
Natalizumab Efficacy

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Multiple Sclerosis

- ◆ US prevalence: ~ 400,000
- ◆ Females:males: 2:1
- ◆ Median age of onset: 30 years
- ◆ ~85% begin as relapsing form
- ◆ Pathophysiology
 - Inflammation, white matter > gray matter
 - Autoimmune etiology
 - Sequelae: demyelination, axonal transection, neurodegeneration

Impact on Patients

◆ Physical Disability

- Median time to requiring cane/crutch: 15 years
- Median time to wheelchair confinement: 25 years
- During relapsing-remitting stage, unresolved relapses are major contributor

◆ Cognitive Dysfunction

- Prevalence: 43 to 65%
- Affects employment, activities of daily living, family and social contacts

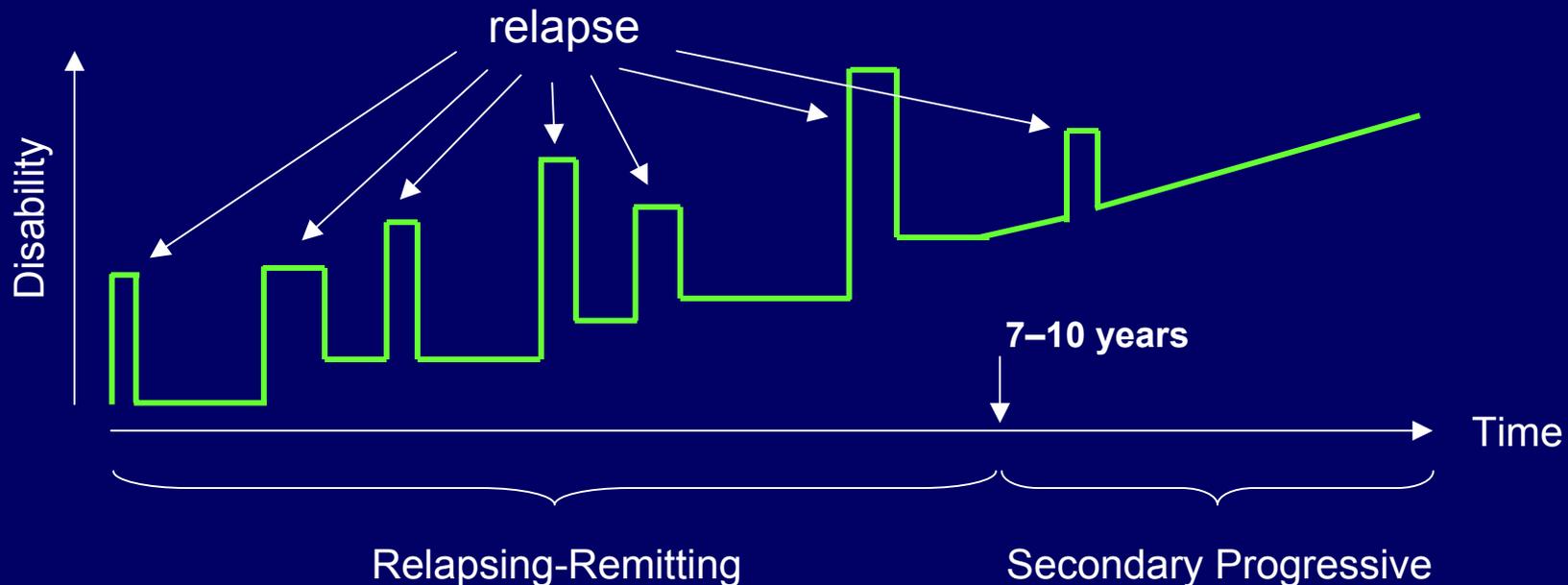
◆ Life shortening

- 5- to 7-year decrease in life expectancy
- 2- to 7-fold increase in suicide risk
- ~50% MS patients die of disease-related causes

Outcomes Measured in MS Clinical Trials

- ◆ Clinical Relapses
- ◆ Disability Progression
- ◆ MS lesions by Magnetic Resonance Imaging

MS Relapses



- ◆ Approximately 40% of relapses result in residual disability
- ◆ Relapse frequency in initial stages predicts future disability

The Expanded Disability Status Scale (EDSS)



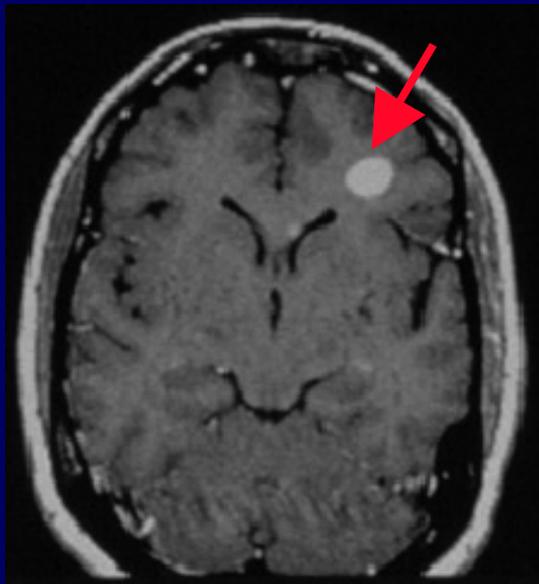
- ◆ 2-step (1 point) increase considered clinically significant

The Multiple Sclerosis Functional Composite (MSFC)

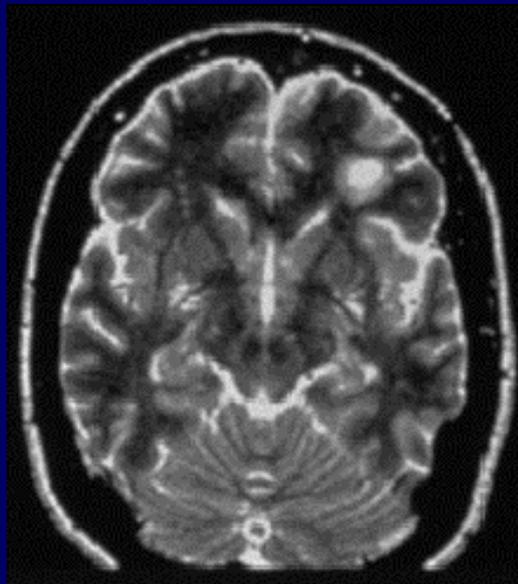
- ◆ Alternative scale that correlates with and supplements EDSS
- ◆ Composite score of
 - Ambulation: Timed 25-ft Walk
 - Upper Extremity Dexterity: 9-Hole Peg Test
 - Cognition: Paced Auditory Serial Addition Test (PASAT)
- ◆ Lower scores indicate worsening

MRI Assessment of MS Lesions

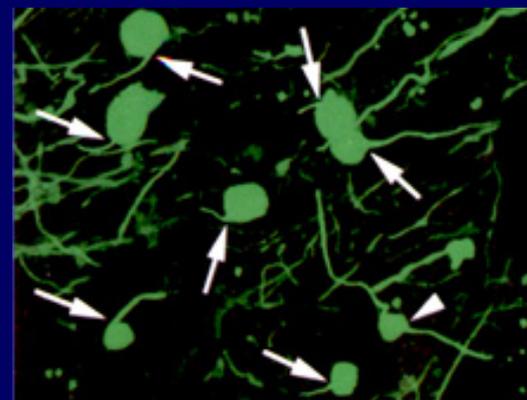
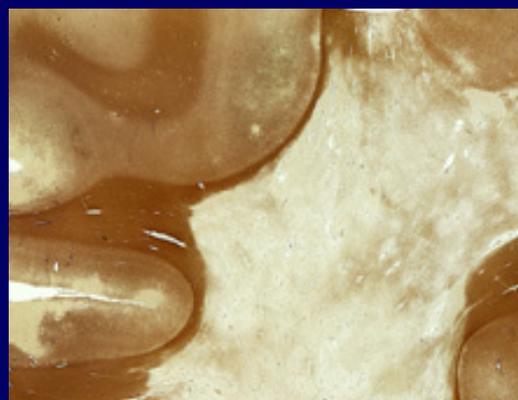
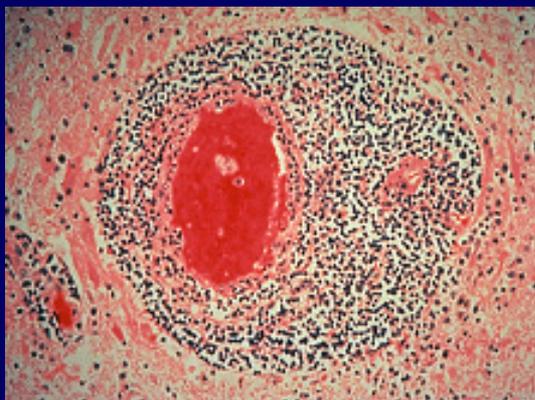
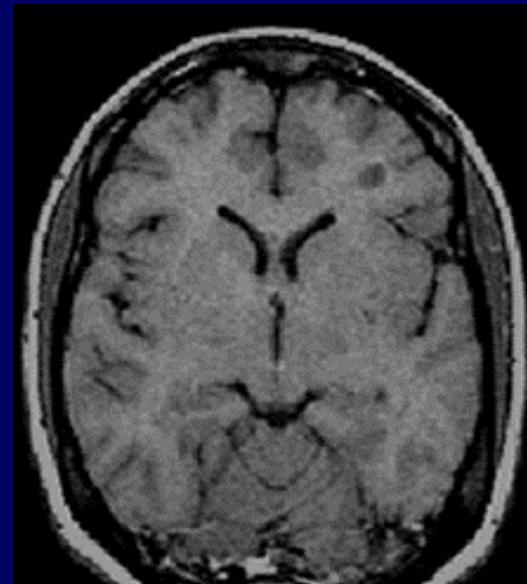
Gd-enhancing



T2-hyperintense



T1-hypointense



Disease-Modifying Therapies Approved for Relapsing Forms of MS

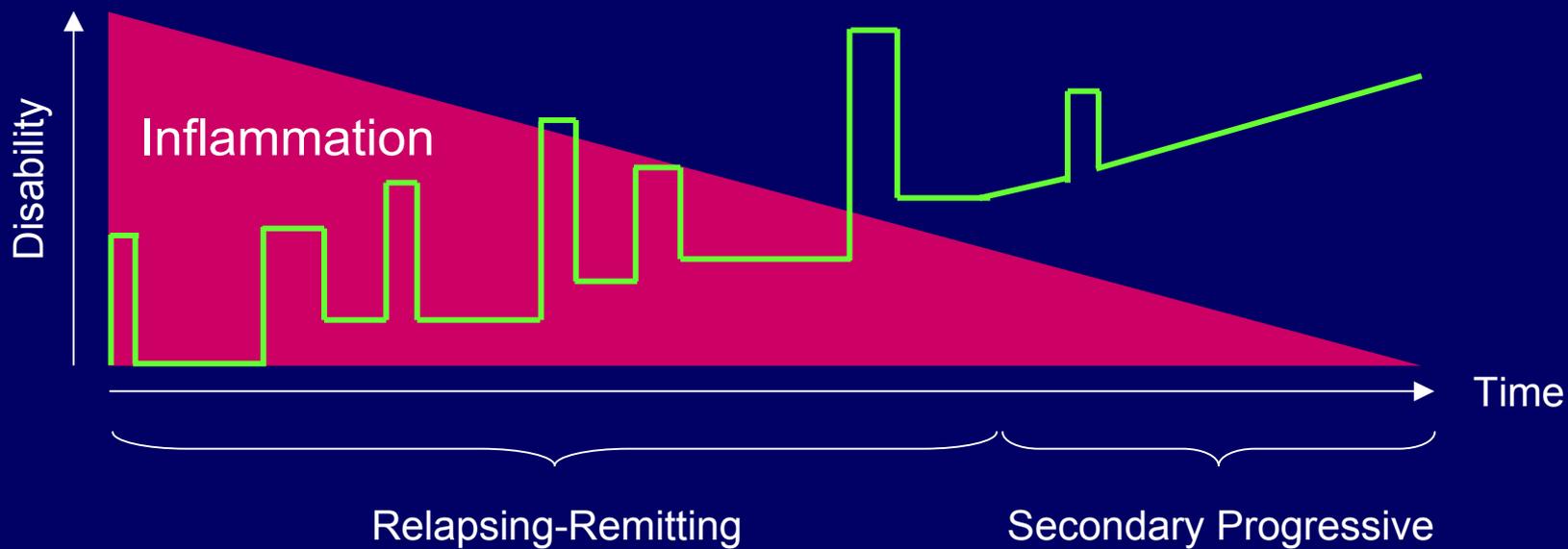
	Reduction in Relapse Rate	Reduction in Disability Progression	Side Effects
Interferon-β	29 – 32%	30 – 37%	<ul style="list-style-type: none"> • Injection-site reactions • Flu-like symptoms • Depression • Liver toxicity
Glatiramer Acetate	29%	Not significant	<ul style="list-style-type: none"> • Injection-site reactions • Lipoatrophy • Acute systemic reactions

Unmet Need in MS

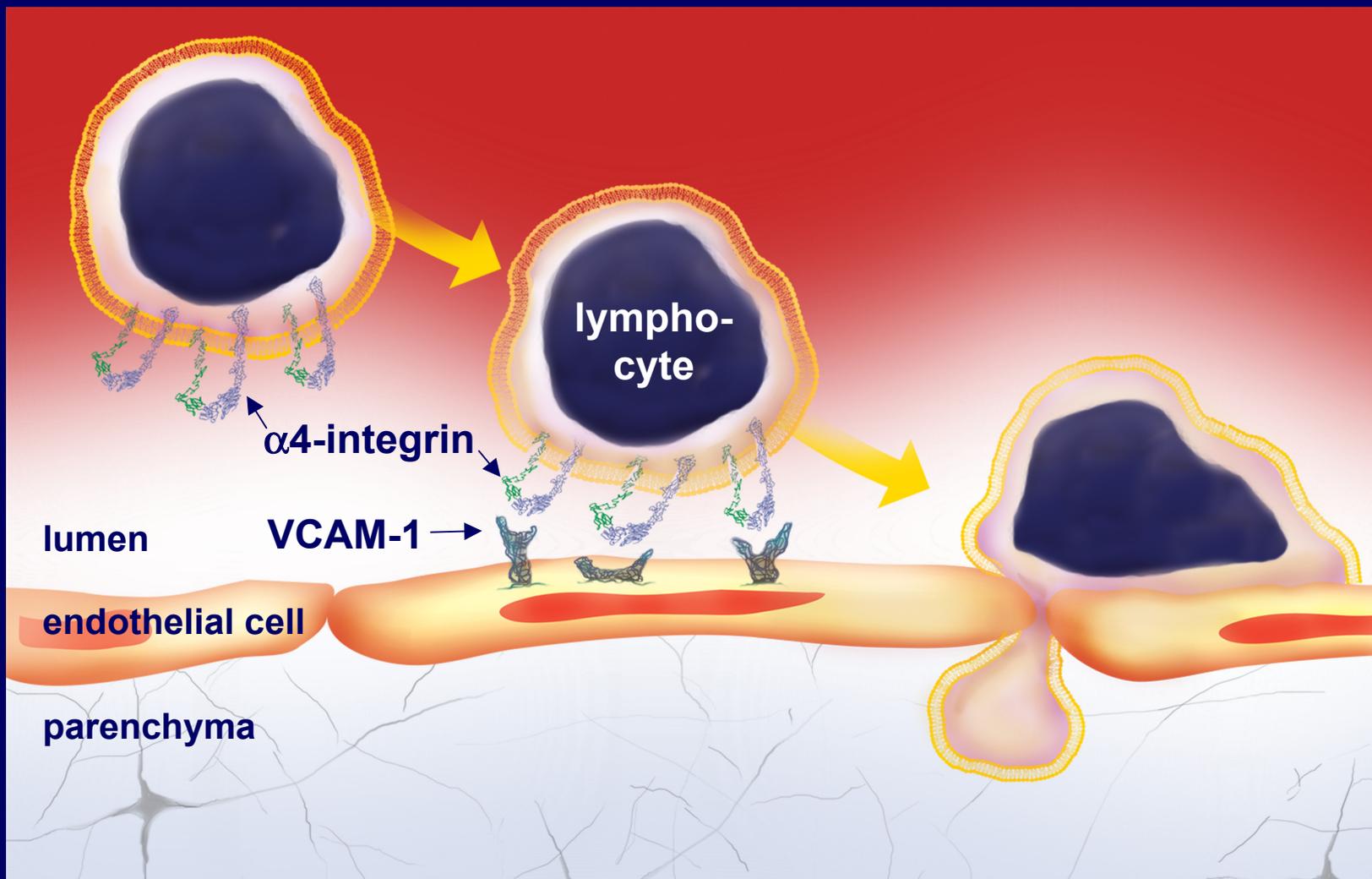
- ◆ Most patients experience disease progression on therapy
 - 62 to 75% relapse within 2 years
 - 20 to 27% worsen by ≥ 1 point on EDSS within 2 years

- ◆ Adherence to therapy is poor
 - 15 to 20% of patients discontinue therapy annually
 - Approximately 50,000 patients have attempted treatment but quit

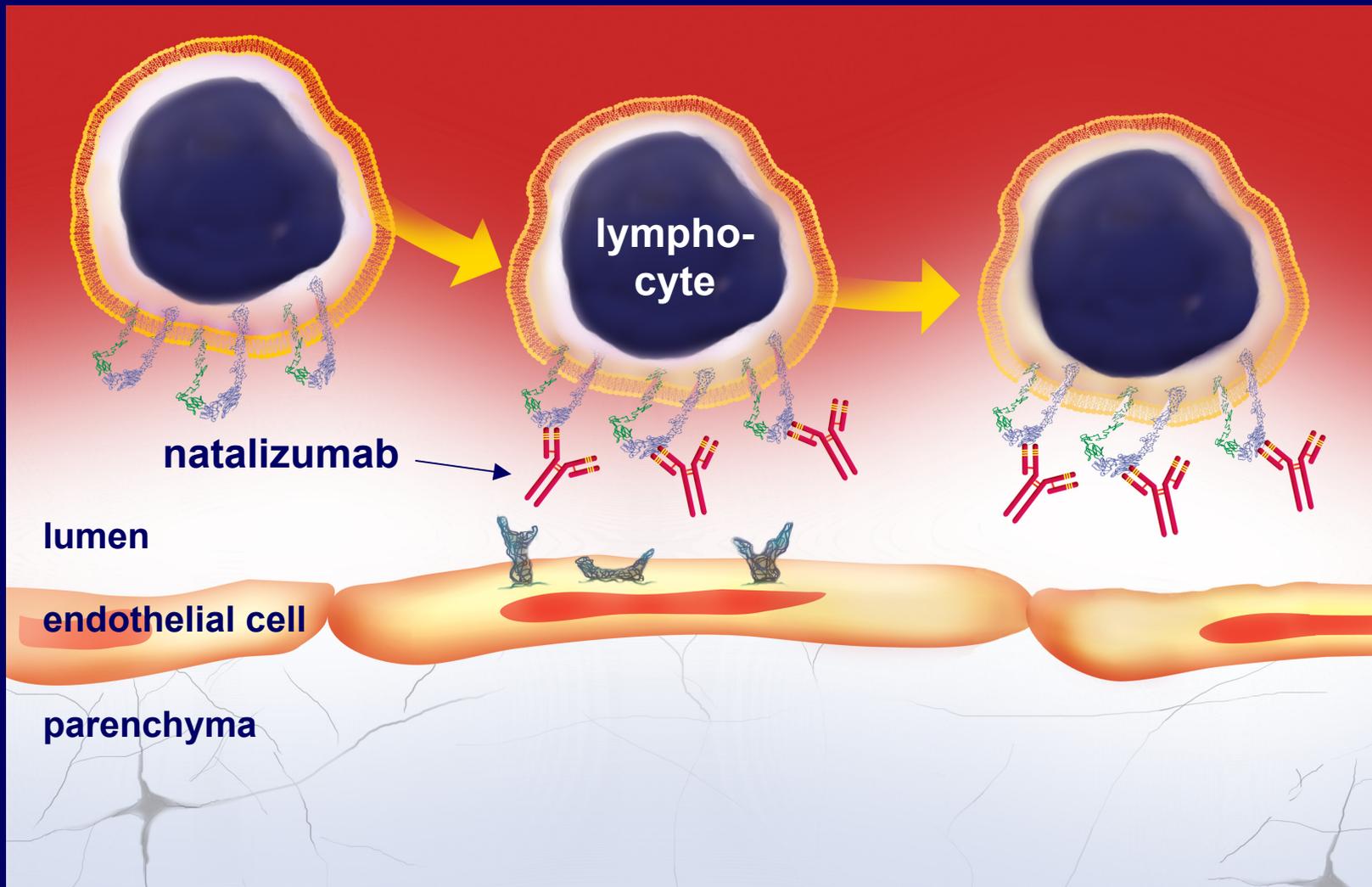
Inflammation in MS



Integrins Mediate Leukocyte Adhesion During Inflammation

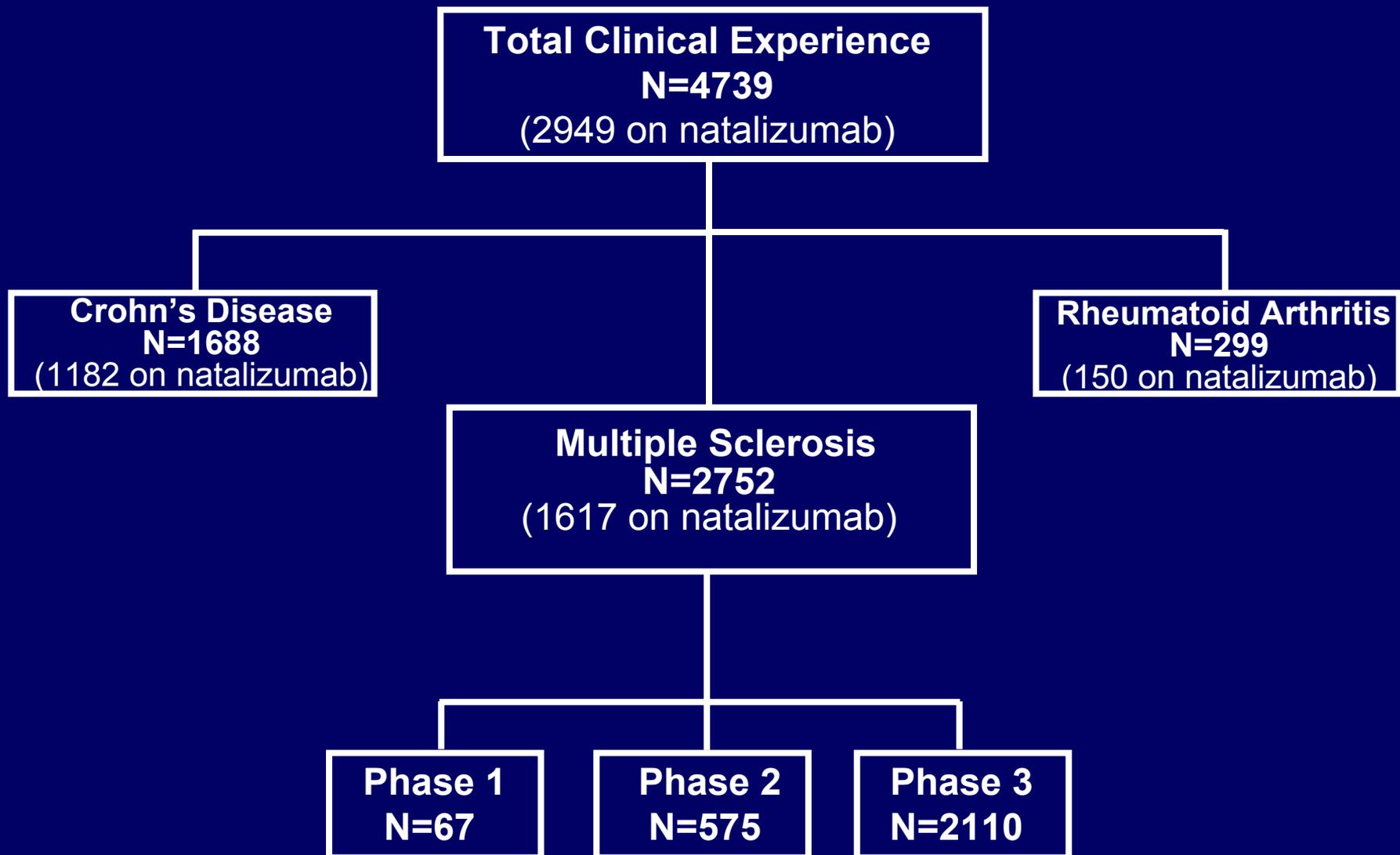


Natalizumab Inhibits the Trafficking of Leukocytes into Inflamed Tissues



Natalizumab Clinical Study Program

Placebo-Controlled Studies



Natalizumab Phase 3 Studies in MS

Monotherapy Study (1801)

Randomized, double-blind

Treatment-naïve RRMS

EDSS 0 - 5.0, 1 relapse in prior yr

Natalizumab

vs

Placebo

N = 942 (2:1)

Add-on Study (1802)

Randomized, double-blind

RRMS, disease activity on IFN β

EDSS 0 - 5.0, 1 relapse in prior yr

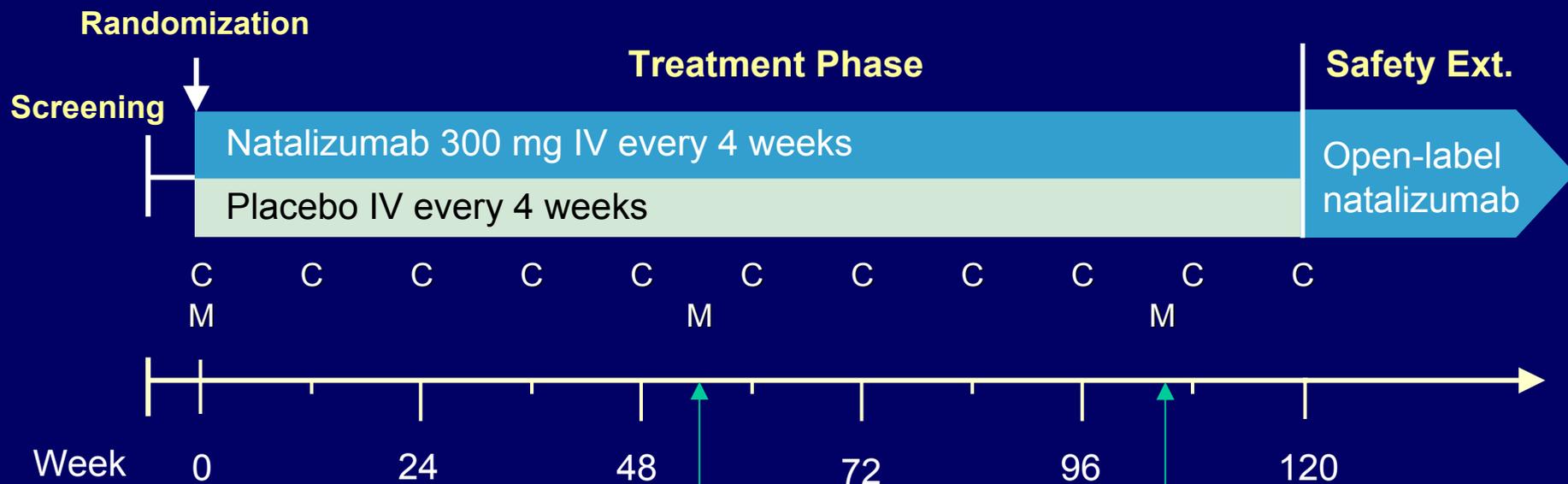
Natalizumab + IFN β

vs

Placebo + IFN β

N = 1171 (1:1)

Phase 3 Study Design



1-Year End Points:

- 1° : Relapse rate
- 2° : • New, enlarging T2 lesion #
- Gd+ lesion #
- Proportion relapse-free

2-Year End Points:

- 1° : EDSS progression
- 2° : • Relapse rate
- T2 lesion volume
- T1 hypointense lesion #
- MSFC

C = clinical evaluation, M = MRI scans

Natalizumab Phase 3 Studies in MS

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Treatment-naïve RRMS

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Natalizumab

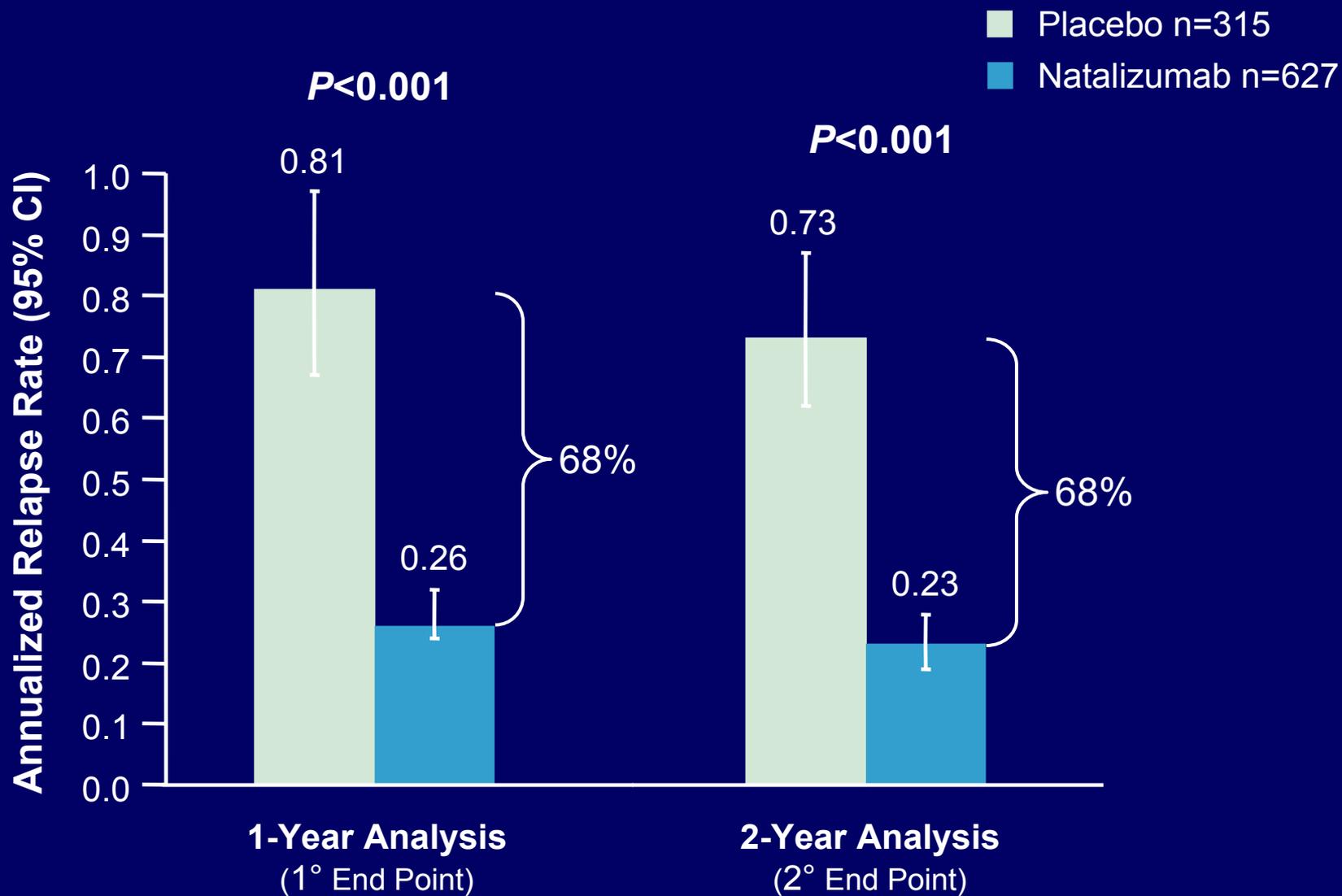
vs

Placebo

N = 942 (2:1)

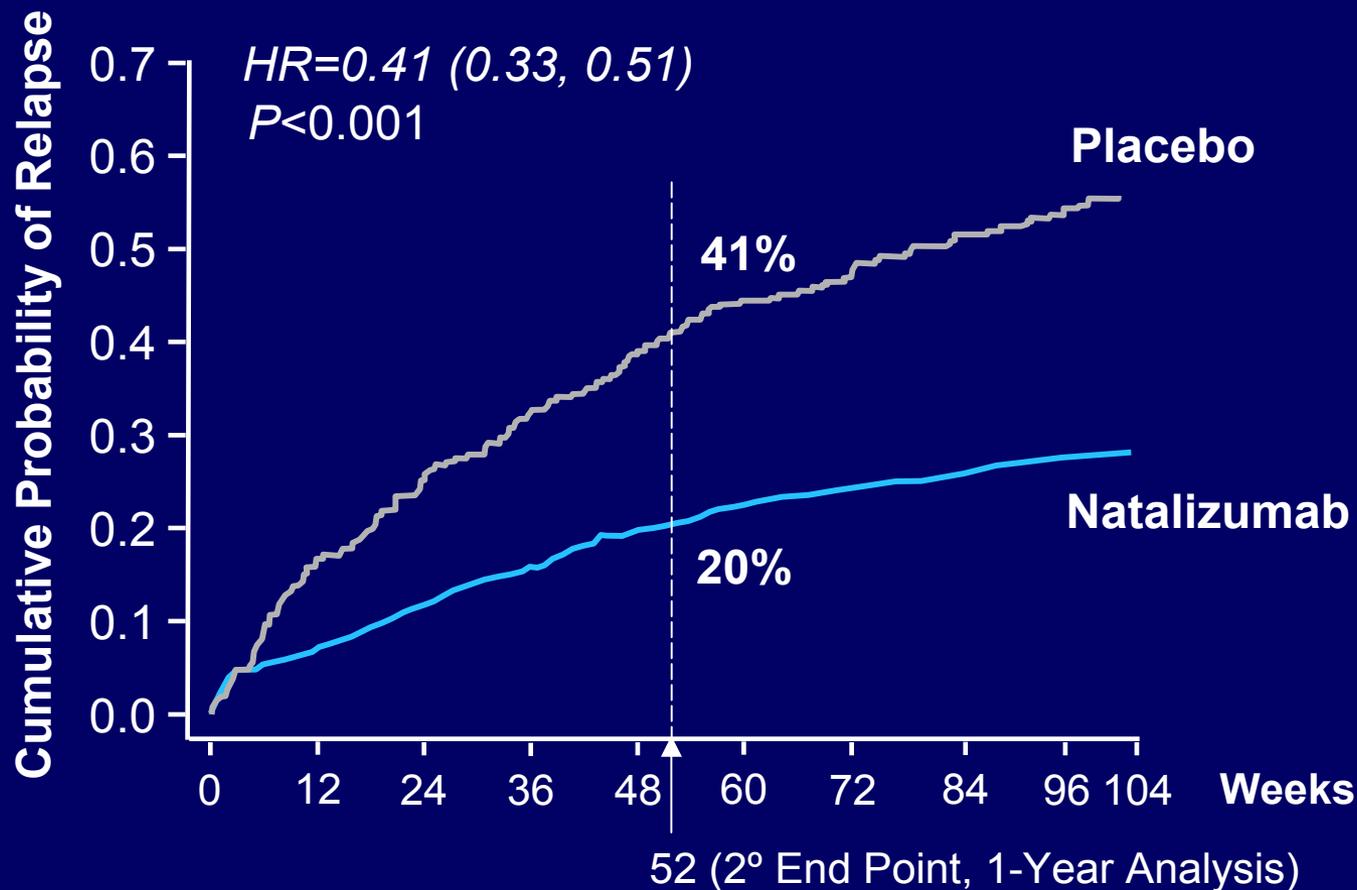
Annualized Relapse Rate

Monotherapy Study (1801)



Risk of Relapse

Monotherapy Study (1801)



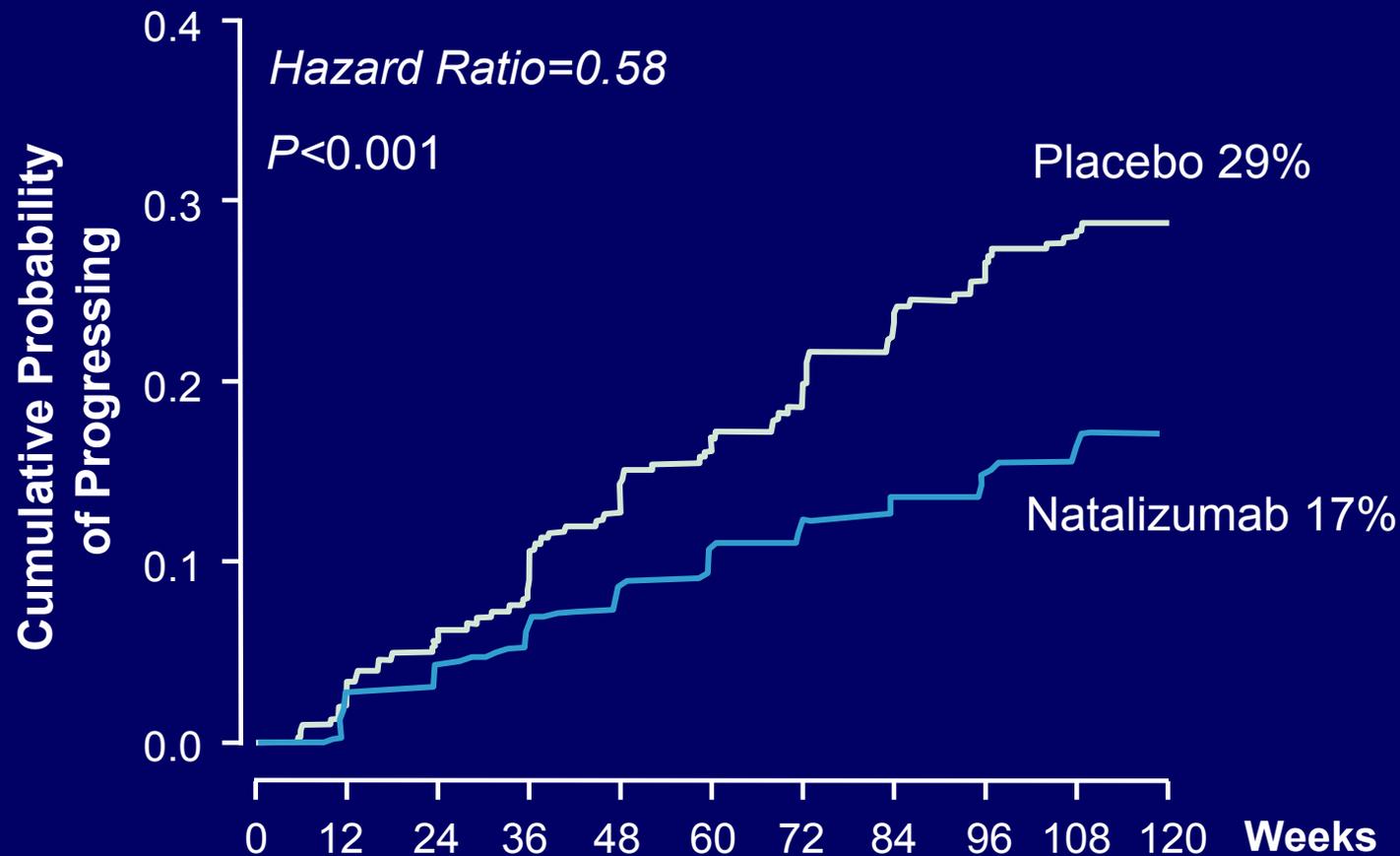
Number of Patients at Risk

Placebo	315	229	182	154	133
Natalizumab	627	542	487	447	424

Time to EDSS Progression

Monotherapy Study (1801)

Progression defined as 2- step increase in EDSS, sustained for 3 months

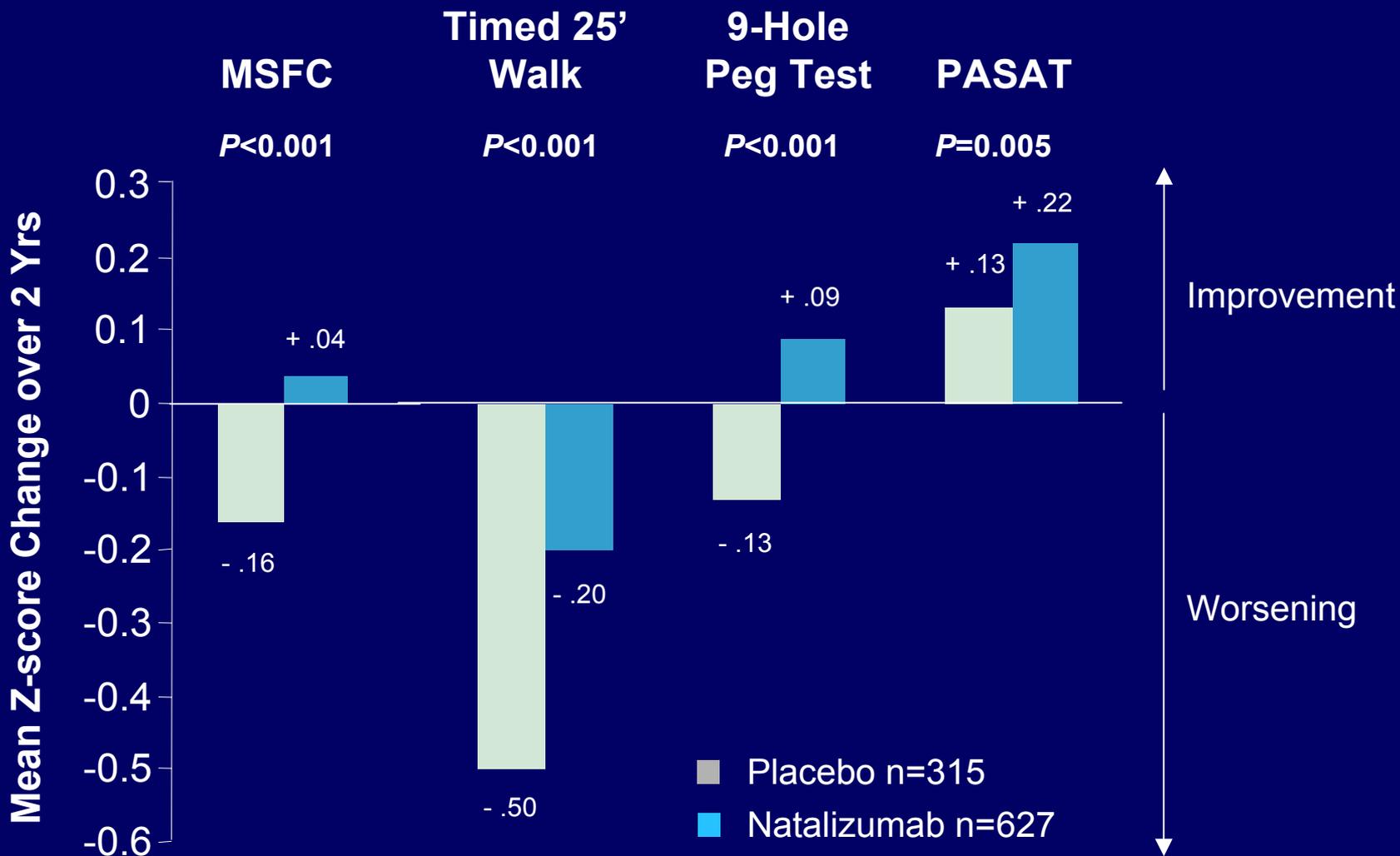


Number of Patients at Risk

Placebo	315	283	248	229	208
Natalizumab	627	582	546	517	490

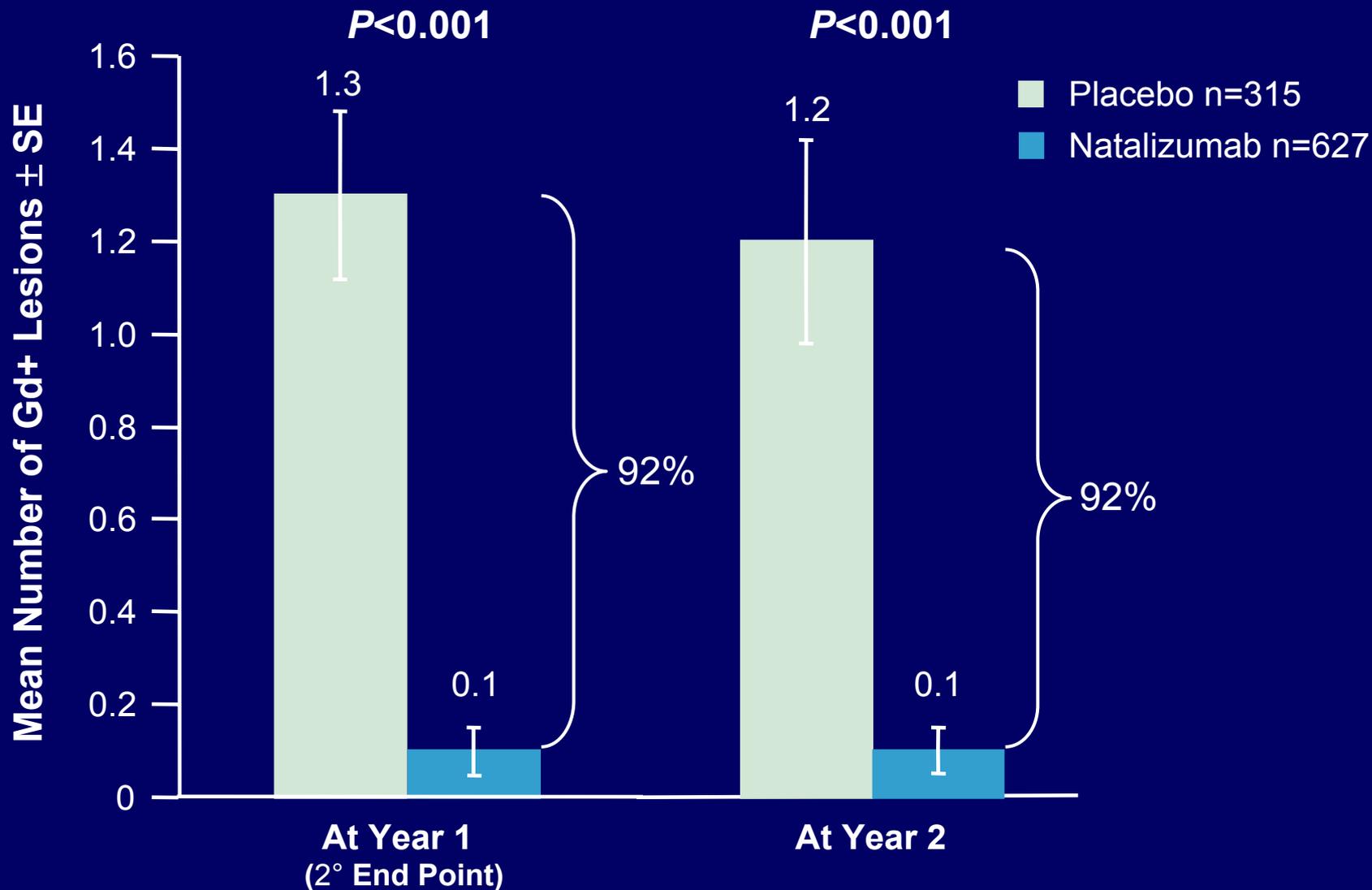
Multiple Sclerosis Functional Composite (MSFC)

Monotherapy Study (1801)



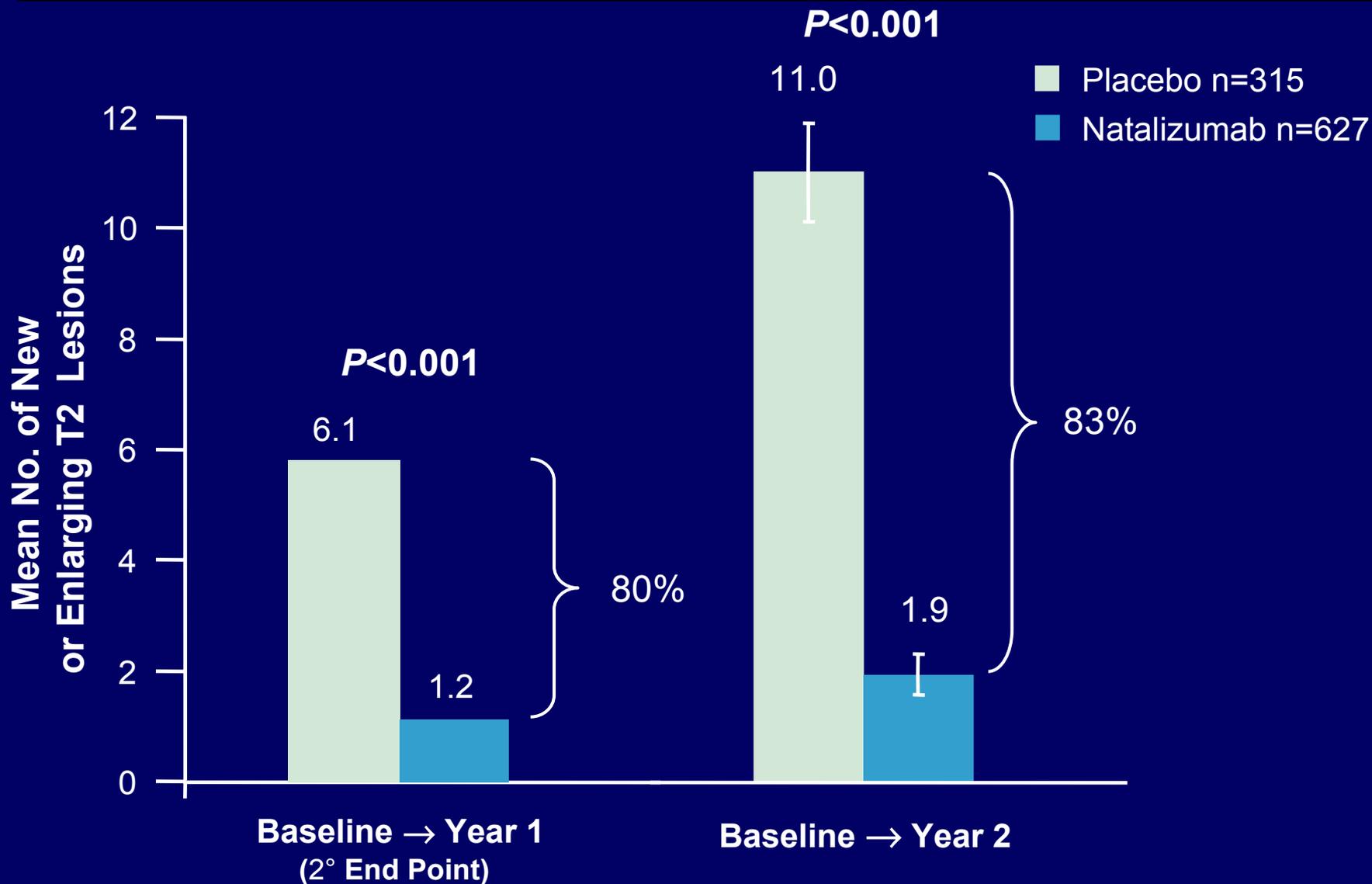
Number of Gd-Enhancing Lesions

Monotherapy Study (1801)



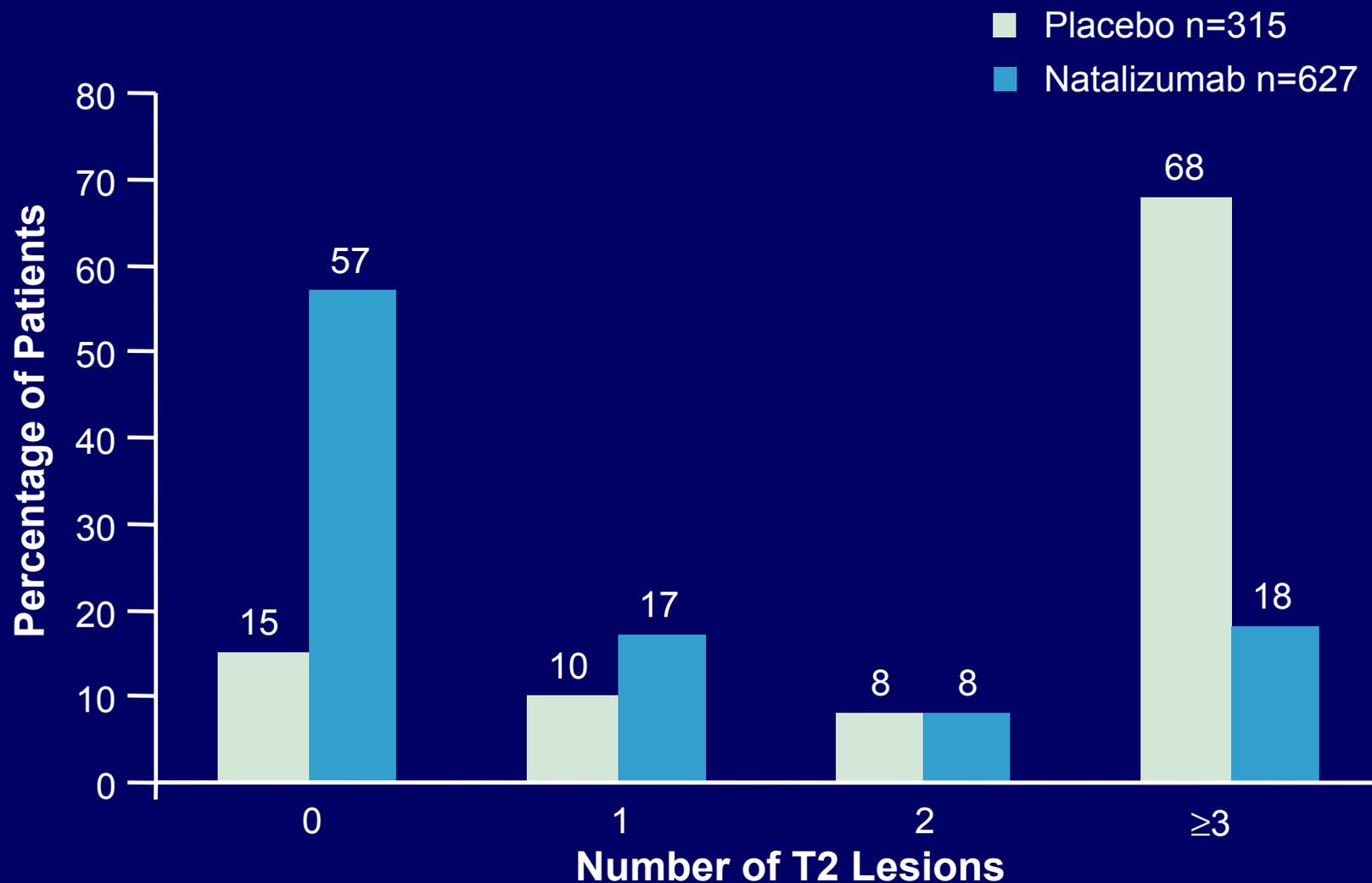
Number of New or Enlarging T2 Lesions

Monotherapy Study (1801)



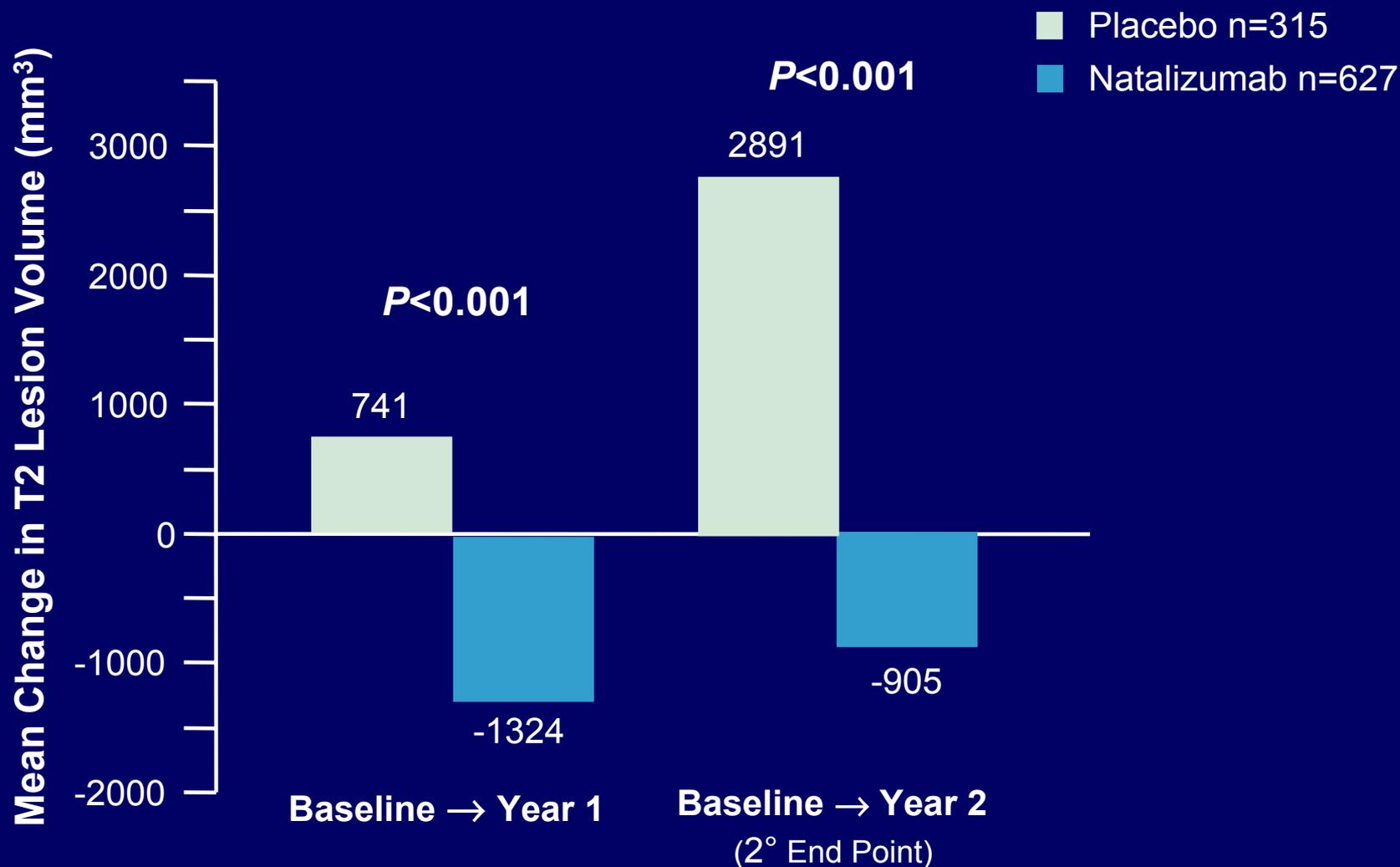
Number of New or Enlarging T2 Lesions (2 Yrs)

Monotherapy Study (1801)



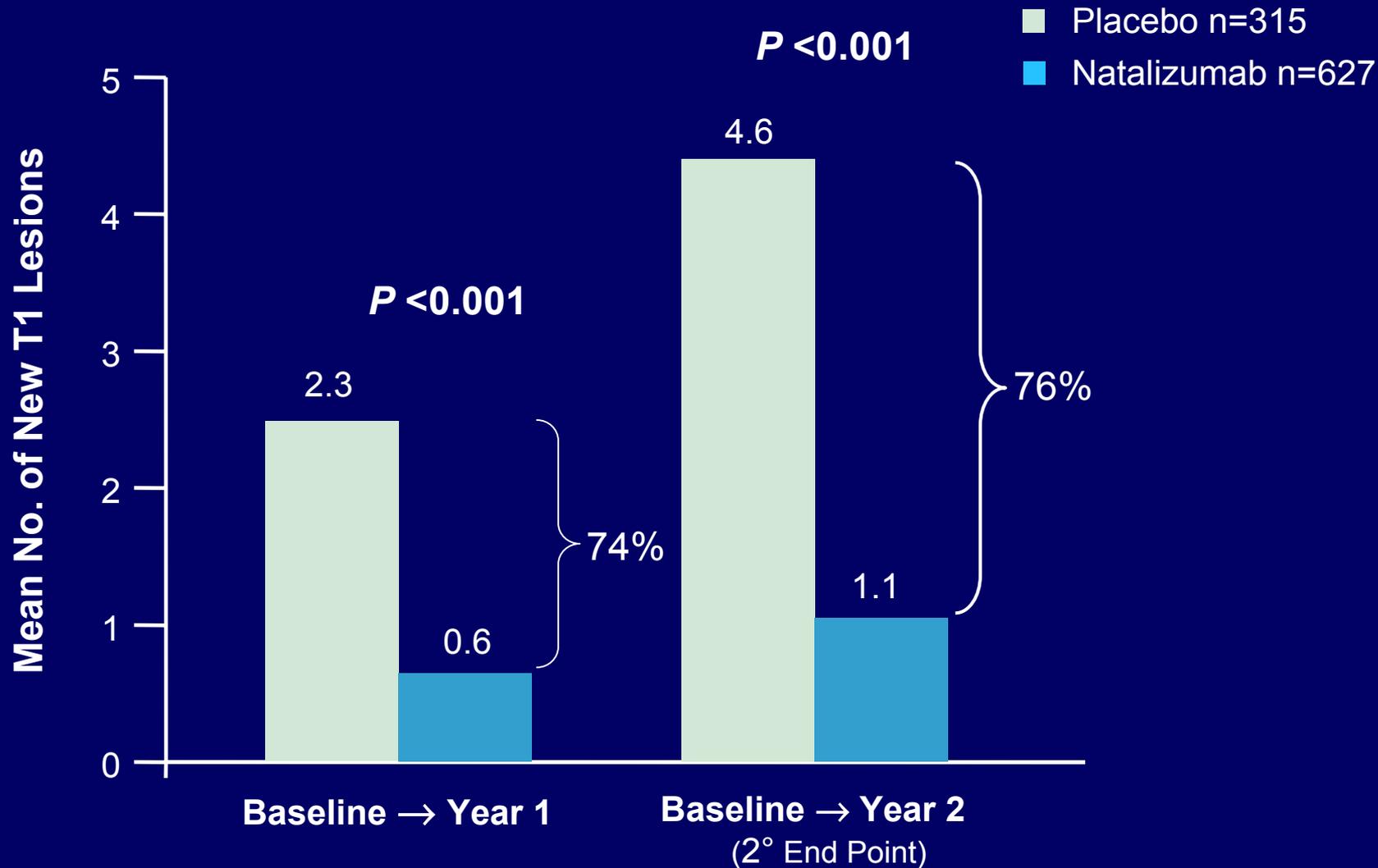
Change in T2 Lesion Volume

Monotherapy Study (1801)



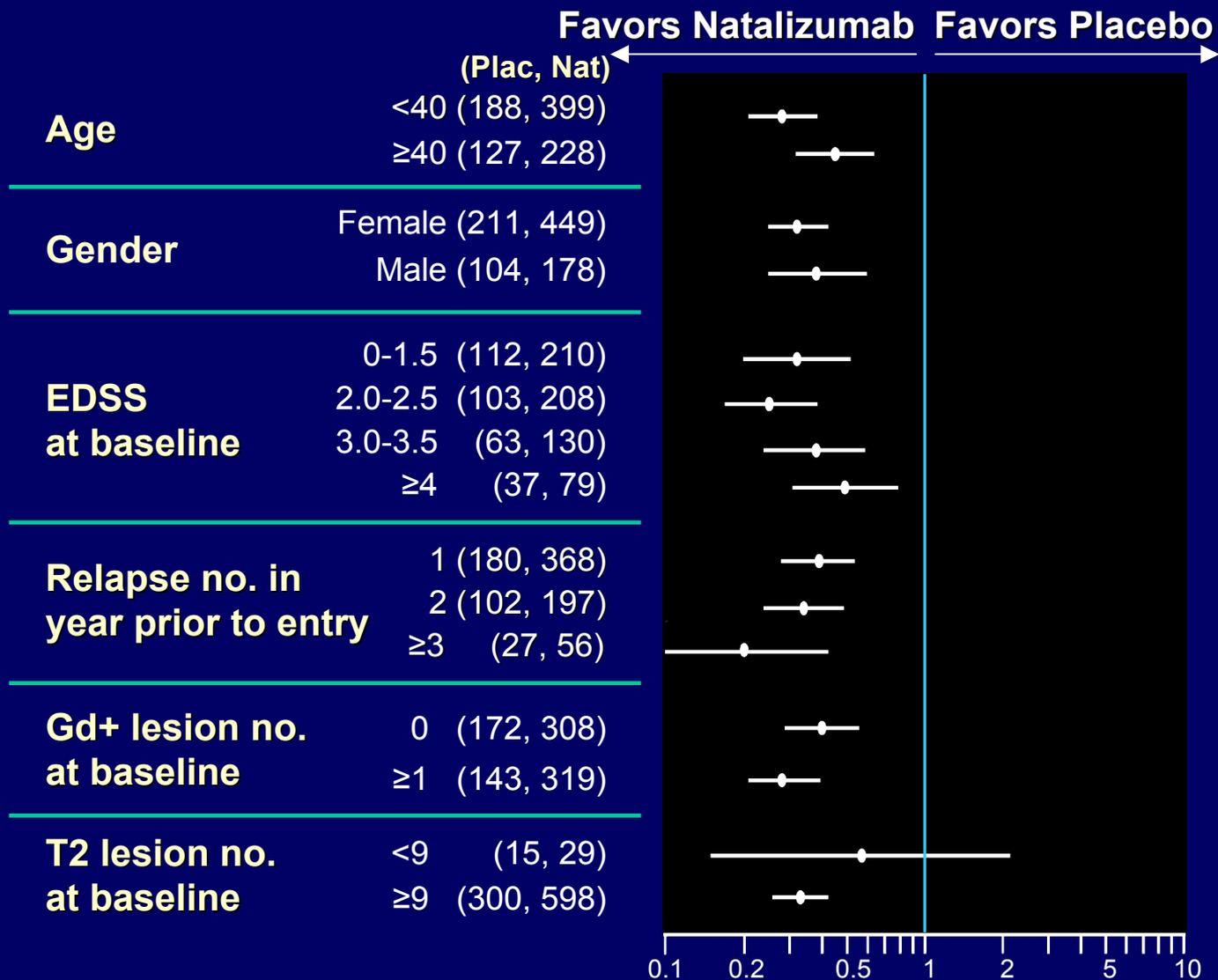
Number of New T1-Hypointense Lesions

Monotherapy Study (1801)



Relapse Rate Ratio in Subgroups

Monotherapy Study (1801)



Natalizumab Phase 3 Studies in MS

Add-on Study (1802)

Randomized, double-blind

RRMS, disease activity on IFN β

EDSS 0 - 5.0, 1 relapse in prior yr

Natalizumab + IFN β

vs

Placebo + IFN β

N = 1171 (1:1)

Add-On Study (1802)

Clinical Measures

◆ Relapse rate

- 1-Year analysis: 53% ↓, $P < 0.001$
- 2-Year analysis: 55% ↓, $P < 0.001$

◆ EDSS progression

- Hazard Ratio = 0.76, $P = 0.024$

◆ Risk of Relapse

- Hazard Ratio = 0.50, $P < 0.001$
- % relapsing at wk 52: placebo 50% vs natalizumab 28%, $P < 0.001$

◆ MSFC

- Composite: $P < 0.001$
 - Timed 25-ft Walk: $P < 0.001$
 - 9-hole Peg Test: $P < 0.001$
 - PASAT: $P = 0.159$

Add-On Study (1802)

MRI Measures

- ◆ Mean number of Gd-enhancing lesions
 - 89% ↓, $P < 0.001$
- ◆ Mean number of new or enlarging T2 lesions
 - 83% ↓, $P < 0.001$
- ◆ Mean change in T2 lesion volume
 - Placebo 558 mm³ ↑ vs natalizumab 260 mm³ ↓, $P < 0.001$
- ◆ Mean number of new T1-hypointense lesions
 - 44% ↓, $P < 0.001$

Efficacy Summary

- ◆ Efficacy demonstrated on all primary and secondary end points
- ◆ Magnitude of efficacy as monotherapy compelling
- ◆ Add-on study confirmed efficacy in patients breaking through active treatment
- ◆ Strong attenuation of inflammation and accumulation of plaque burden as seen on MRI
- ◆ Benefit seen consistently across subgroups