
Clinical Perspective on Tysabri

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Response to Questions from Committee Members

Incidence of Infection, Malignancy, and Death

Placebo-Controlled and Cumulative MS Experience

	Placebo-Controlled		Cumulative Experience N=2283
	Placebo n=1135	Natalizumab n=1617	
Overall infection, %	73.9	73.7	65.6
Herpes infection	6.1	7.2	6.1
Serious infection	2.3	2.4	2.2
Serious herpes infection	0	0	0
Opportunistic infection	0	0.12	0.13
PML	0	0.06	0.09
Malignancy	1.3	0.7	0.7
Death	0.3	0.1	0.3

Ability to Detect a Relative Risk of 1.5 for Various Adverse Events

5000 Patients, 5-Year Follow Up, 20% Annual Drop Out, 13500 Patient-Years

Event	Rate in Placebo- Controlled MS Studies (Per 100 Yrs)
Serious infection	1.40
Malignancy	0.38
Breast cancer	0.14
Serious opportunistic infections	0.07

Study fully powered to detect small increases
in rare adverse events

Number Needed to Treat to Obtain Favorable Outcome Over 2 Years

Natalizumab + Avonex[®]

	Placebo	Active Drug	Relative Treatment Effect	Absolute Difference	NNT*
Annualized relapse rate	0.75	0.34	55%	0.41	2
Proportion relapsing	0.68	0.46	32%	0.22	5
Proportion progressing	0.29	0.23	21%	0.06	17

* NNT = 1/Absolute rate (or risk) reduction; values always rounded up to full integer

Number Needed to Treat to Obtain Favorable Outcome Over 2 Years

Natalizumab

	Placebo	Active Drug	Relative Treatment Effect	Absolute Difference	NNT*
Annualized relapse rate	0.78	0.26	68%	0.52	1
Proportion relapsing	0.54	0.28	48%	0.26	4
Proportion progressing	0.29	0.17	41%	0.12	9

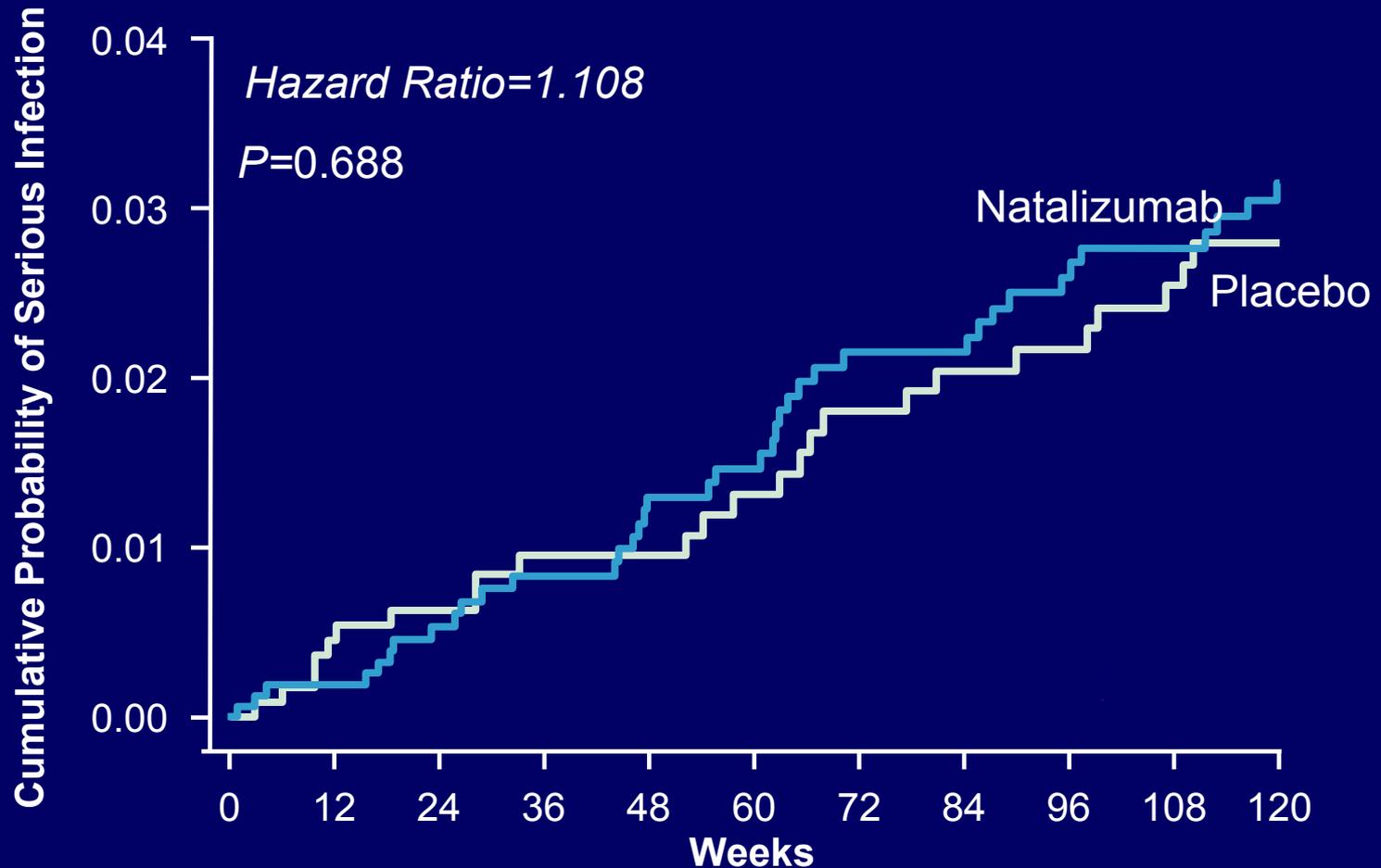
* NNT = 1/Absolute rate (or risk) reduction; values always rounded up to full integer

Impact of Natalizumab

- ◆ For every 1000 patients treated with natalizumab for 2 years, compared to no treatment, there will be:
 - 1000 fewer relapses
 - 260 more patients remaining free of relapse
 - 120 more patients remaining free of progression by 1-point on the EDSS scale
 - 60 fewer hospitalizations due to MS relapse
 - 40 fewer patients requiring aids for ambulation

Risk of Serious Infection

Placebo-Controlled Studies of MS



Number of Patients at Risk

Placebo	1135	1115	1023	936	902	837	822	805	795	788	617
Natalizumab	1617	1579	1412	1328	1298	1169	1154	1139	1129	1115	898

Hypersensitivity Reactions on Natalizumab

- ◆ 25 (4%) patients with 27 hypersensitivity reactions
 - 12 patients had urticaria or generalized urticaria
 - 1 had allergic dermatitis
 - 8 had reactions called “hypersensitivity”*
 - 5 had reactions called “anaphylactic/anaphylactoid” (urticaria+other signs)
- ◆ 15 reactions occurred on second infusion
- ◆ 8 patients (1.3%) with reactions reported as serious
 - 5 “anaphylactic/anaphylactoid”
 - 3 called “hypersensitivity” NOS

*1 patient who had a “hypersensitivity” reaction was redosed and then had an “anaphylactic/anaphylactoid” reaction

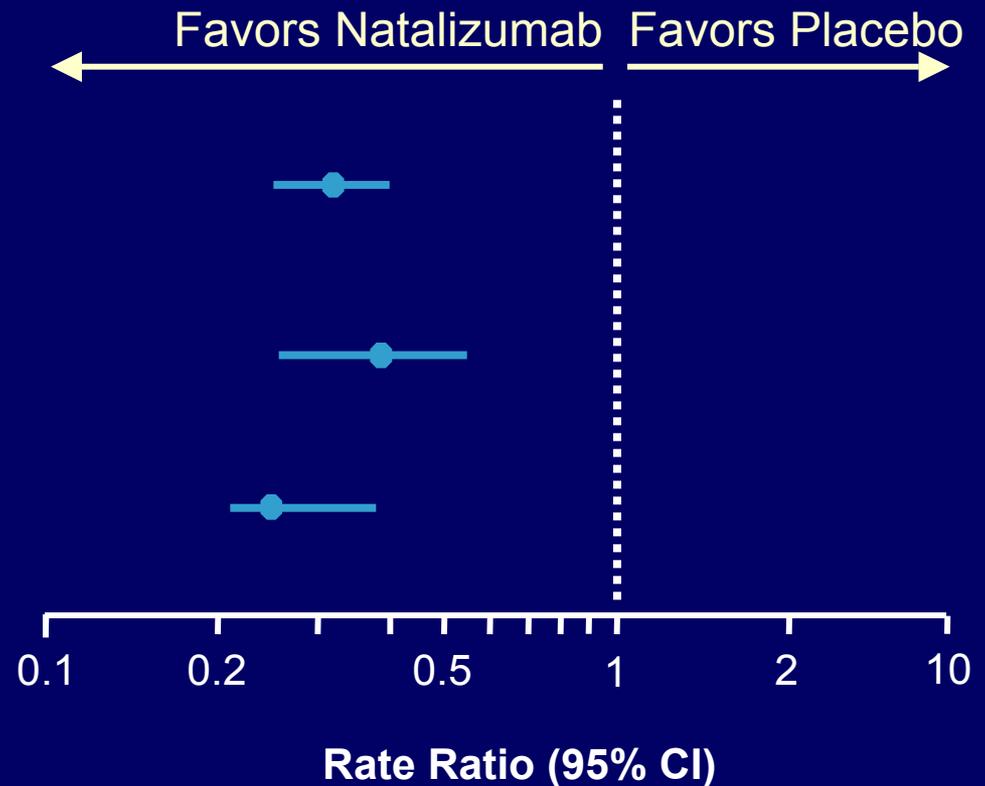
Annualized Relapse Rate Over 2 Years By Gd+ Lesions at Baseline

Patient Population
(natalizumab, placebo)

All patients (627, 315)

0 Gd+ lesions (308, 172)

≥1 Gd+ lesions (319, 143)

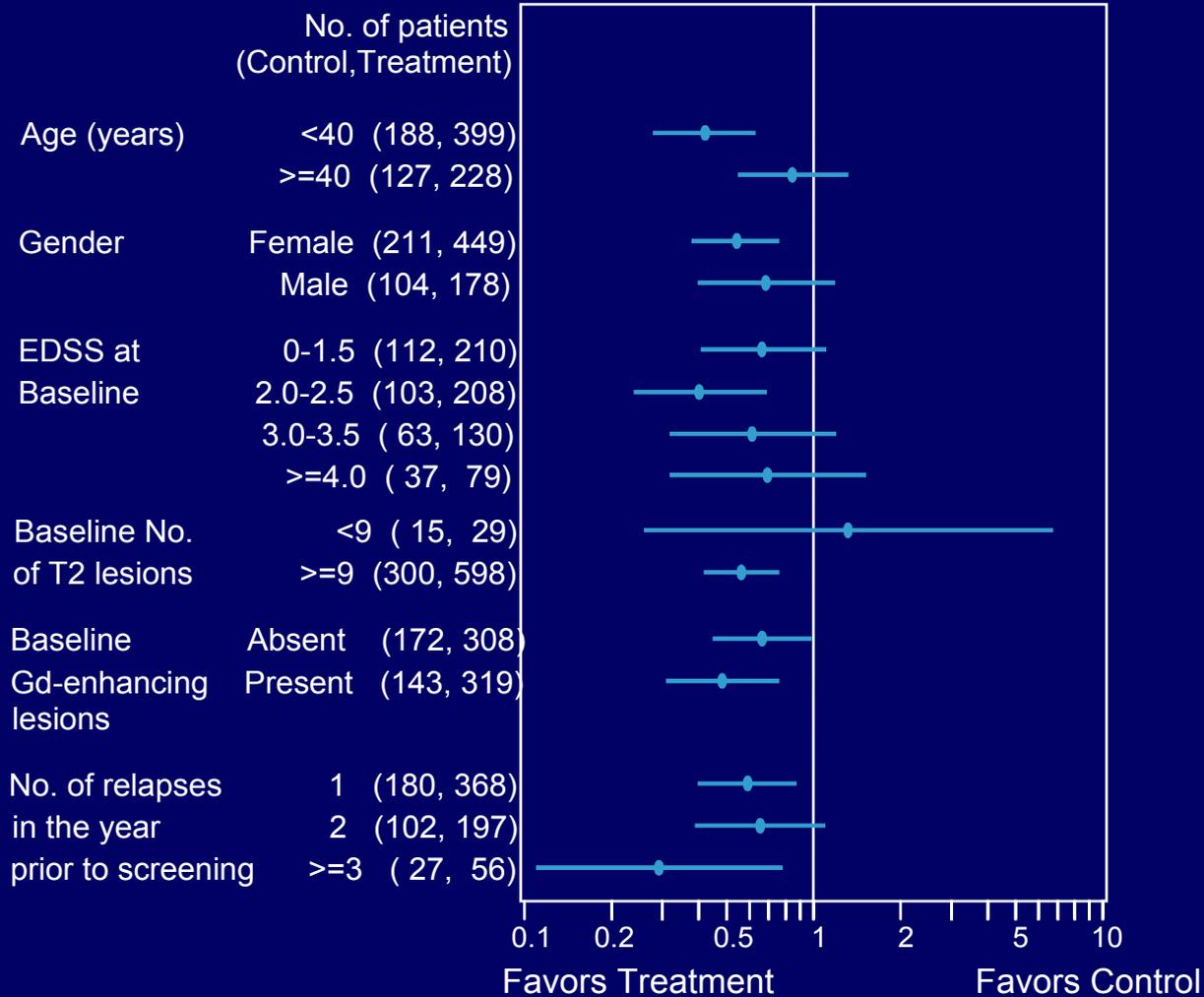


3-1: Natalizumab Treatment Duration and Exposure

	Multiple sclerosis	Crohn's disease	Total
<i>Exposed at any time</i>			
Number exposed to natalizumab	2321 (100)	1598 (100)	3919 (100)
Number exposed for 1 year or more	1254 (54)	689 (43)	1943 (50)
Number exposed for 2 years or more	1121 (48)	319 (20)	1440 (37)
Number exposed for 3 years or more	111 (5)	35 (2)	146 (4)
Mean exposure (years)	1.64	1.06	1.40
Median exposure (years)	1.65	0.69	0.98
Overall exposure (person-years)	3804	1701	5505
<i>Placebo-controlled studies</i>			
Number exposed to natalizumab	1617 (100)	1182 (100)	2799 (100)
Number exposed for 1 year or more	1189 (74)	0	1189 (42)
Number exposed for 2 years or more	1121 (69)	0	1121 (40)
Mean exposure (years)	1.80	0.36	1.19
Median exposure (years)	2.30	0.39	0.46
Overall exposure (person-years)	2910	425	3336

NOTE: Numbers in parentheses are percentages.

2-10: Hazard Ratios (With 95% CIs) for Time to Onset of Sustained Progression in Disability in Sub-Populations ¹¹⁵



2-9: Ratios (Natalizumab:Placebo) of Relapse Rates (With 95% CIs) in Sub-Populations

