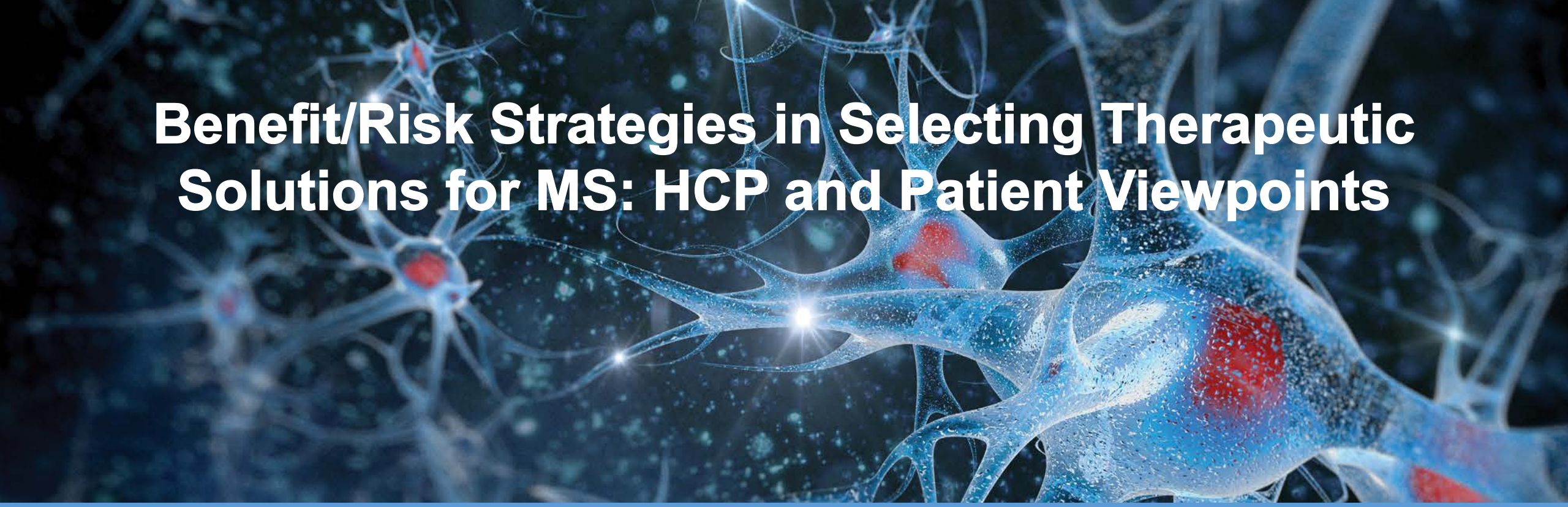


Benefit/Risk Strategies in Selecting Therapeutic Solutions for MS: HCP and Patient Viewpoints

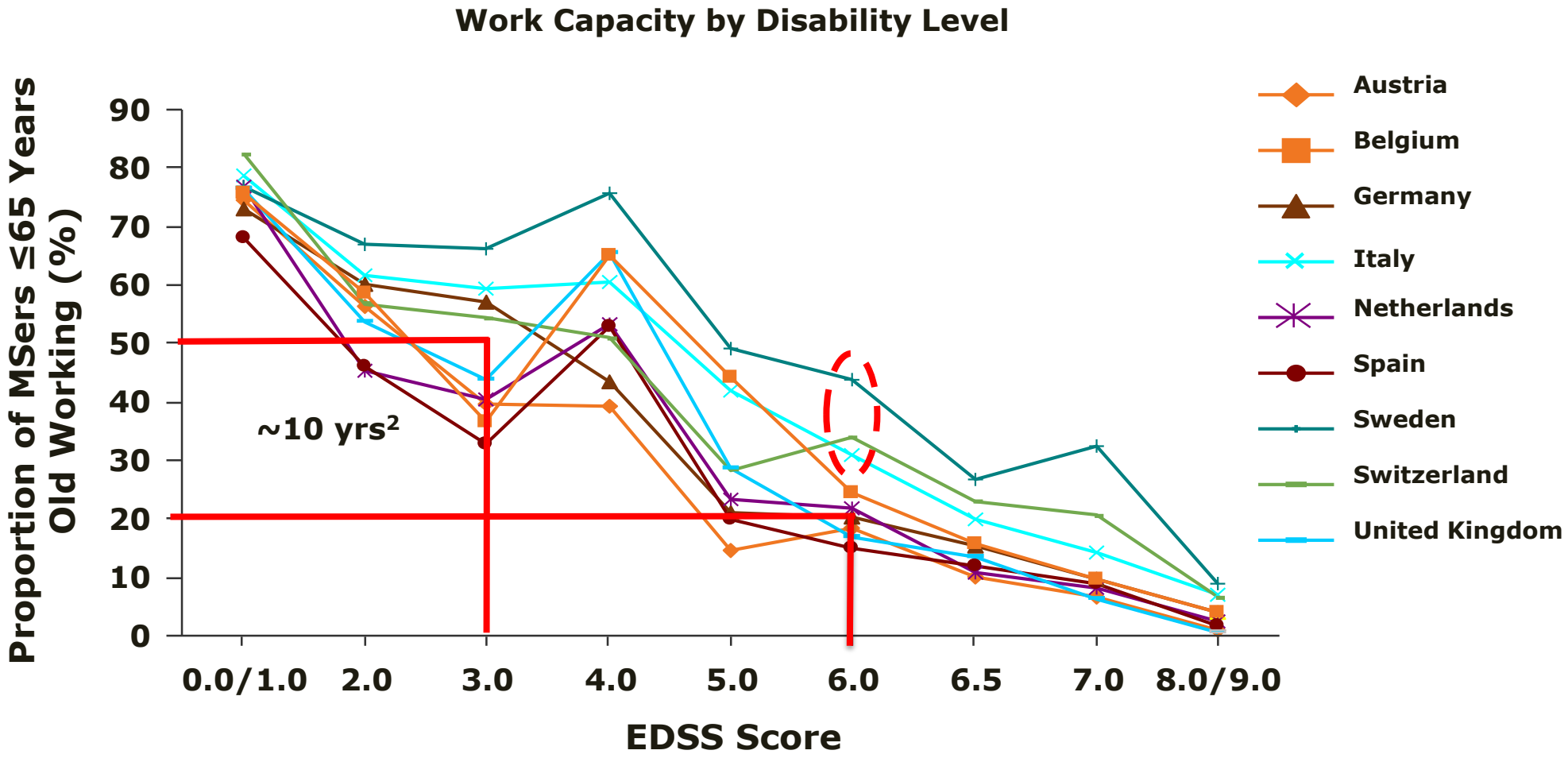
gmsa
Global Multiple Sclerosis Academy

This resource is supported by an educational grant from Merck KGaA, Darmstadt, Germany.

Learning Objectives

- Review the benefit/risk strategies in selecting therapy for MS patients while assessing treatment regimens that carry acceptable or diminished risk of disease progression
- **Explore emergent concepts in the management of MS, focusing on targeting T- and B-cells including:**
  - **Risks associated with continuous immunosuppression**
  - **Action on the inflammatory activity in the CNS compartment**
- Identify strategies that simplify patient dosing and side effects to:
  - Increase treatment compliance
  - Improve patients' quality of life
  - Slow disease progression

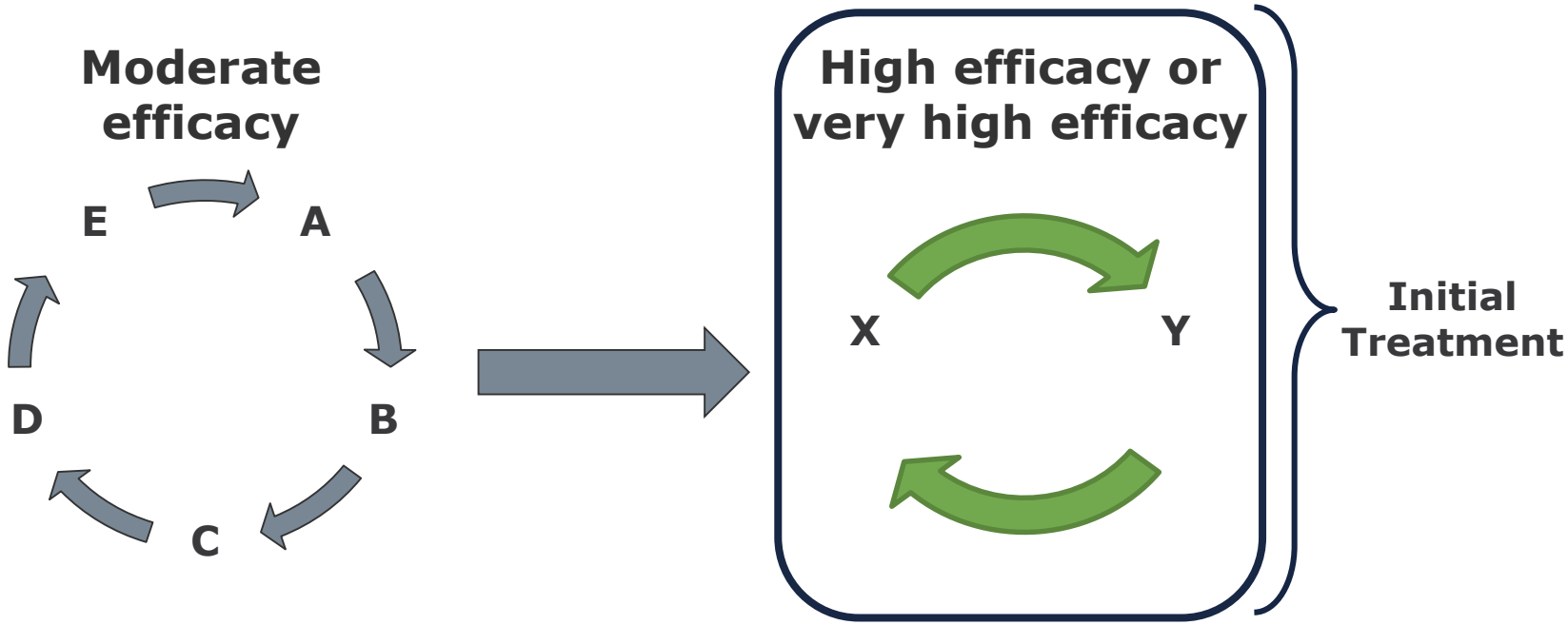
As Disability of MS Advances, Work Capacity Decreases



The proportion of MSers employed or on long-term sick leave is calculated as a percentage of MSers aged 65 or younger.

1. Kobelt G et al. *J Neurol Neurosurg Psychiatry*. 2006;77:918-926; **2.** Pfleger CC et al. *Mult Scler*. 2010;16:121-126.

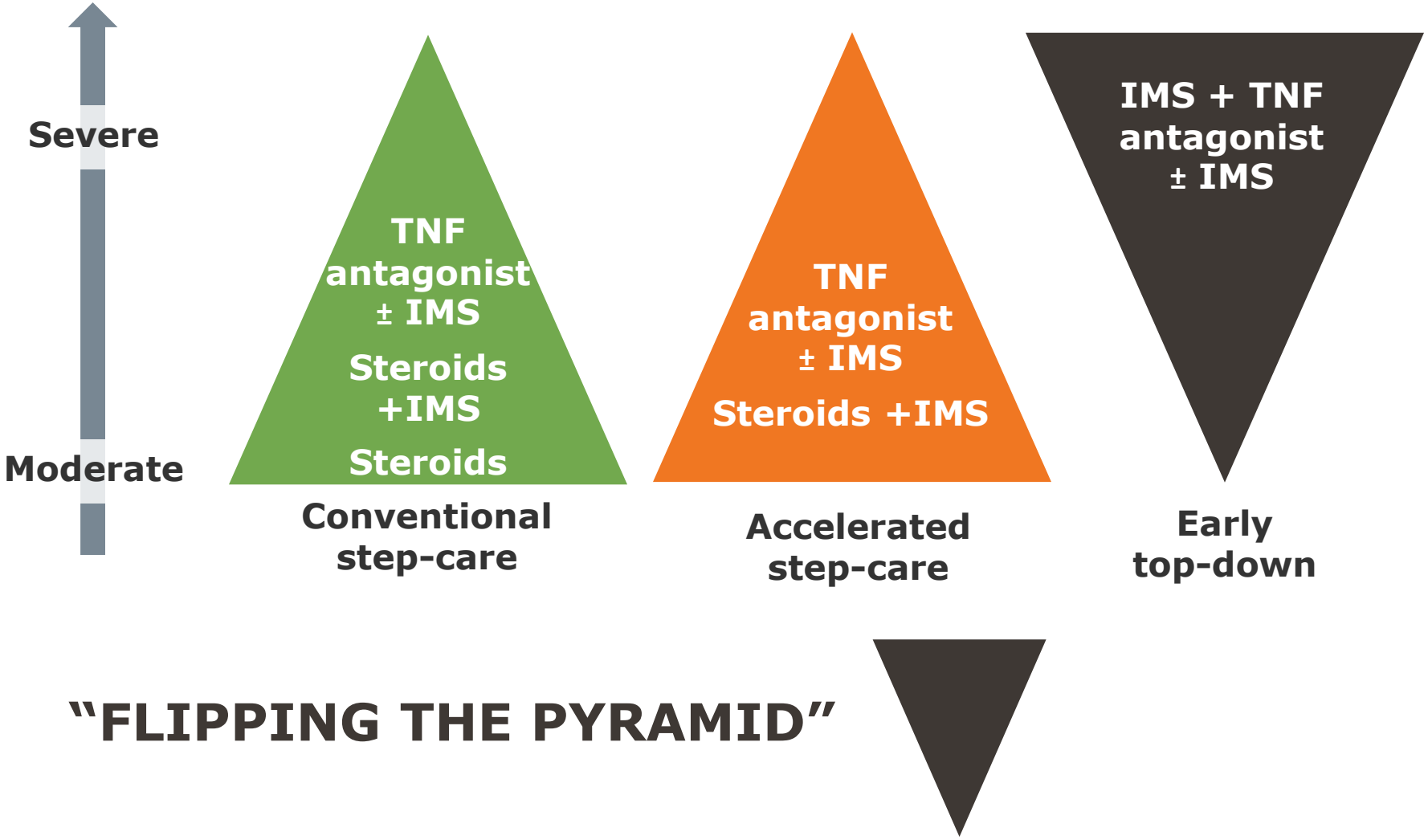
The Traditional Approach to MS Treatment



- Heterogeneity of disease course across different MSers and over time can affect treatment response[1-3]
- Depending on the definition used, up to 49% of MSers treated with a first-line injectable therapy (IFNB) still have clinical disease activity[1]

1. Rio J et al. *Ann Neurol* 2006;59:344-52; **2.** Miller A et al. *J Neurol Sci* 2008;274:68-75; **3.** Rudick RA et al. *Lancet Neurol* 2009;8:545-59.
Figure adapted from Rio J et al. *Curr Opin Neurol* 2011; 24:230-7.

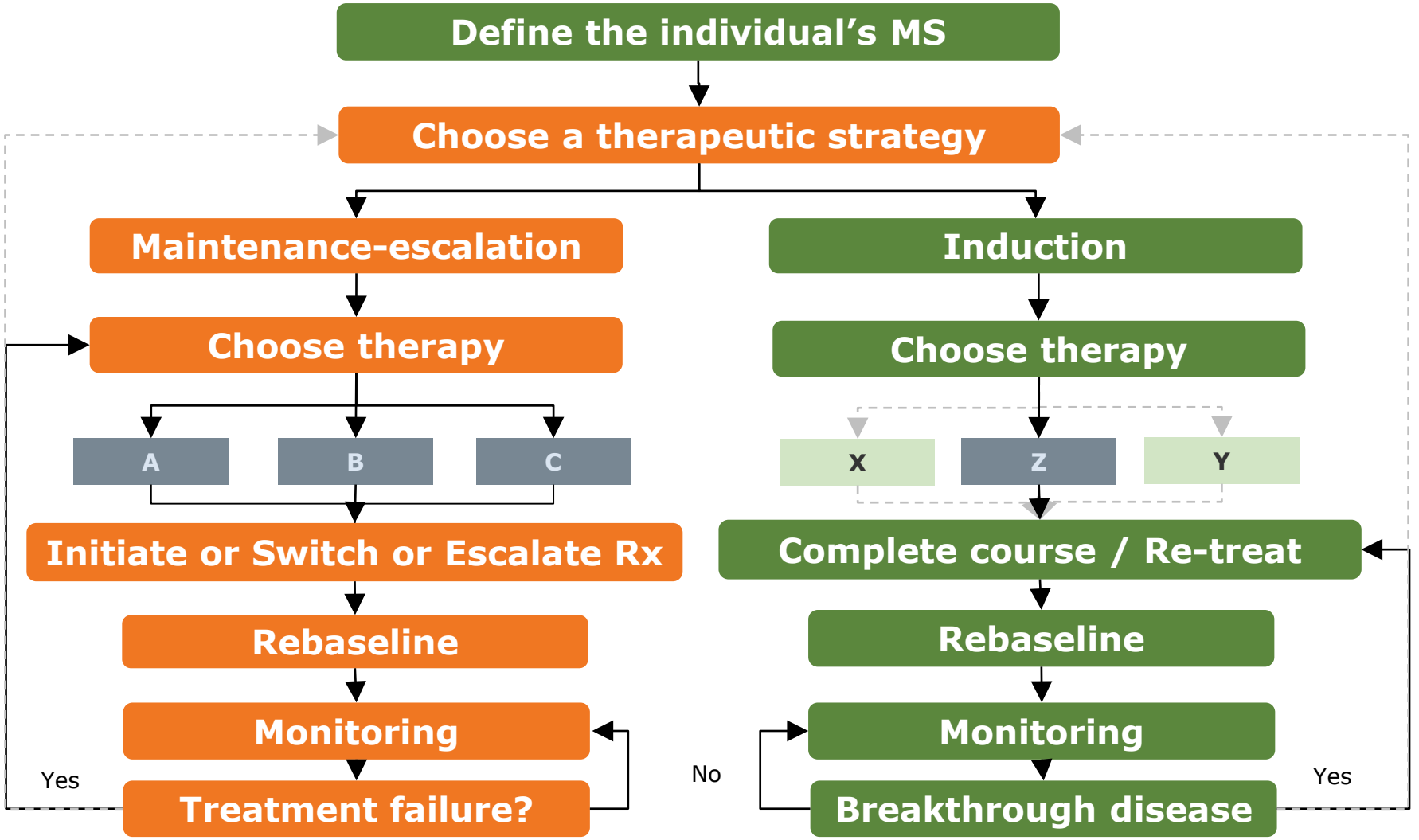
Treating Beyond Symptoms with a View to Improving Outcomes in Inflammatory Bowel Diseases



Sandborn et al. *Journal of Crohn's and Colitis*. 2014(8):927–935.

T2T-NEDA ALGORITHM

T2T = treating-to-target; NEDA = no evident disease activity



- MS prognosis based on clinical and MRI indices
- Life style and goals
- Shared goals for therapy

- Patient's preferences?
- Your choice?

- Patient's preferences?
- Your choice?

- Only one licensed induction therapy at present

Rebaselining:

- ifn-β, natalizumab, fingolimod, teriflunomide, dimethyl-fumarate=3-6 months
- glatiramer acetate=9 months
- alemtuzumab=24 months

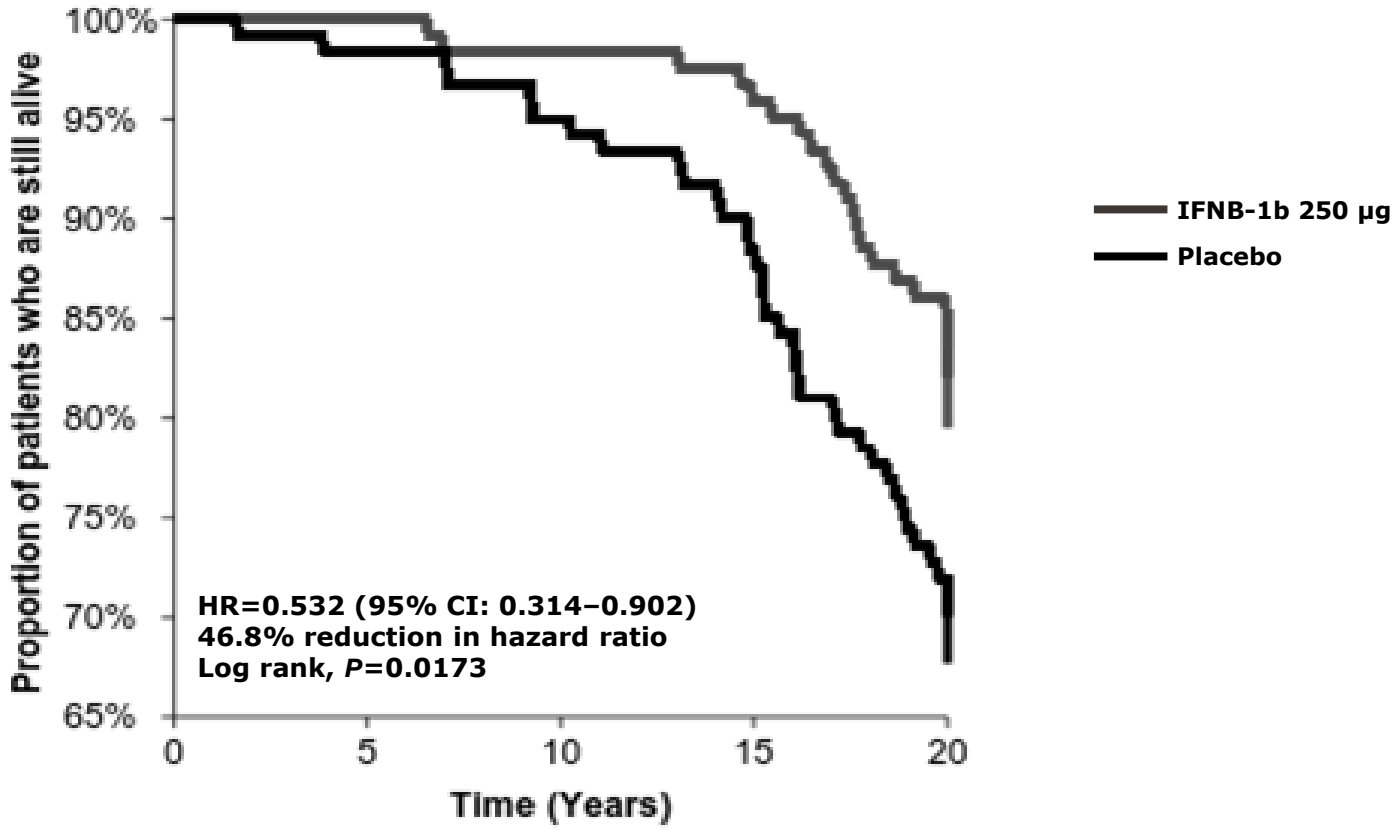
Individual measures:

- Evidence of disease activity?
- Tolerability/safety?
- Adherence?
- Drug or inhibitory markers, e.g. NABs?

Ifn-β = interferon-beta; NABs = neutralizing antibodies; Rx = treatment.

Interferon-beta Reduced Mortality by 46.8% vs Placebo Over 20 Years

Early treatment with IFNB1b: associated with 46.8% reduction in the hazard rate for mortality-NNT 8



At risk:					
IFNB-1b 250 µg	124	124	121	118	104
Placebo	123	120	117	109	88

Goodin DS, et al. *Neurology*. 2012, Goodin DS, *BMJ Open*. 2012.

Inflammation Drives Acute Axonal Loss and Primes Surviving Axons for Degeneration Later

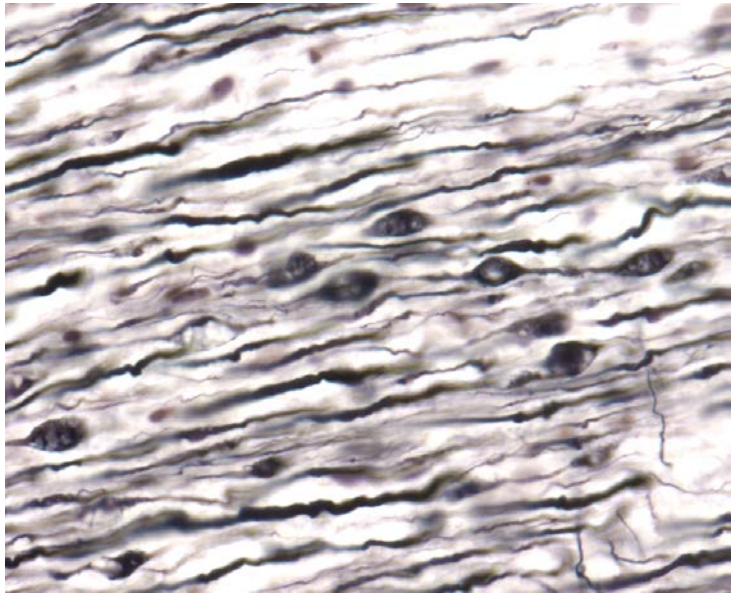
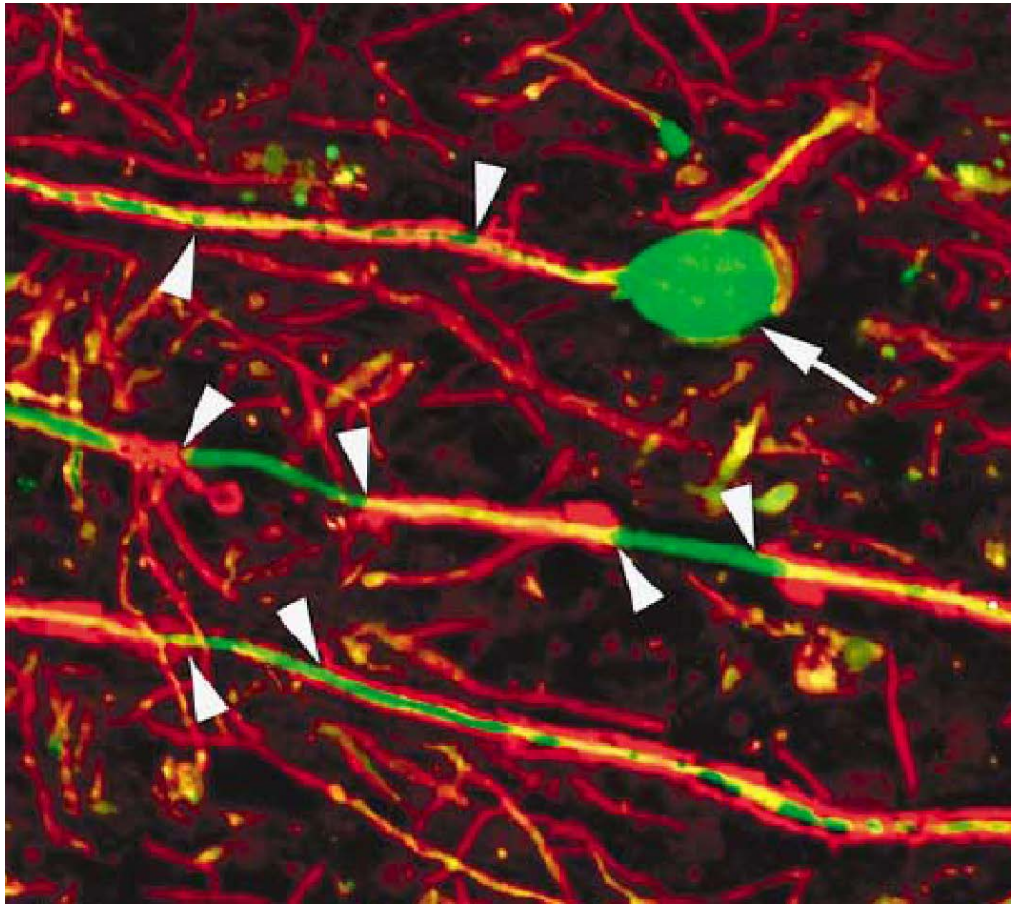


TABLE 2. DISTRIBUTION AND NUMBER OF TRANSECTED AXONS IN MULTIPLE-SCLEROSIS LESIONS.

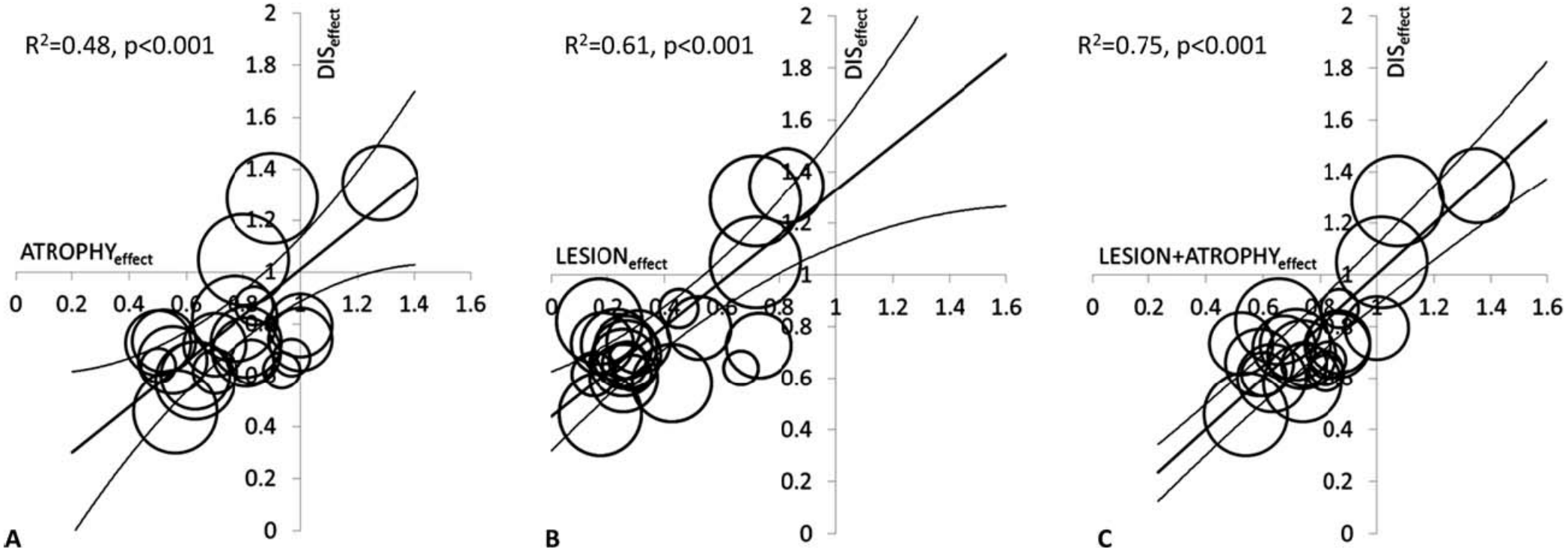
TISSUE (NO. OF PATIENTS)	NO. OF LESIONS ANALYZED	NO. OF TRANSECTED AXONS/mm³*
Active lesions (3)	5	11,236±2775
Chronic active lesions (4)	13	
Edge		3138±688
Core		875±246
Nonlesion white matter (5)	11	17±2.8
Control white matter (4)	5	0.7±0.7



11,000 to 1

Trapp, et al. *NEJM*. 1998;338:278-285.

Treatment Effect on Disability Predicted by Effect on T2-lesion Load and Brain Atrophy



Meta-analysis of treatment effect on EDSS worsening (y) vs effects on MRI lesions and brain atrophy, individually or combined, in 13 placebo-controlled RRMS trials (13,500 patients)

Sormani MP et al. Ann Neurol. 2014;75:43-49.

No Evident Disease Activity: NEDA

Treat-2-target

What is NEDA?

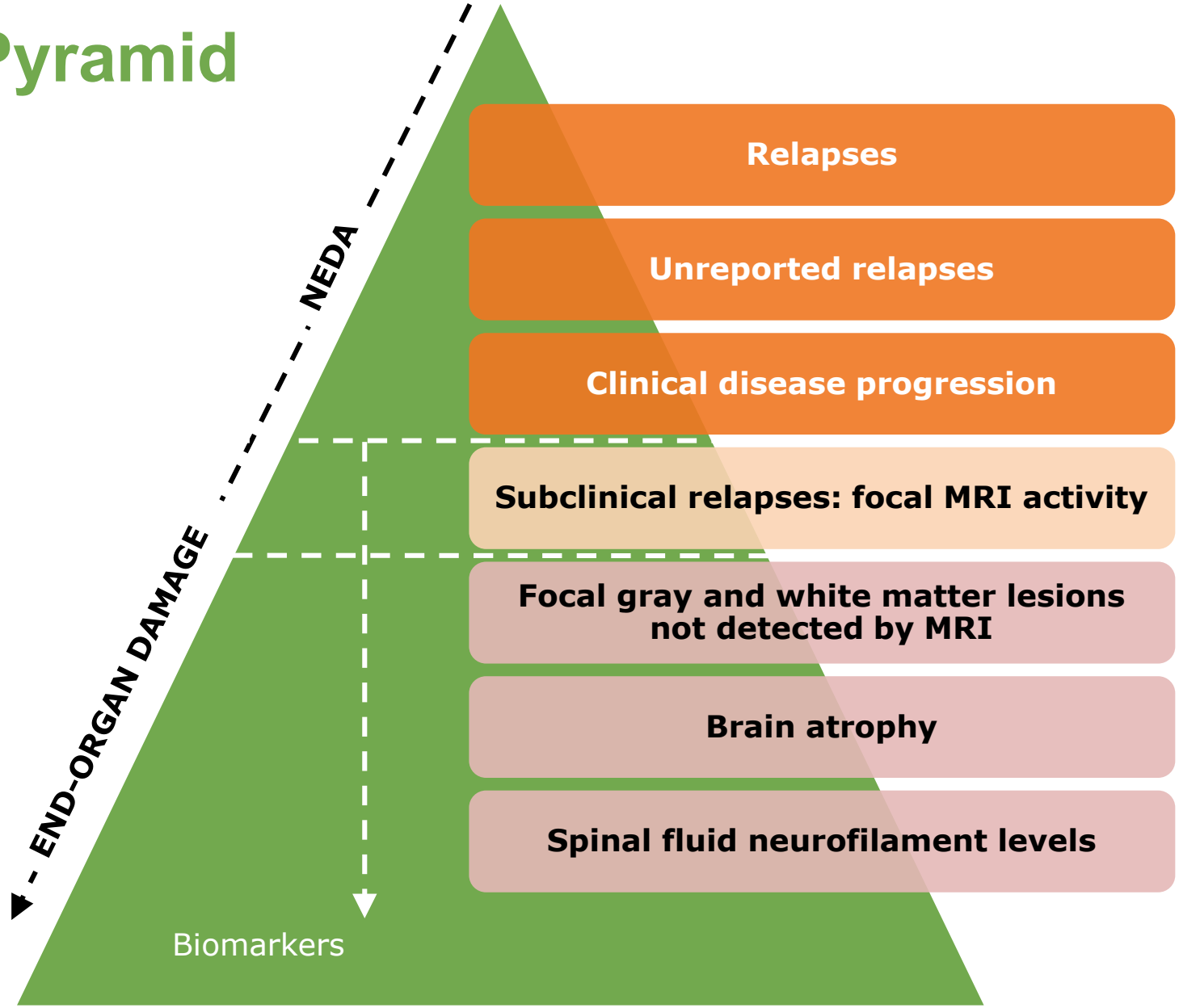
× No relapses
× No sustained disability progression (EDSS)
× No MRI activity
  × No new or enlarging T2 lesions
  × No Gd-enhancing lesions

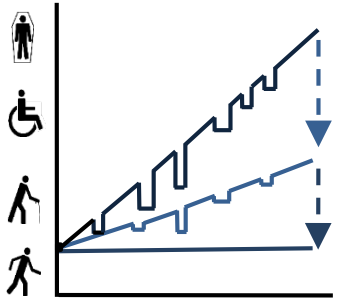
DAF[1,2]

Gd, gadolinium.

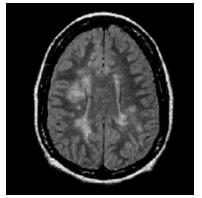
1. Havrdova E, et al. *Lancet Neurol*. 2009; 8:254–260; **2.** Giovannoni G, et al. Lancet Neurol 2011; 10:329–337.

MS Pyramid

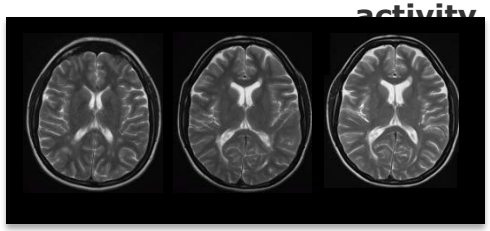




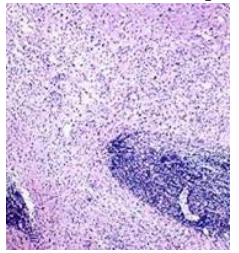
Clinical activity



Focal MRI activity

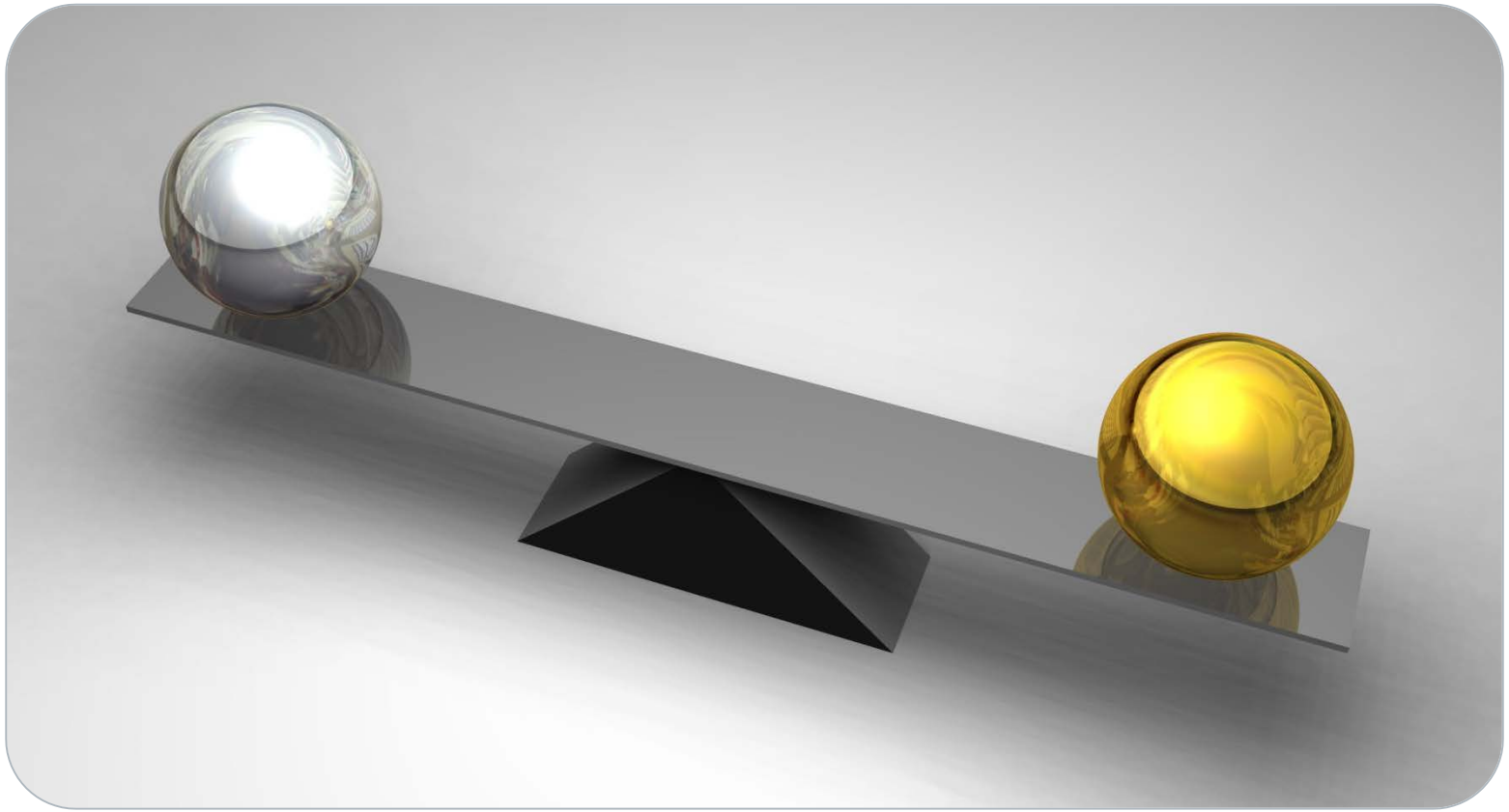


Hidden focal and diffuse MRI activity

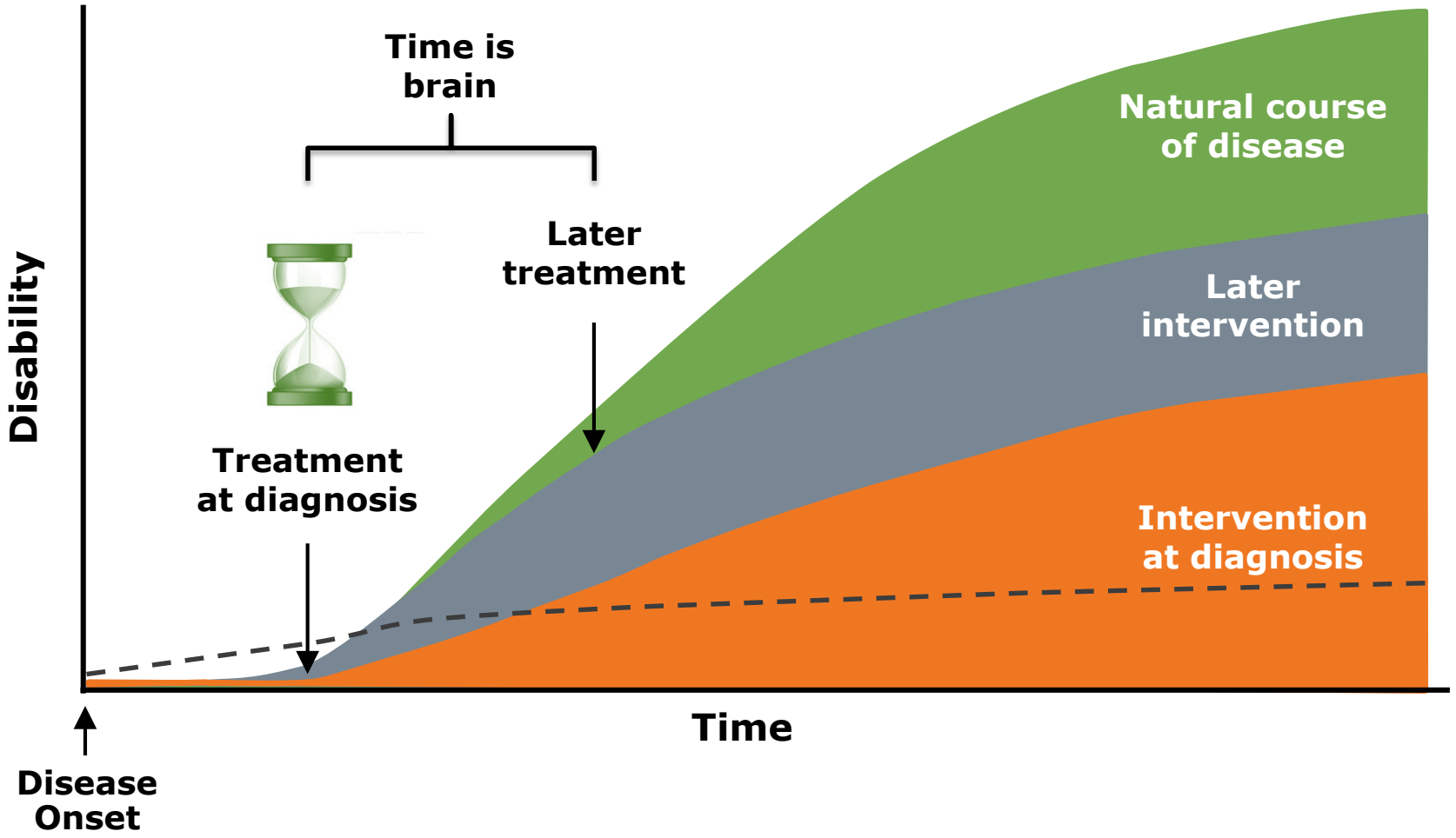


Microscopic or biochemical pathology

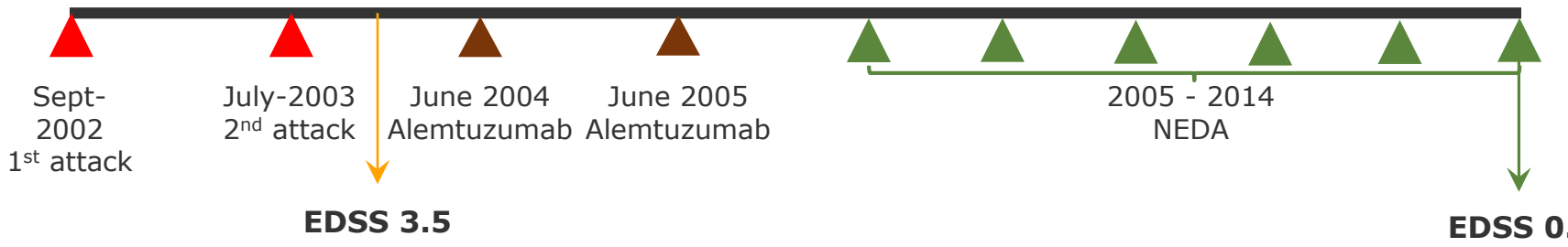
Risk vs Benefit



Theoretical Model: Treat Early and Effectively

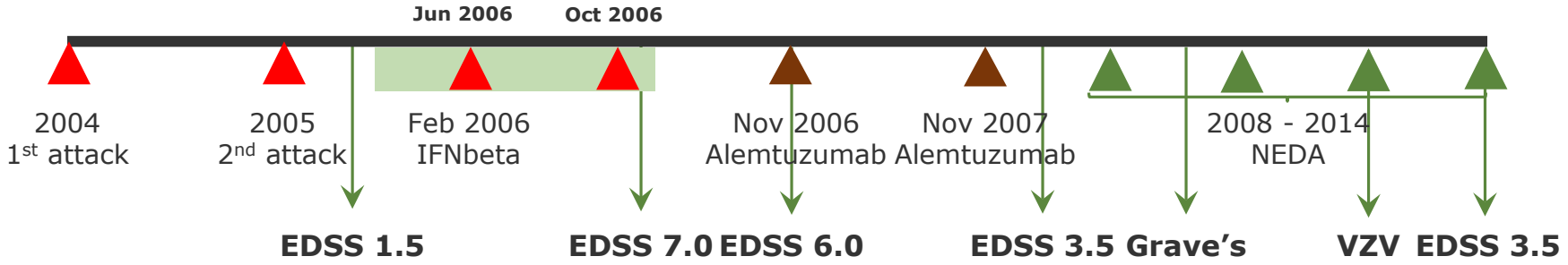


Early – Highly Active Treatment Enhances Outcome



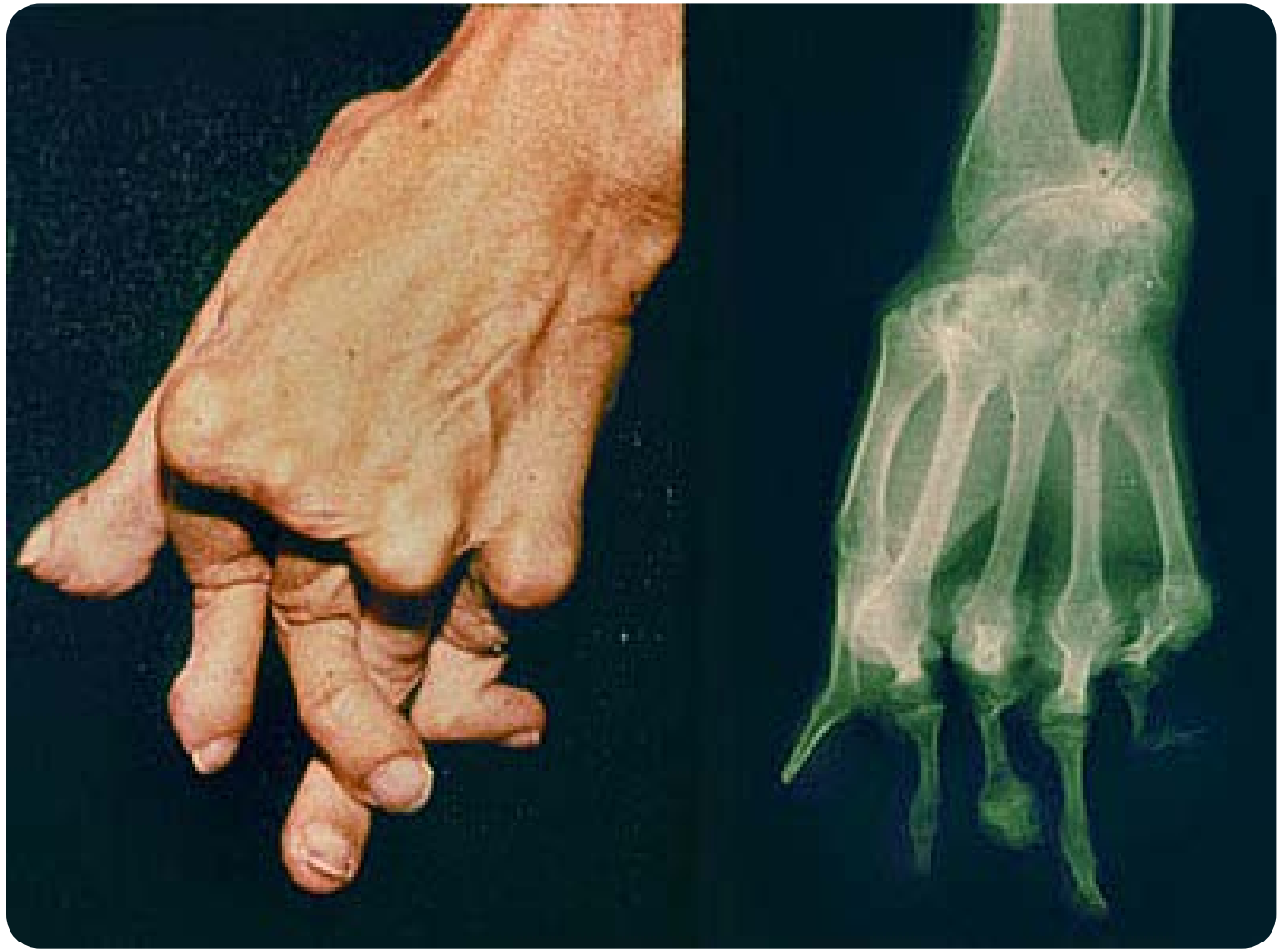
EDSS = 0.0: fully functional

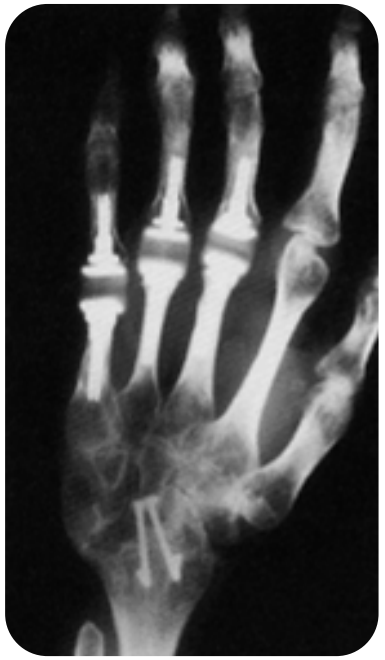
20 month vs. 32 month delay or 2 relapses

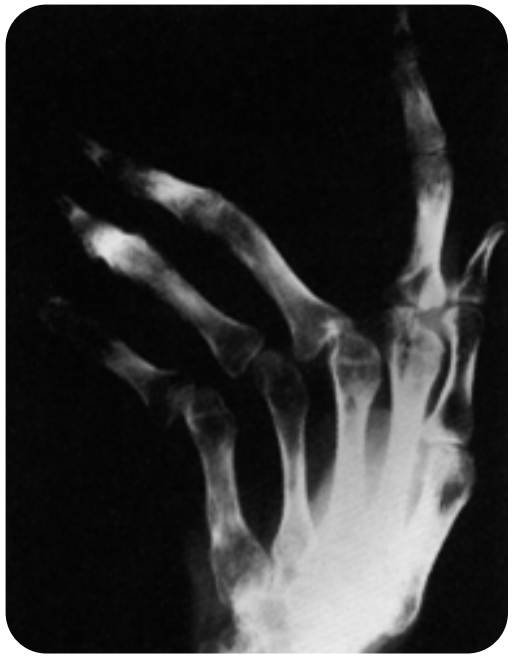


EDSS = 3.5: unable to run, play tennis or walk down stairs quickly without the use of a handrail

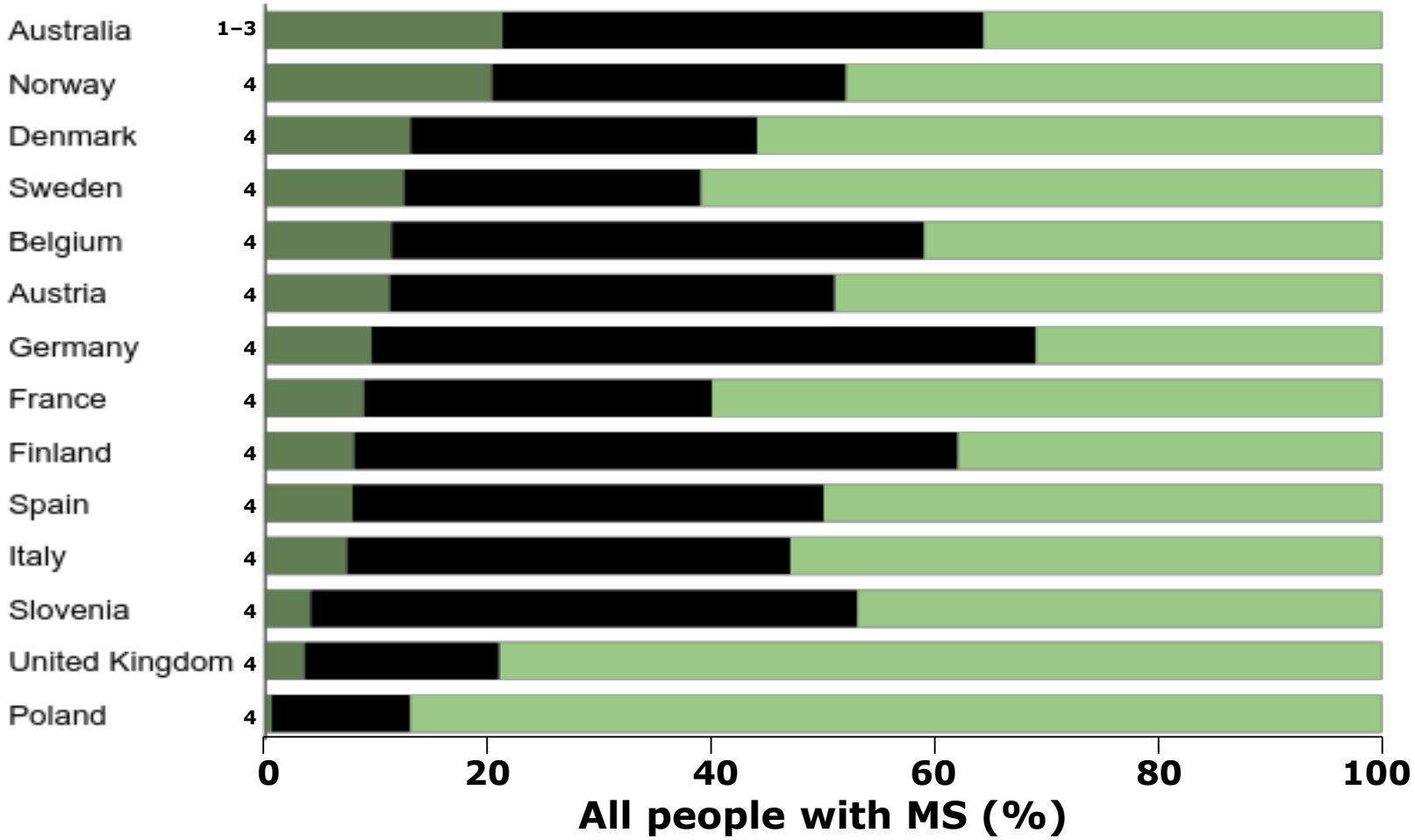
Cost of Delayed Access to Highly Active Treatment







Large Disparities Exist Among Countries in Access to Disease-Modifying Therapies



Newer DMT
Established DMT
No DMT

All data are from 2013

Established DMTs
DMTs approved for relapsing forms of MS during the 1990s and reformulations or generic versions of these substances

Newer DMTs
DMTs approved for relapsing forms of MS that have a different mechanism of action from established DMTs

DMT, disease-modifying therapy.

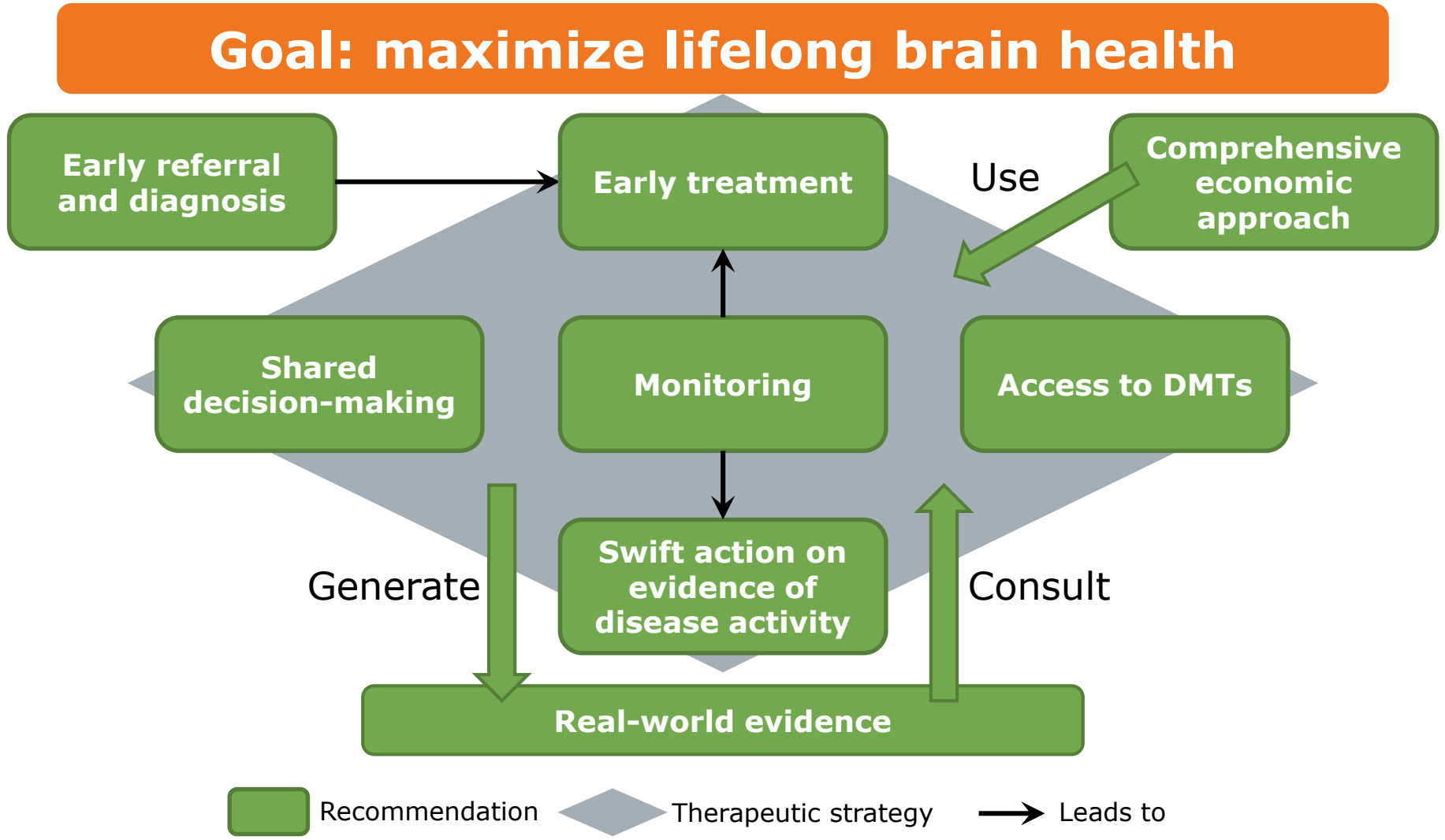
1. Hollingworth S *et al. J Clin Neurosci* 2014;21:2083–7; **2.** World Bank, 2015. http://data.worldbank.org/indicator/SP.POP.TOTL; **3.** MSIF, 2013. http://www.atlasofms.org; **4.** Wilsdon T *et al.* 2013. http://crai.com/sites/default/files/publications/CRA-Biogen-Access-to-MS-Treatment-Final-Report.pdf. Figure reproduced from Giovannoni G *et al. Brain health: time matters in multiple sclerosis.* Available at: www.msbrainhealth.org

Multiple Sclerosis: Unmet Medical Needs

- Disease-modifying drugs (DMDs) are not completely effective in all patients.
- 7 to 49% of relapsing–remitting MS (RRMS) patients do not adequately respond to DMDs
- Current Options Injection/Infusion
  - Needle phobia (25% of population)
  - Clinic infusion visit required

Rudick RA, Polman CH. *Lancet Neurol*. 8, 545–559 (2009).

The Goal of Treating MS Should Be to Maximize Lifelong Brain Health



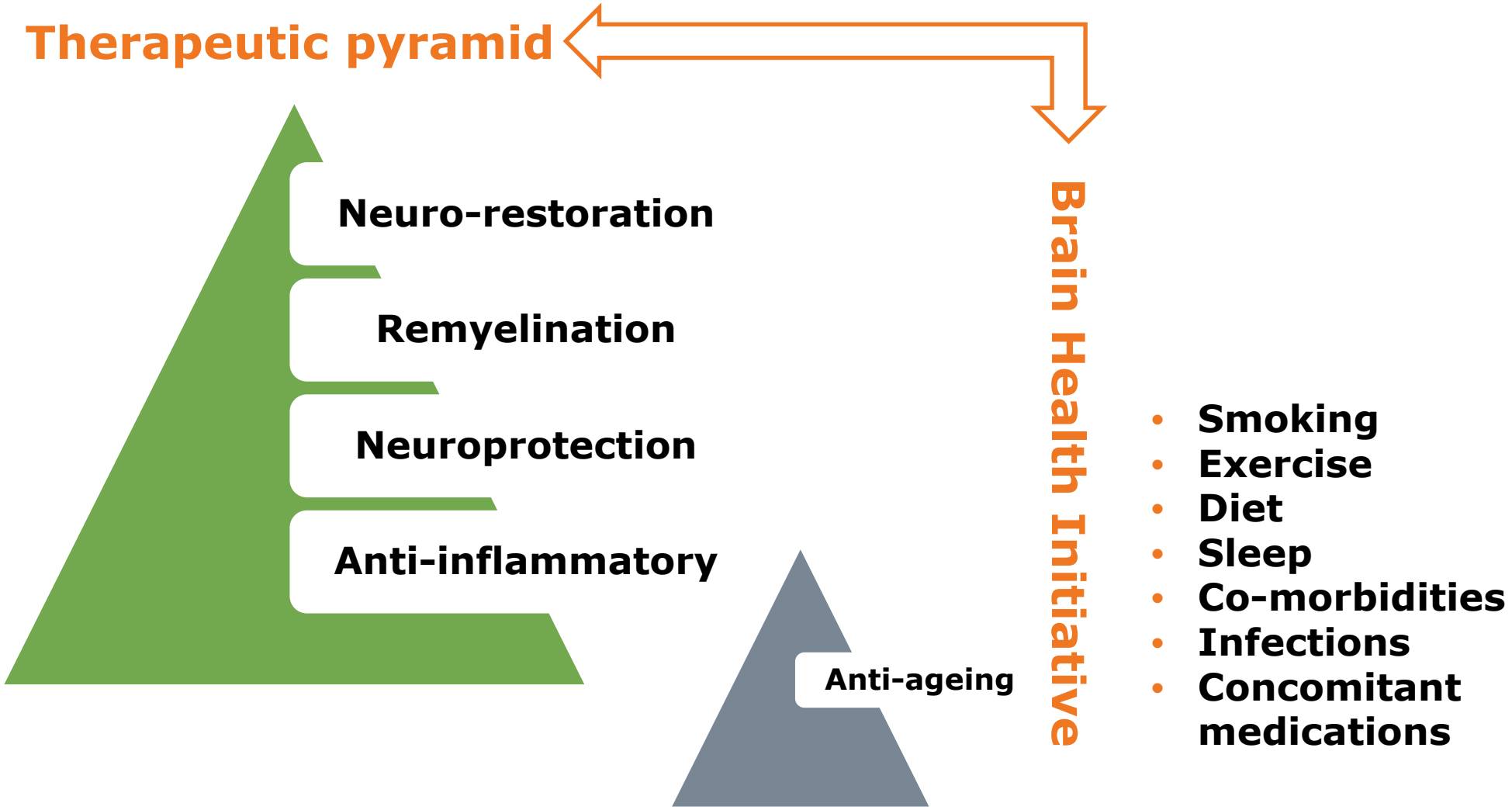
Our Vision Is to Create a Better Future for People with MS and Their Families

Your voice will help to effect this change

Be an early adopter

Pledge your support of the report's recommendations at www.msbrainhealth.org

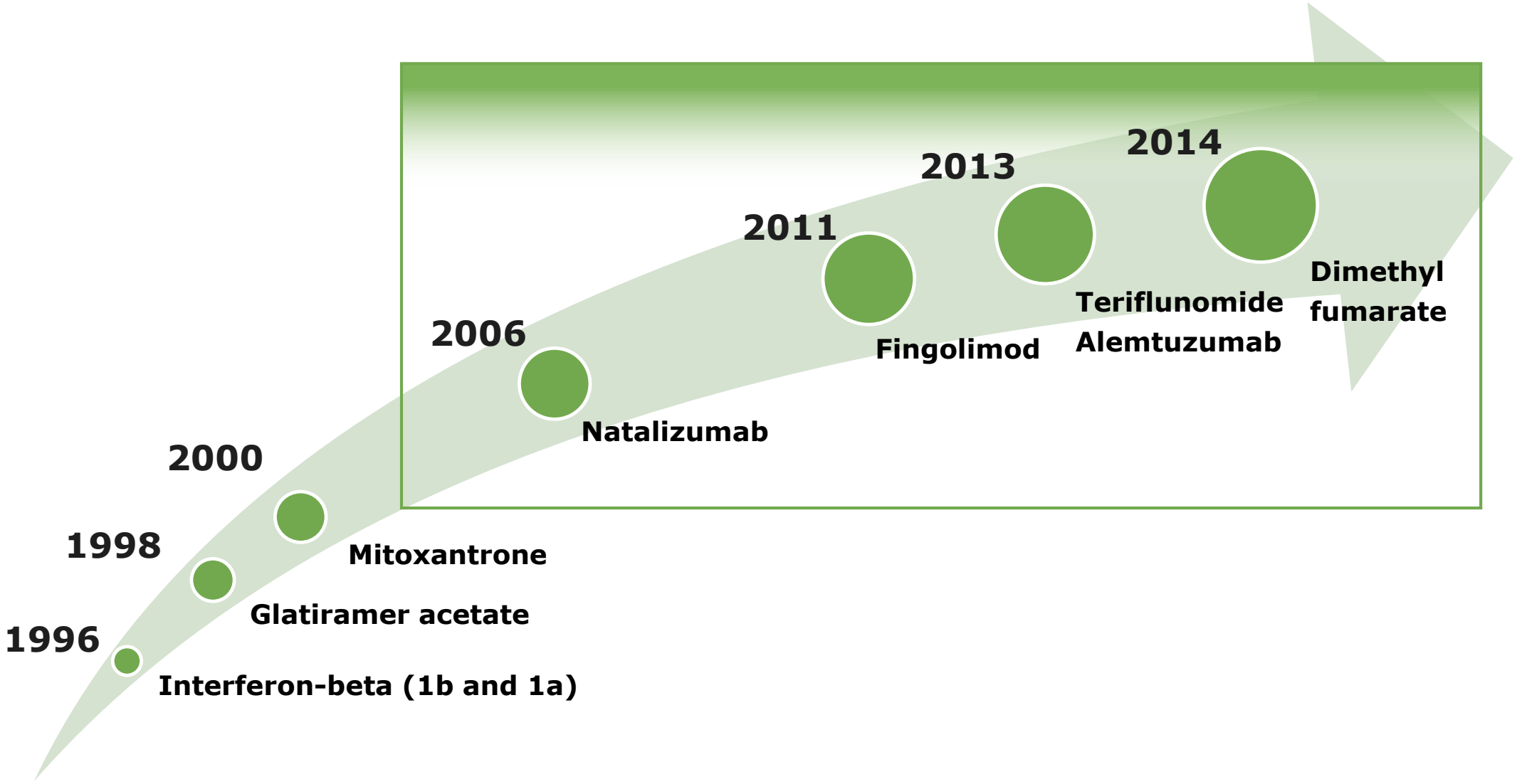
Therapeutic Hierarchy



Strategies to Reduce Time Spent with the Clinician and Enhance Adherence

- Dosing Schedule – 10 days annually for 2 years
- Oral administration – More appealing than needles
- Low Discontinuation Rate – Less anxiety for the patient and demand for HCP time
- Less Monitoring – Depends on the progression of MS and patient specific needs

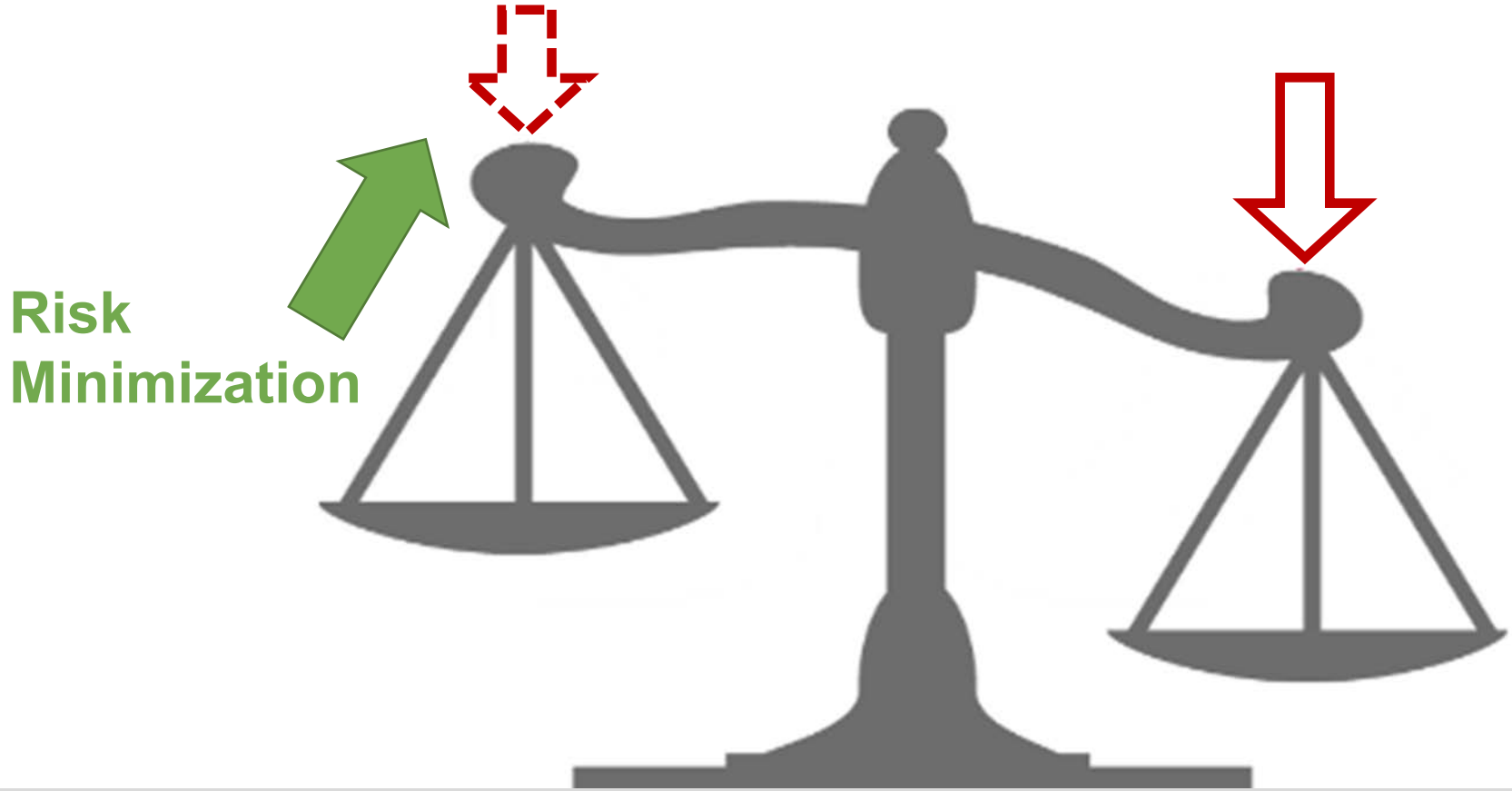
Evolution In Disease Modifying Drugs For Relapsing Remitting Multiple Sclerosis



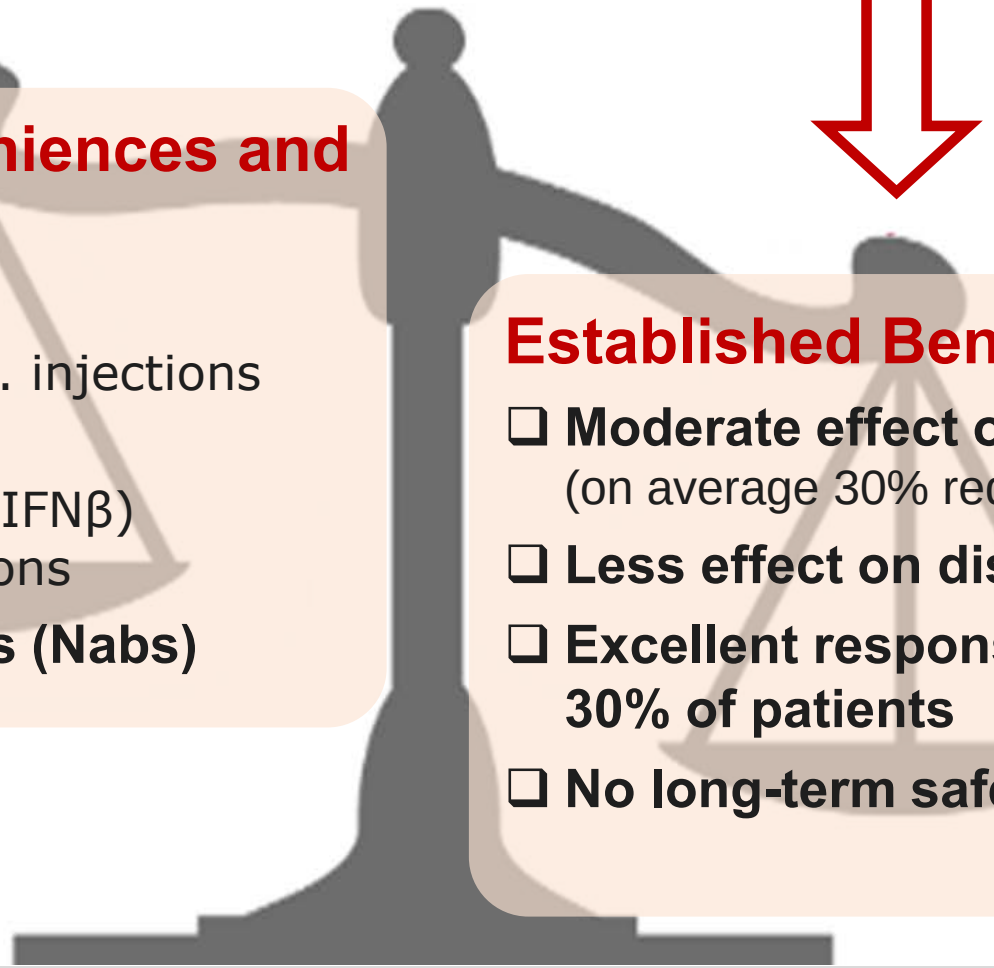
Disease modifying drugs: Benefit/risk evaluation

Established Inconveniences and Risks
- Convenience
- Monitoring
- Tolerability
- Safety

Established Benefits
- Treatment efficacy



Interferon Beta: Benefit/Risk Evaluation



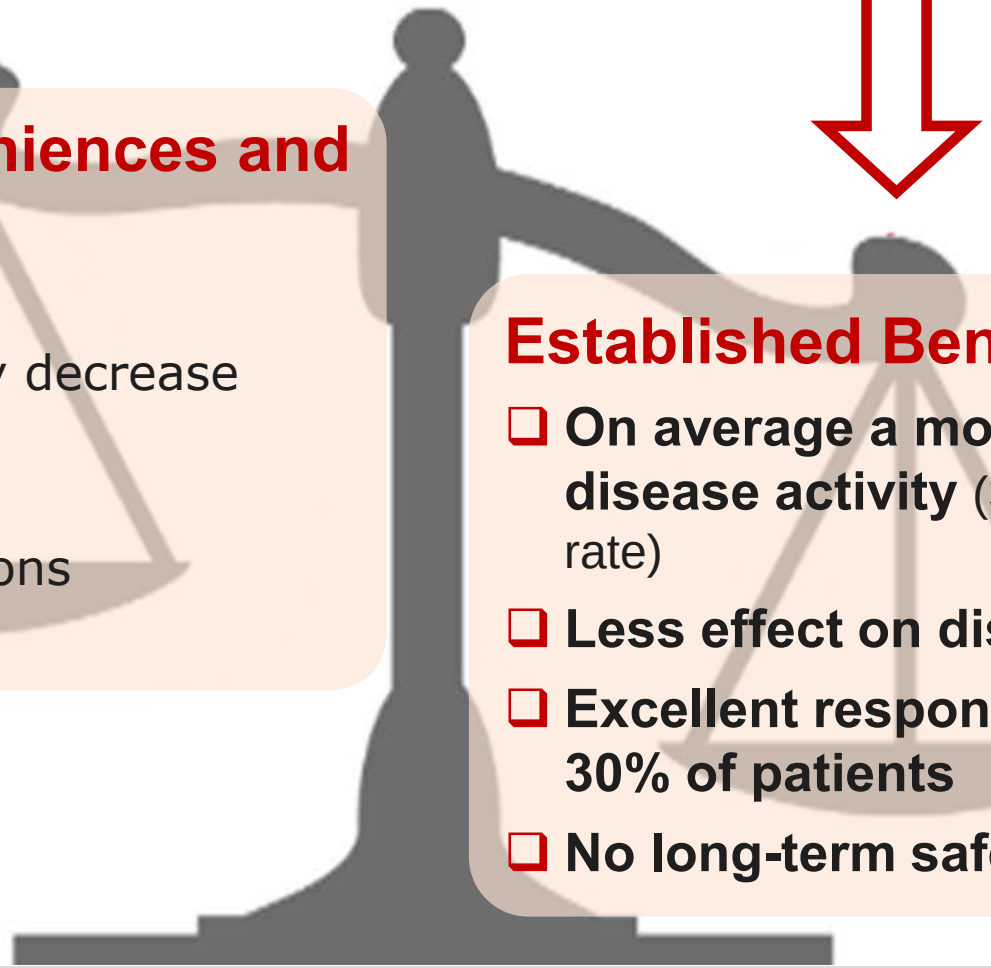
Established Inconveniences and Possible Risks

- ❑ **Injectable**
  - Frequent s.c. or i.m. injections
- ❑ **Trivial side effects**
  - Flu-like symptoms (IFNβ)
  - Injection site reactions
- ❑ **Neutralizing Antibodies (Nabs)**

Established Benefits

- ❑ **Moderate effect on disease activity** (on average 30% reduction in relapse rate)
- ❑ **Less effect on disability progression**
- ❑ **Excellent response in approximately 30% of patients**
- ❑ **No long-term safety concerns**

Glatiramer Acetate: Benefit/Risk Evaluation



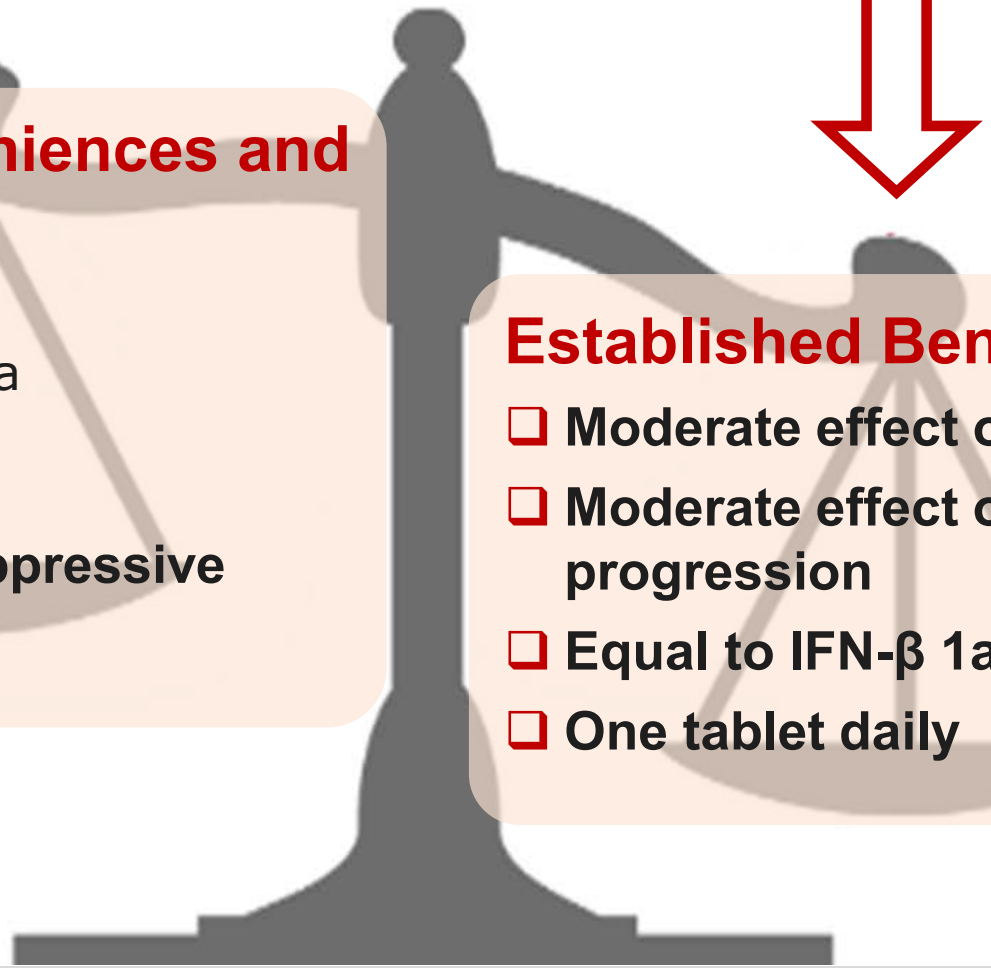
Established Inconveniences and Possible Risks

- **Injectable**
  - Daily injections may decrease adherence
- **Trivial side effects**
  - Injection site reactions
  - Systemic reactions

Established Benefits

- **On average a moderate effect on disease activity** (30% reduction in relapse rate)
- **Less effect on disability progression**
- **Excellent response in approximately 30% of patients**
- **No long-term safety concerns**

Teriflunomide: Benefit/risk Evaluation



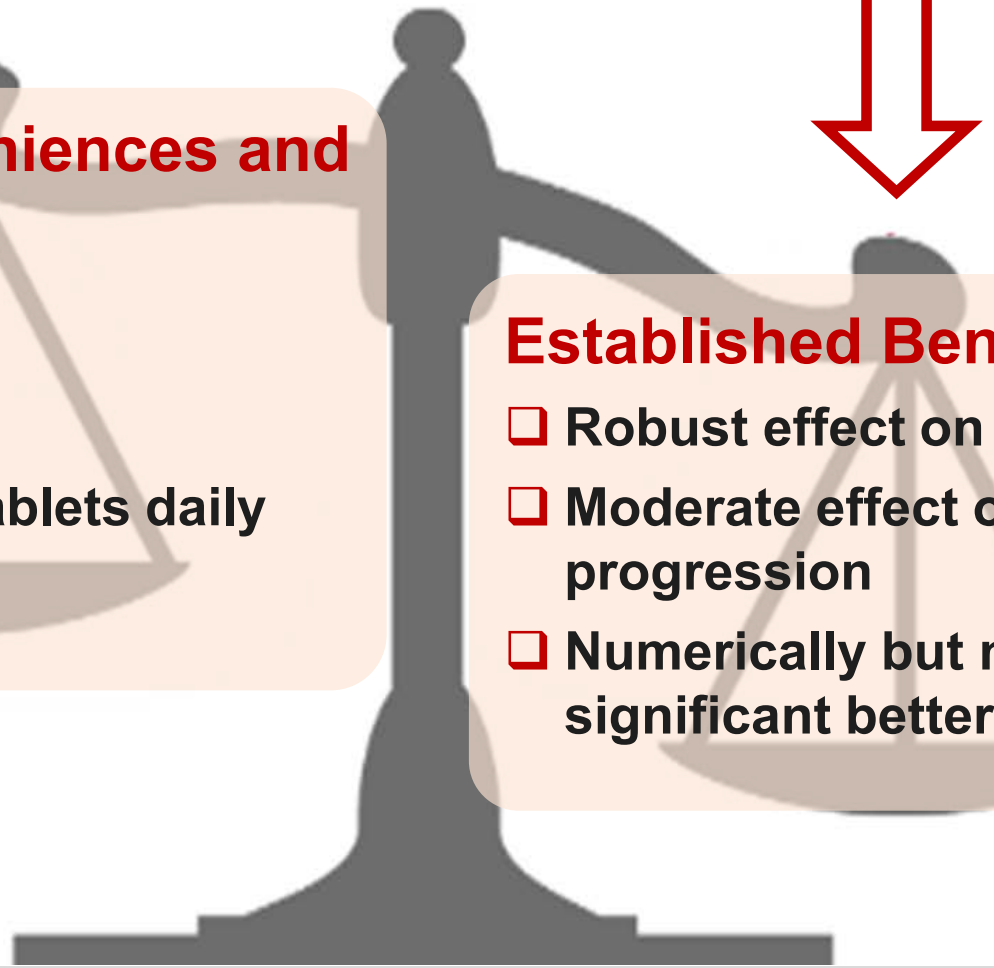
Established Inconveniences and Possible Risks

- **Adverse effects**
  - Diarrhea and nausea
  - Hair thinning
  - ALT increase
- **Potentially immunosuppressive properties**

Established Benefits

- **Moderate effect on disease activity**
- **Moderate effect on disability progression**
- **Equal to IFN-β 1a SC**
- **One tablet daily**

Dimethyl Fumarate: Benefit/Risk Evaluation



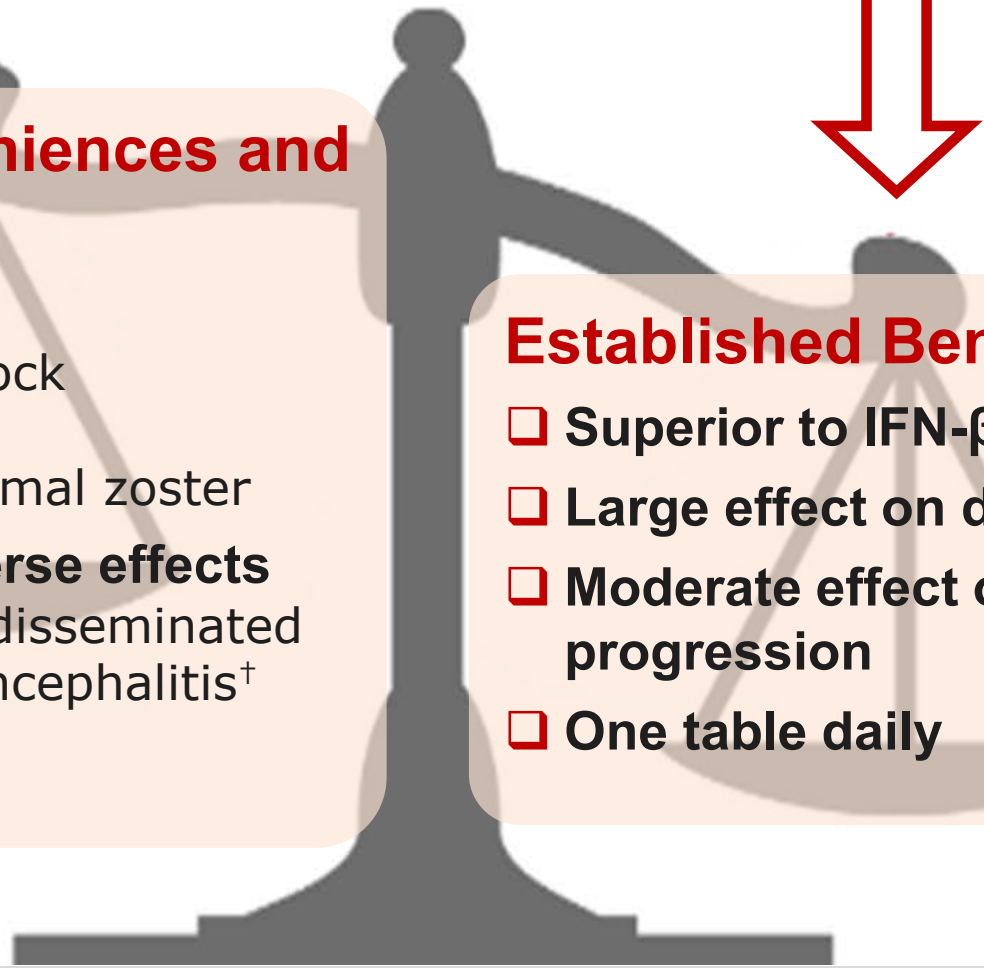
Established Inconveniences and Possible Risks

- ❑ **Adverse effects**
  - Flushing
  - Abdominal pain
- ❑ **Administered as two tablets daily**
- ❑ **Low risk of PML**

Established Benefits

- ❑ **Robust effect on disease activity**
- ❑ **Moderate effect on disability progression**
- ❑ **Numerically but not statistically significant better than GA**

Fingolimod: Risks/Inconveniences>Benefits



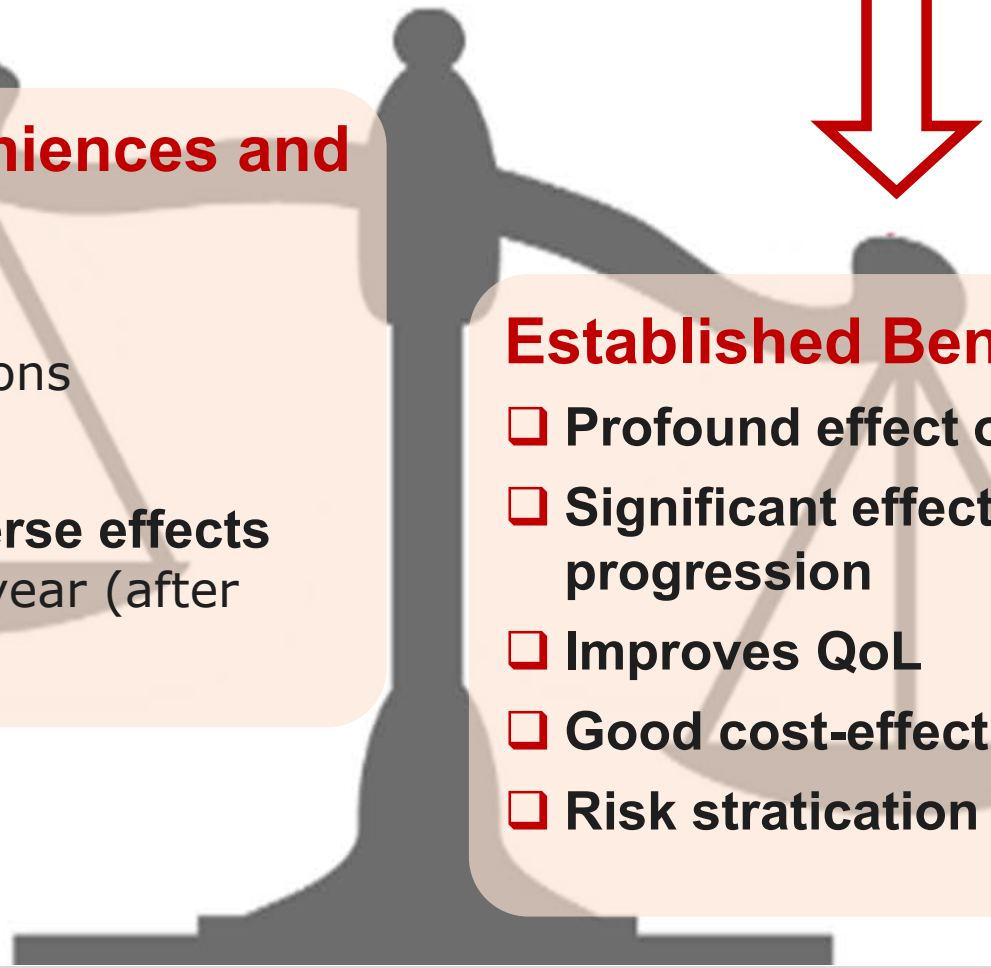
Established Inconveniences and Possible Risks

- **Adverse effects**
  - Bradycardia, A-V block
  - Retinal edema
  - Infections: dermatomal zoster
- **Infrequent severe adverse effects**
  - Serious infections: disseminated varicella†, herpes encephalitis†
  - Skin cancers
  - Single case of PML

Established Benefits

- **Superior to IFN-β 1a**
- **Large effect on disease activity**
- **Moderate effect on disability progression**
- **One table daily**

Natalizumab: Benefits>risks/inconveniences



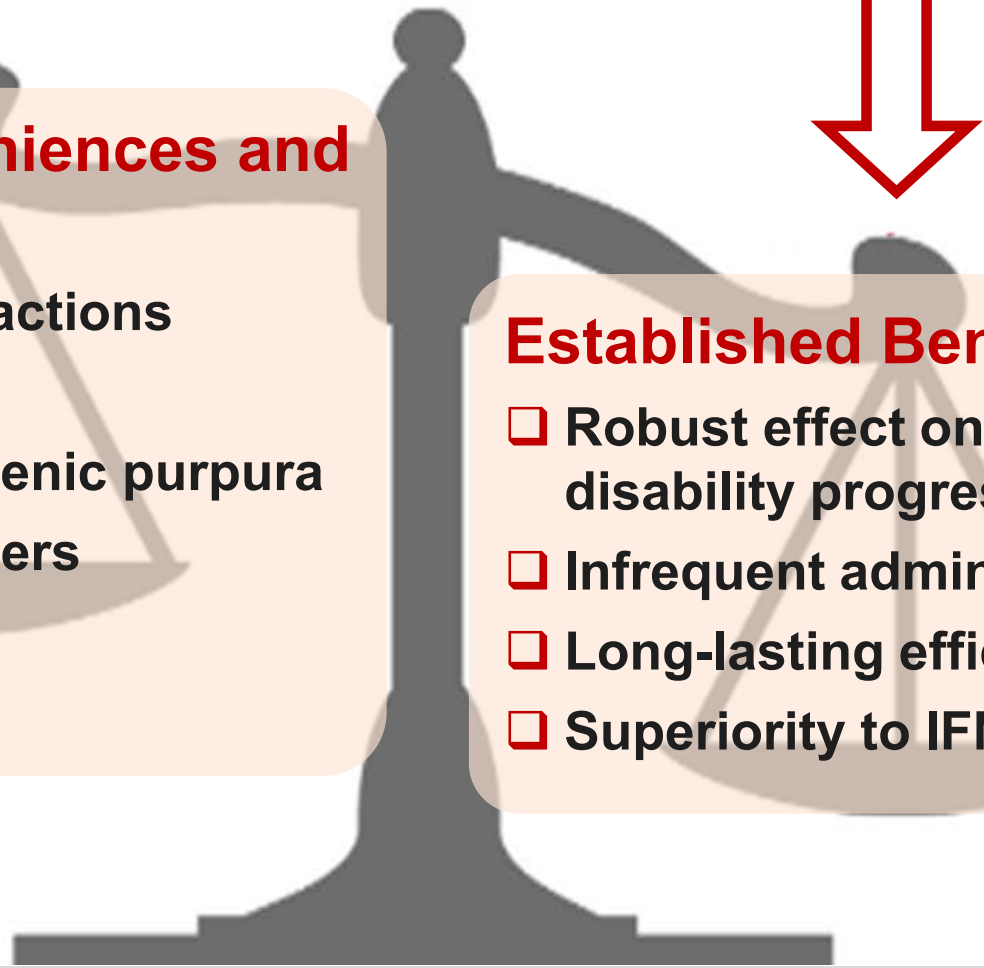
Established Inconveniences and Possible Risks

- ❑ **Intravenous infusions**
  - Rare infusion reactions
- ❑ **Rare Nabs**
- ❑ **Infrequent severe adverse effects**
  - PML in 2:1000 per year (after 2 years)

Established Benefits

- ❑ **Profound effect on disease activity**
- ❑ **Significant effect on disability progression**
- ❑ **Improves QoL**
- ❑ **Good cost-effectiveness**
- ❑ **Risk stratication for PML possible**

Alemtuzumab: Benefits>risks/inconveniences



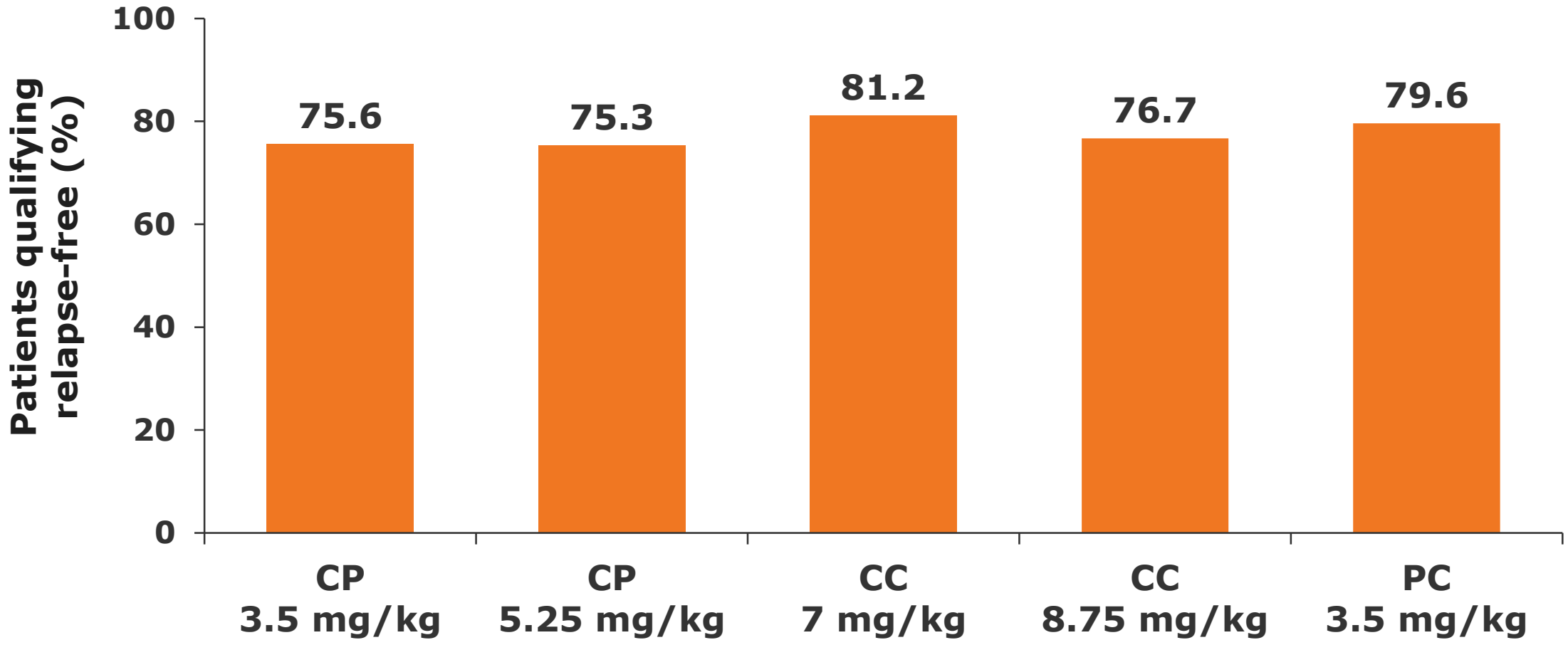
Established Inconveniences and Possible Risks

- ❑ Infusion associated reactions
- ❑ Infections
- ❑ Immune thrombocytopenic purpura
- ❑ Immune thyroid disorders
- ❑ Immune nephropaties
- ❑ Cytopenias

Established Benefits

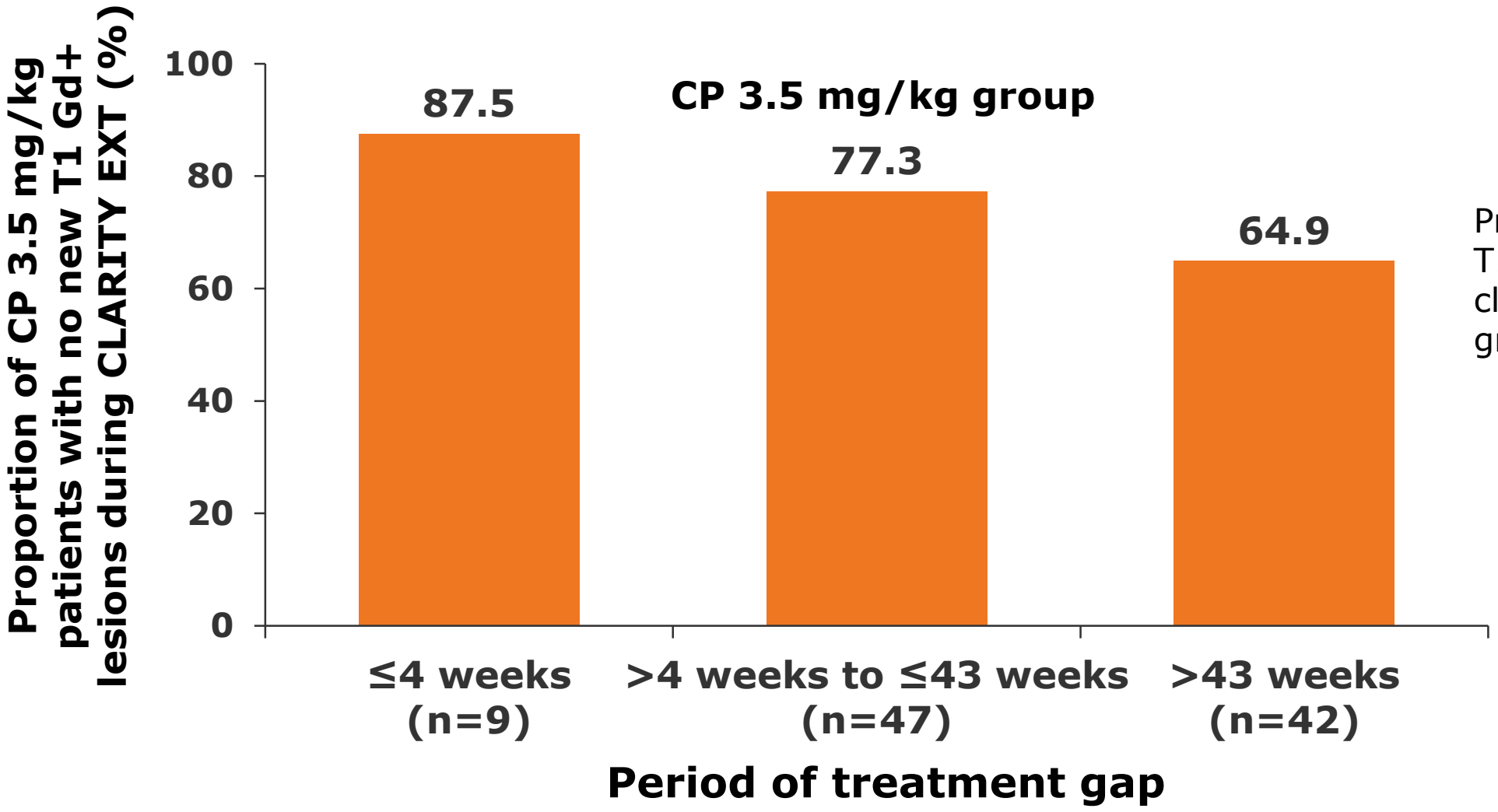
- ❑ Robust effect on disease activity and disability progression
- ❑ Infrequent administration
- ❑ Long-lasting efficacy
- ❑ Superiority to IFN-β 1a sc

75-81 % of Patients Treated in CLARITY were Relapse-Free after 2 Years vs No Additional Treatment



Giovannoni G et al. ECTRIMS Abstract 553 September 2016.

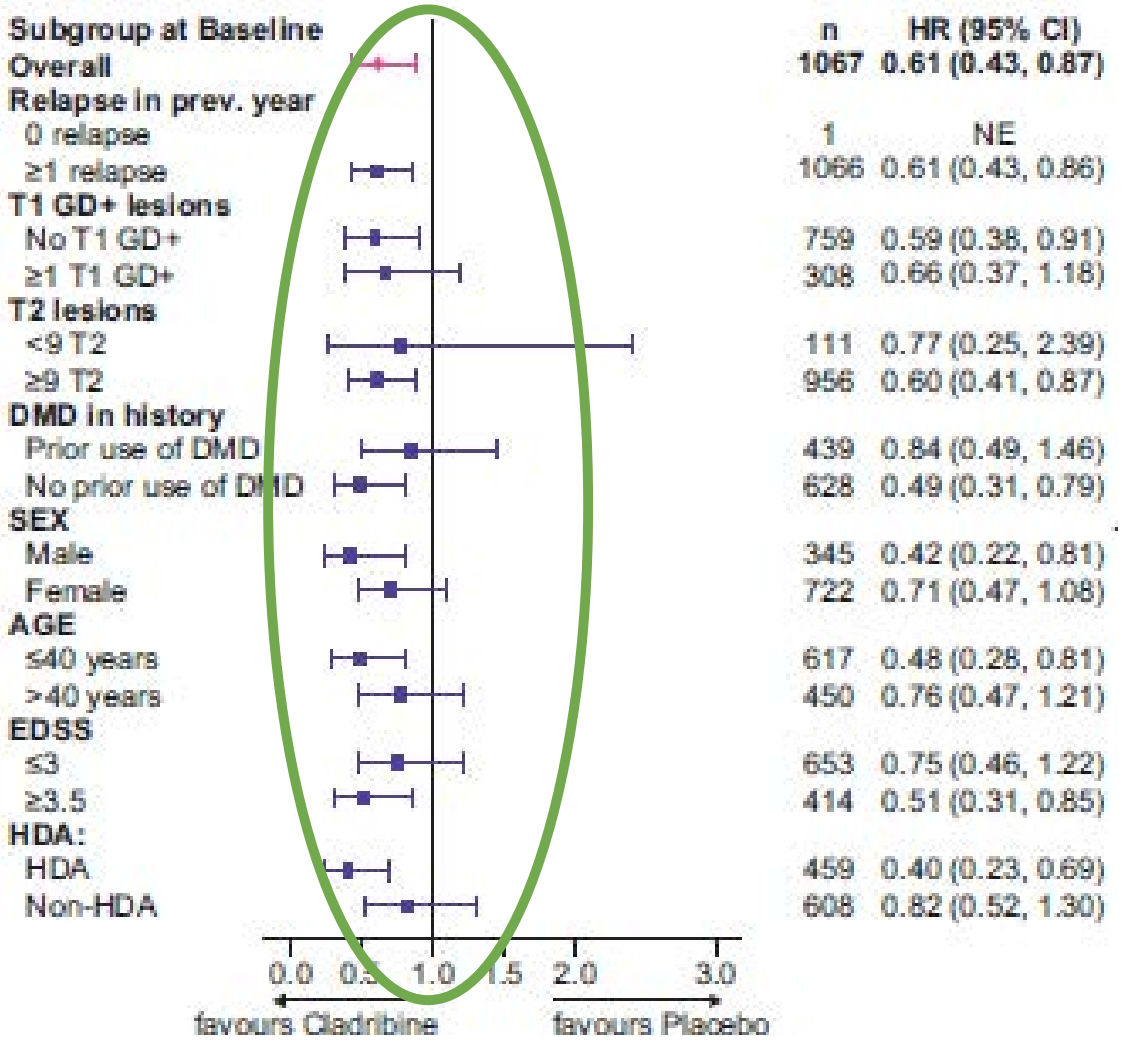
CLARITY EXT: Patients Free from Evidence of MRI Activity



Proportion with no new T1 Gd+ lesions in the cladribine 3.5 mg/kg group

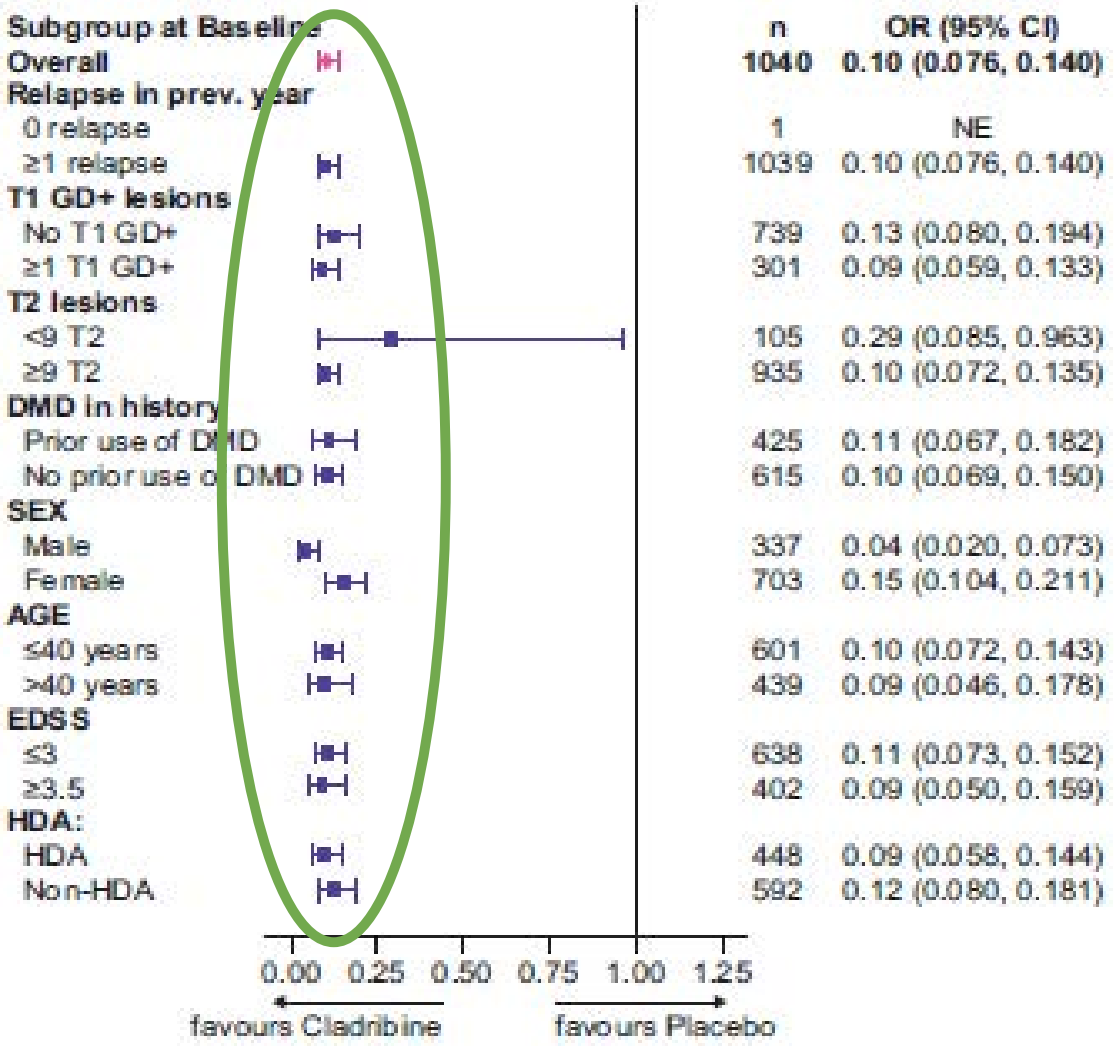
Giovannoni G et al. ECTRIMS Abstract 553 September 2016.

CLARITY: Effects of Cladribine 3.5 mg/kg on Time to 6-Month Confirmed EDSS Progression



Giovannoni G et al. ECTRIMS Abstract 605 September 2016.

CLARITY: Benefits of Cladribine on MRI Outcomes in Pooled Double-Blind Data - T1 gd+ lesions

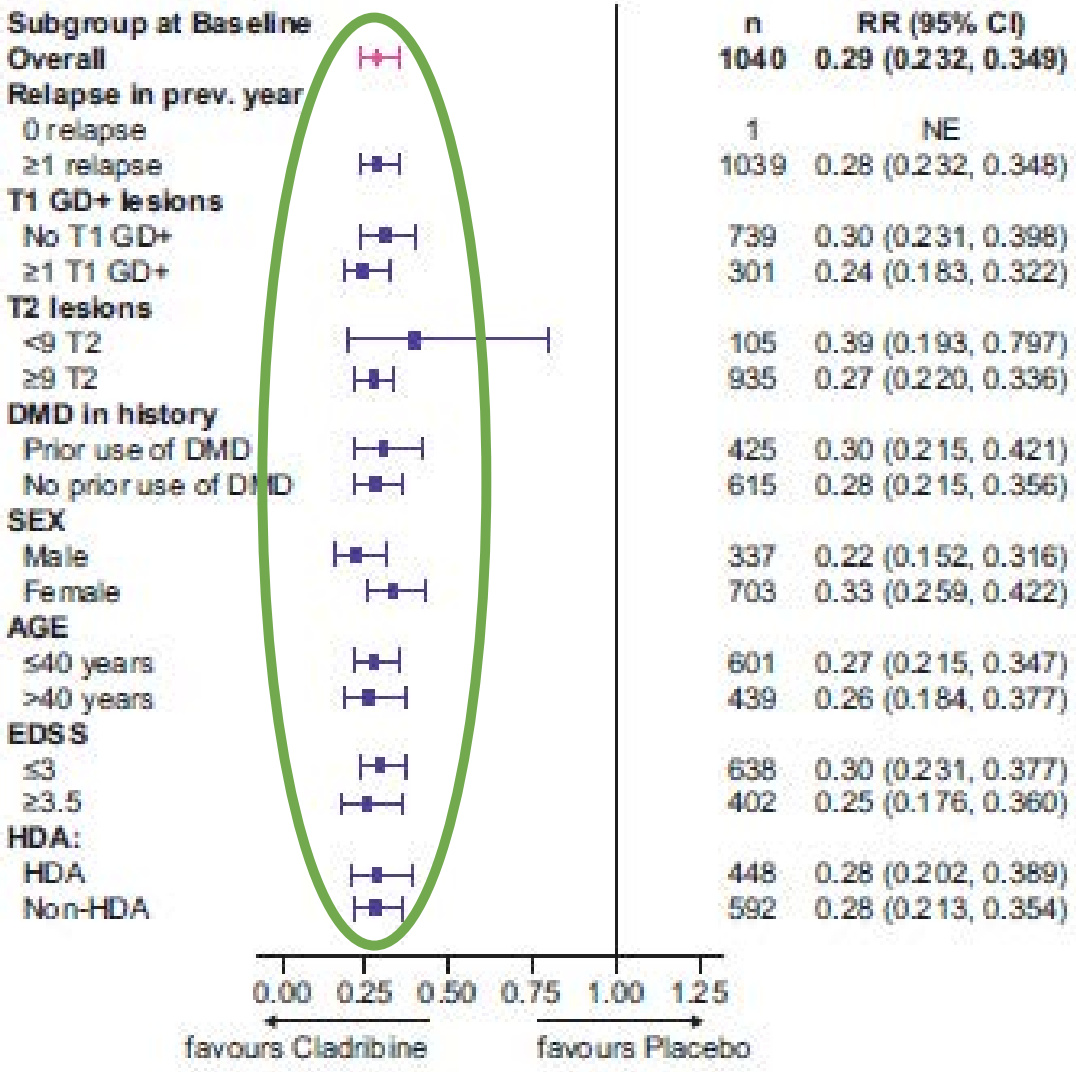


Effects of cladribine 3.5 mg/kg vs placebo on the relative risk ratio of cumulative new T1 gd+ lesions in patient subgroups.

Giovannoni G et al. ECTRIMS Abstract 605 September 2016.

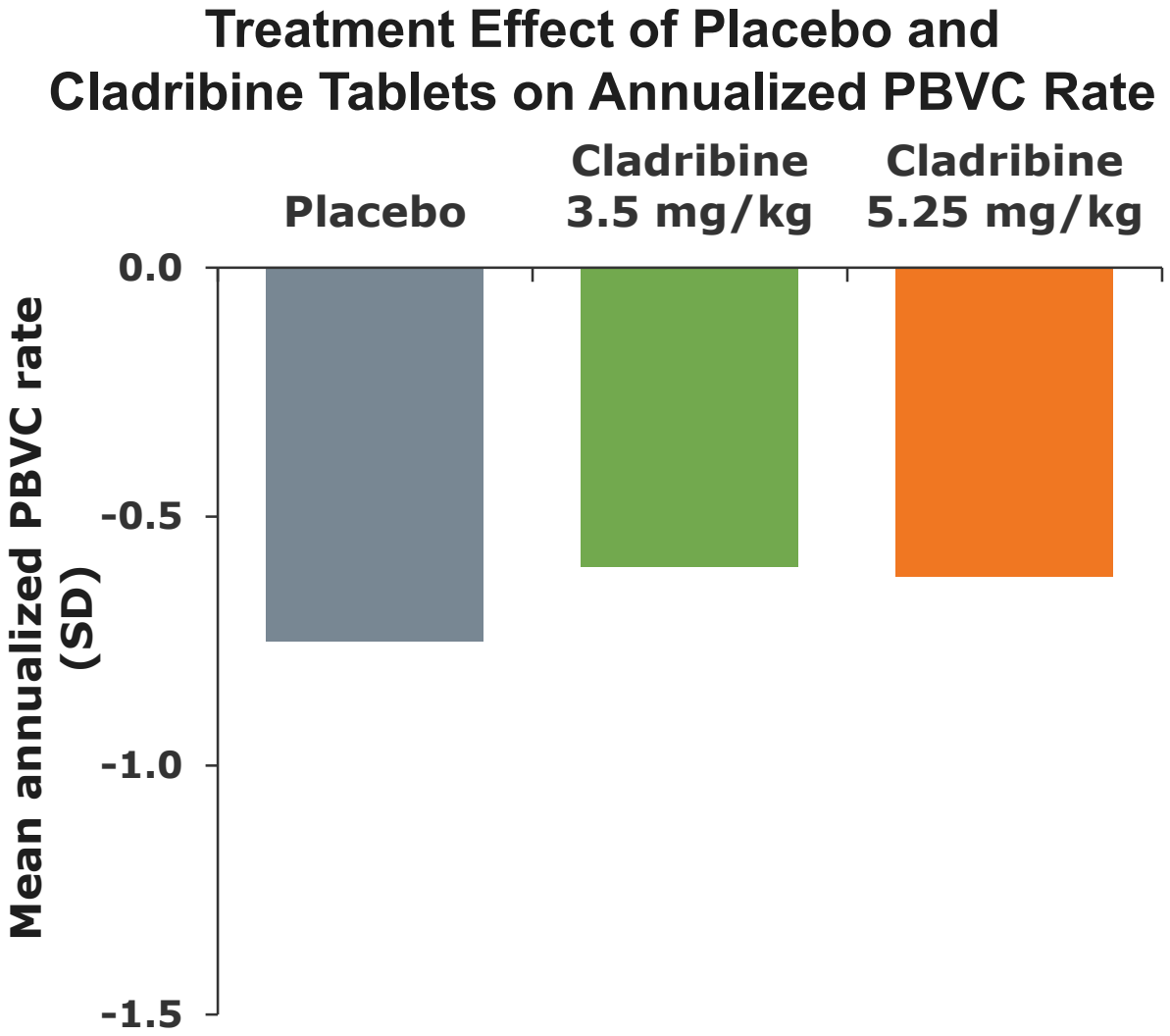
CLARITY: Benefits of Cladribine on MRI Outcomes in Pooled Double-Blind Data – T2 lesions

Effects of cladribine tablets 3.5 mg/kg vs placebo on the relative risk ratio of cumulative active T2 lesions in patient subgroups



Giovannoni G et al. ECTRIMS Abstract 605 September 2016.

CLARITY: Brain Volume Loss in Patients with Relapsing MS

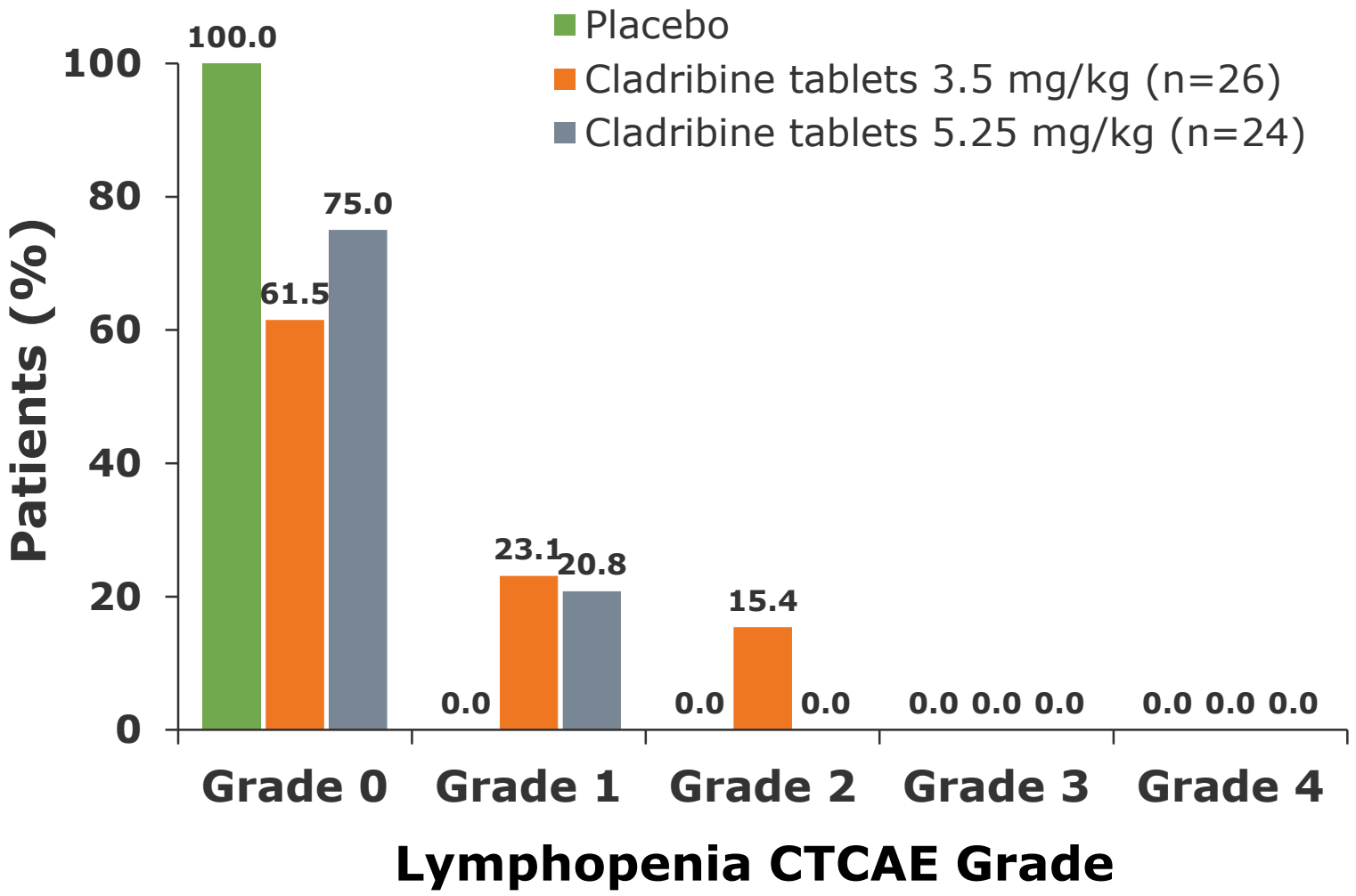


- 3.5 mg/kg or 5.25 mg/kg showed **significantly less brain atrophy** than placebo.
- Brain volume changes showed a correlation between brain atrophy and disability progression
- Treatment with cladribine tablets was associated with **a significantly lower risk of disability progression** compared with placebo.

Stefano ND et al. ECTRIMS Abstract 547 September 2016.

ORACLE-MS: Long-Term Follow-Up Analysis of Patients

Worst Post-Baseline CTCAE Grade in Patients Not Treated During Long Term Follow Up



Leist T et al ECTRIMS Abstract 609 September 2016.

Conclusions

- **MS is a disease that has far-reaching negative implications**
  - Mortality, disability, unemployment, divorce, suicide cognitive impairment, etc.
- **Era of Individualised Profiling**
  - Prognosis, risk, treatment and monitoring
- **New treatment paradigm**
  - Maintenance vs. induction therapy
  - Early highly-effective treatments are now a first-line option
  - Improved risk mitigation tools
  - New treatment paradigm of treat-2-target of NEDA (No Evidence of Disease Activity)
- **Is it fair to make patients wait 20 years for the outcome of an ongoing experiment?**