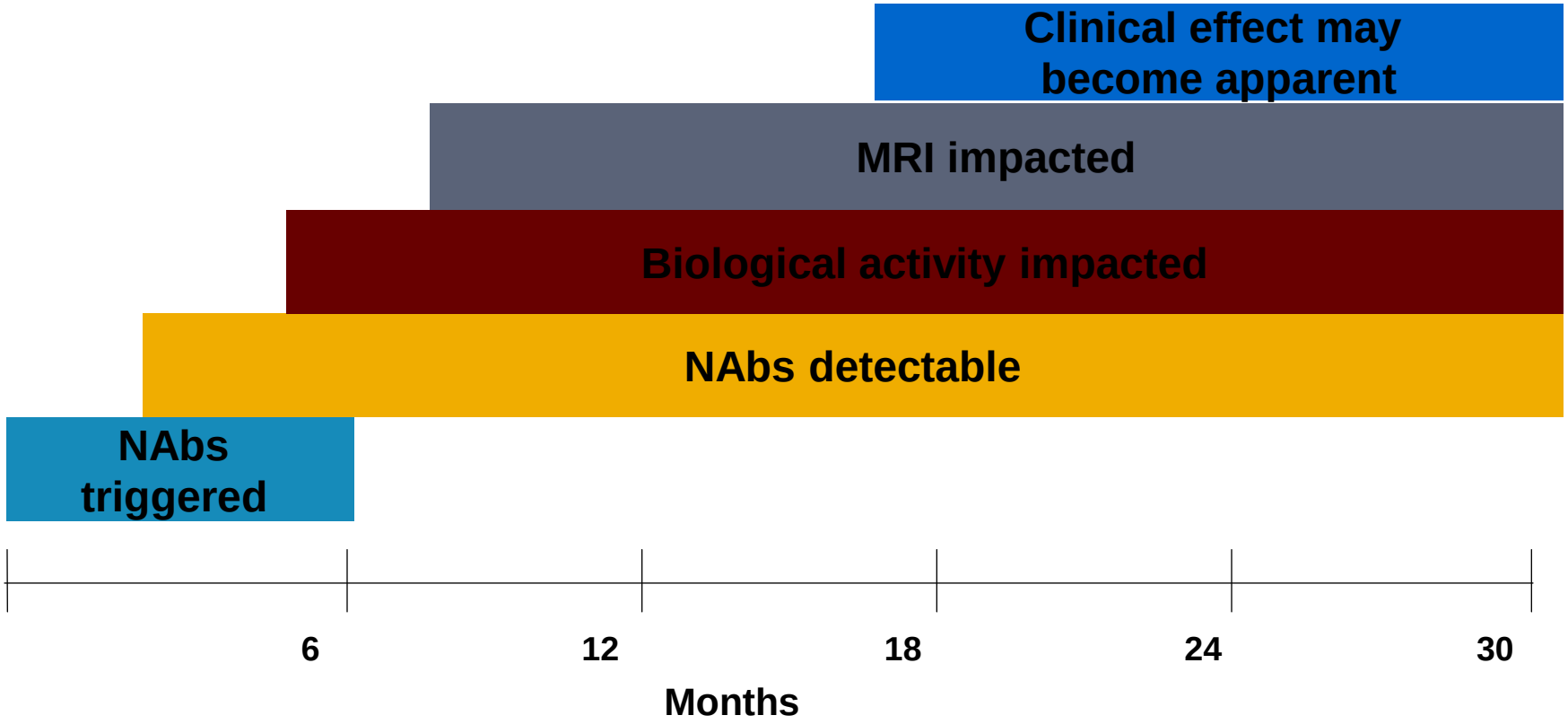
Table 2. Time-to-first relapse and time-to-confirmed EDSS progression using NAb status as a time-dependent covariate, as assessed by the Cox proportional hazards regression model*

Time period	IFNβ-1b, 250 μg	*p*-value†	IFNβ-1b, 500 μg	*p*-value†
Time to first relapse: HR (95% CI)				
Positive (≥20 NU/ml) vs. negative (<20 NU/ml)	1.29 (0.97 to 1.72)	0.09	1.39 (1.04 to 1.85)	0.03
Single model				
Low (≥20 to 100 NU/ml) vs. negative	1.36 (0.96 to 1.92)	0.08	1.09 (0.73 to 1.62)	0.68
Medium (≥100 to 400 NU/ml) vs. negative	1.37 (0.82 to 2.27)	0.23	1.53 (0.95 to 2.48)	0.08
High (≥400 NU/ml) vs. negative	0.95 (0.48 to 1.89)	0.89	1.99 (1.25 to 3.16)	0.004
Medium to high (≥100 NU/ml) vs. negative	1.19 (0.78 to 1.82)	0.42	1.74 (1.22 to 2.48)	0.002

Conclusion:
……On MRI measures, the impact was consistent and convincing, whereas on clinical measures a negative impact of NAbs was not found…….

Mult Scler published online 27 September 2011
DOI: 10.1177/1352458511418629

When Do the Clinical Consequences of NAbs Become Apparent?



Adapted from Sørensen et al. *Eur J Neurol*. 2005;12:817; Bertolotto et al. *J Neurol Neurosurg Psychiatry*. 2002;73:148; and Giovannoni et al. *J Neurol Neurosurg Psychiatry*. 2002;73:465; Panitch et al. *Neurology*. 2002;59:1496.

Conclusion

- nADA are predictive of clinical non-response
- nADA are the best and only surrogate marker for Rx (non) response to date
- Requires routine testing at least in high immunogenic drugs
- Realtively late with IFN
  - Cut off depends on Rx preparation
    - >460 NU for Betaferon
    - >260 NU for IFNb-1a