GIORNATA DELLO SPECIALIZZANDO IN NEUROLOGIA
11 GIUGNO 2019 – CATANIA

Strategia di trattamento nella Sclerosi Multipla:

Induction

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Strategie terapeutiche nella SM

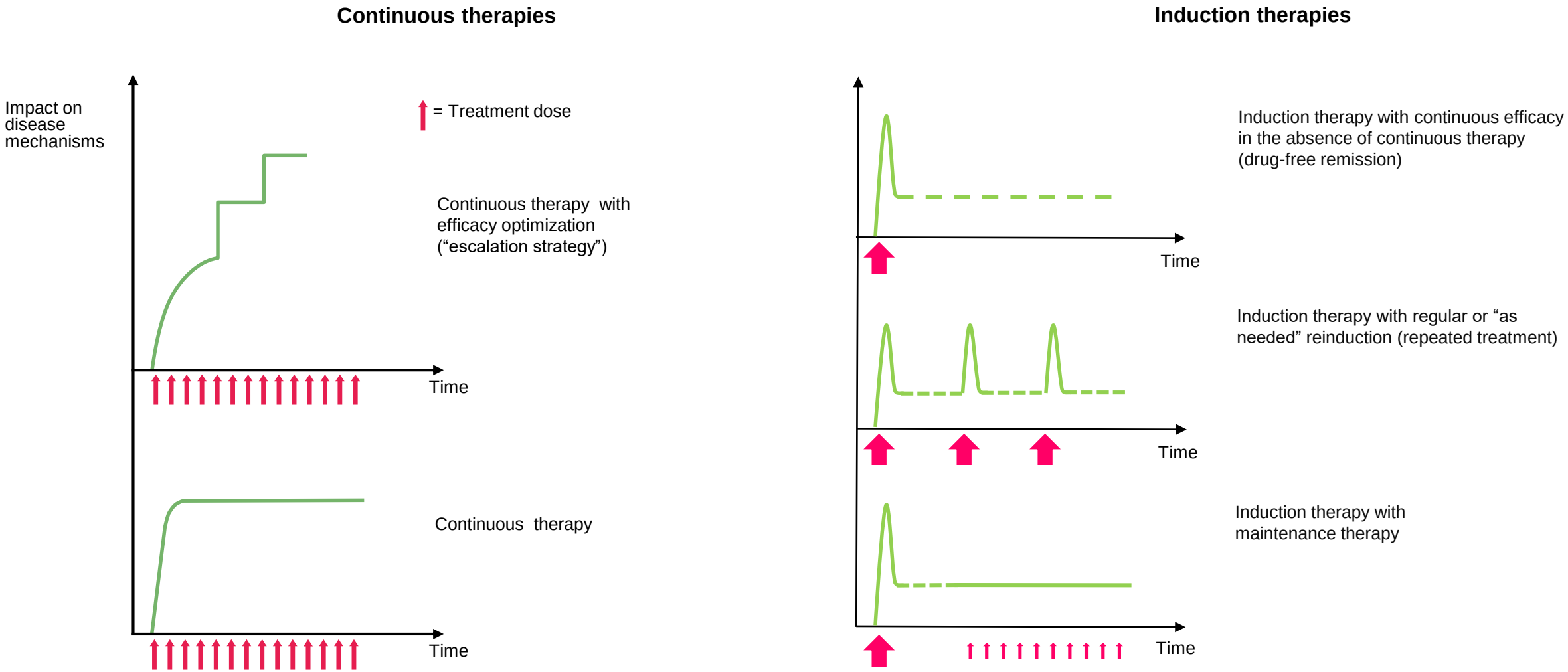


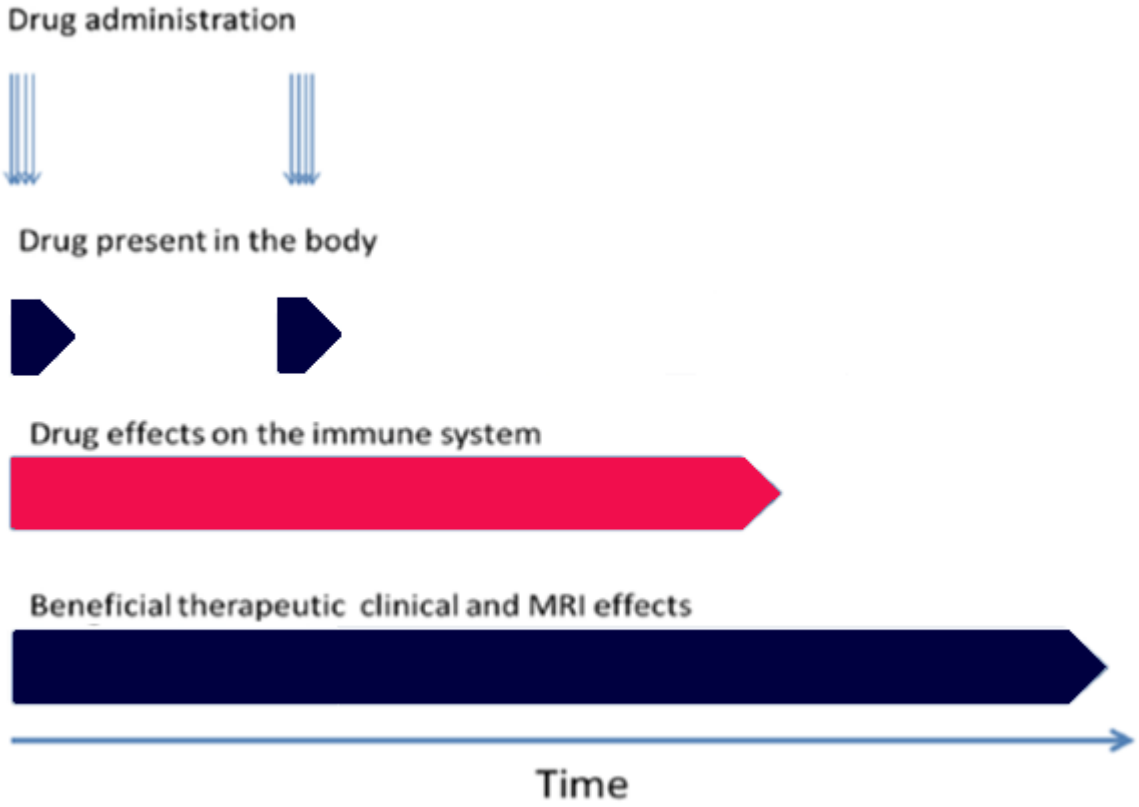
Figure adapted from Wiendl H et al. Neurology 2017;89:1098–100; 2.

Immune Reconstitution Therapy (IRT)

• Somministrazione intermittente per breve periodo e non continua di farmaci ad elevata efficacia

• Efficacia clinica estesa ben oltre il periodo di somministrazione con induzione di remissione a lungo termine

• Induzione di un reset immunitario seguito da graduale ripopolazione linfocitaria attraverso un pathway modificato



Sorensen and Sellebejerg, Pulsed immune reconstitution therapy in multiple sclerosis, Ther Adv Neurol Disord 2019

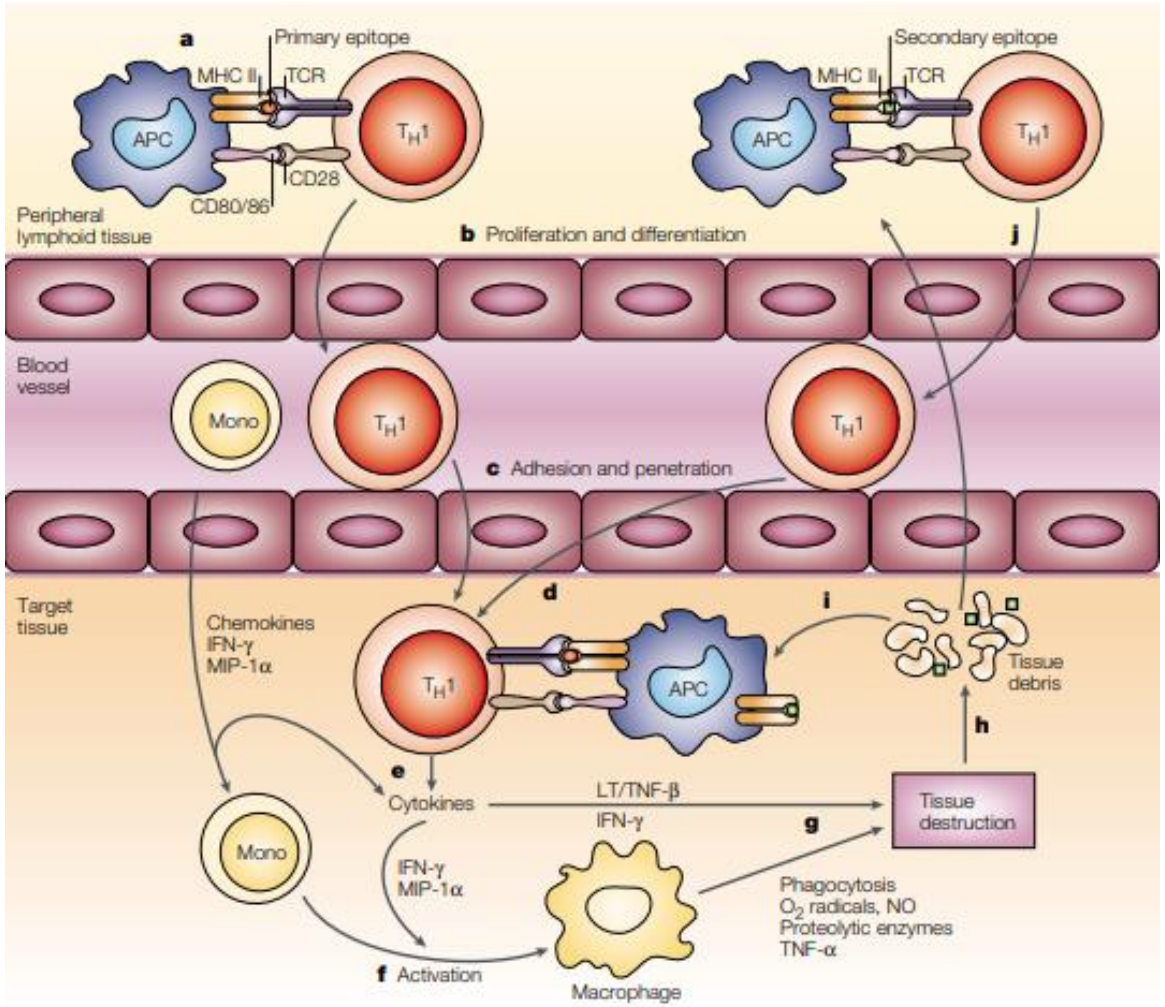
Epitope spreading

1) Presentazione dell'epitopo "trigger" (ignoto) ai linfociti T nel tessuto linfoide periferico

2) Attivazione e differenziazione dei linfociti Th1 autoreattivi

3) Migrazione dei linfociti Th1 nel tessuto target (SNC) dove ulteriori antigeni presentati dalle APC inducono rilascio di chemochine e citochine

4) Reclutamento di monociti dal sangue periferico e attivazione, con rilascio di TNFalfa, NO, enzimi proteolitici e danno tissutale



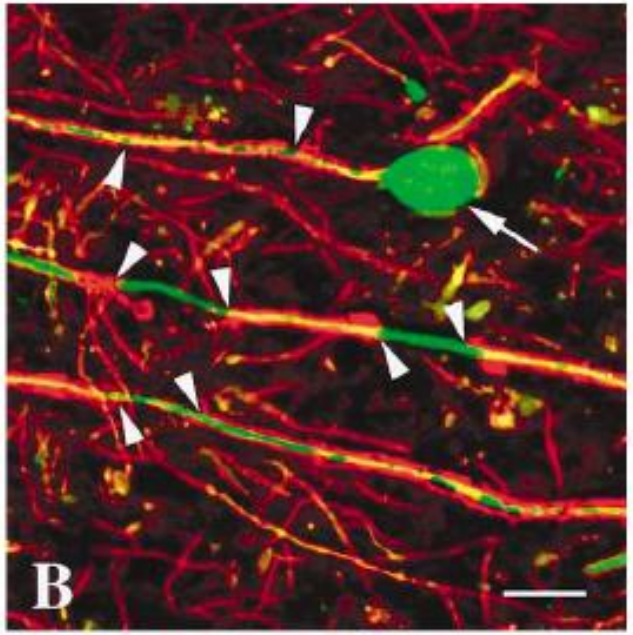
5) Attivazione, differenziazione e migrazione di nuovi linfociti Th1 in seguito a presentazione degli Ag tissutali con aumento del danno tissutale

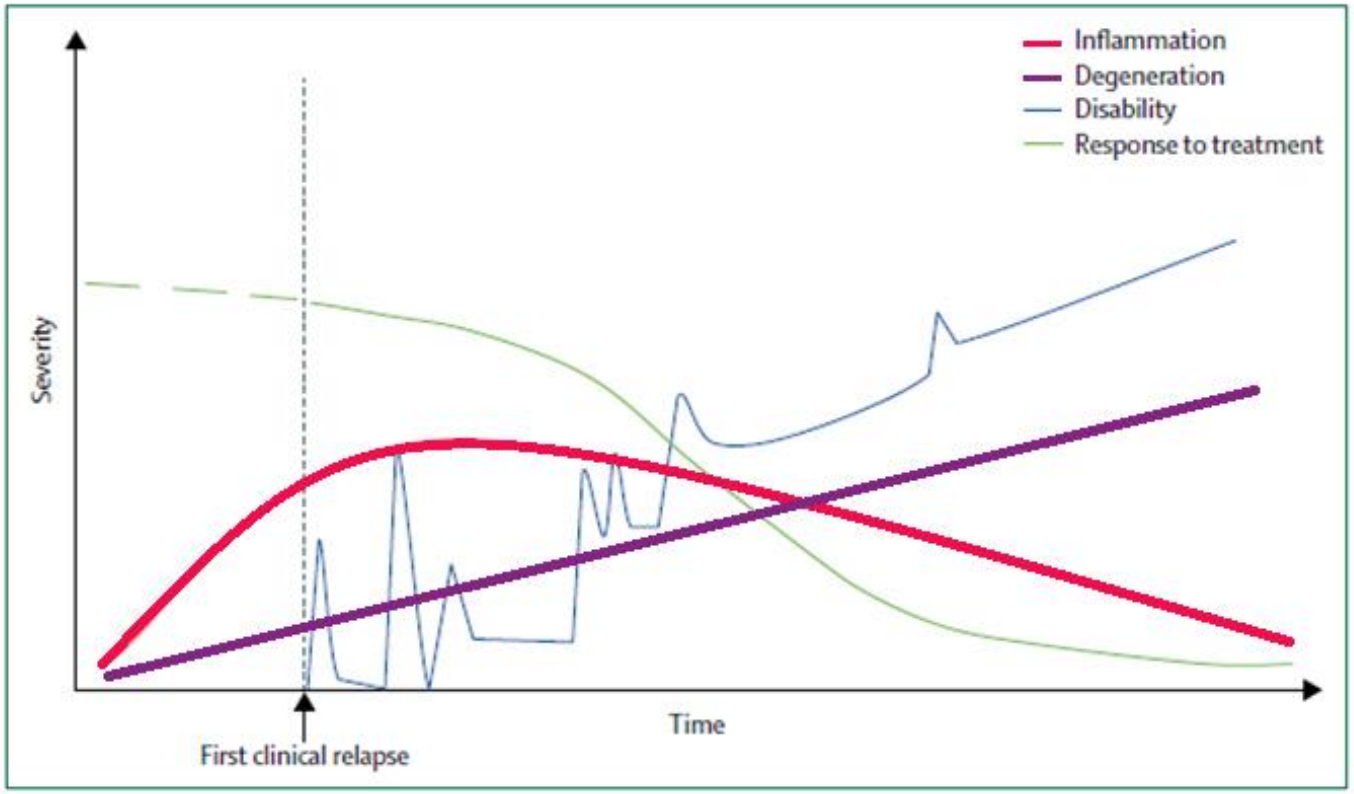
6) L'infiammazione persistente induce la migrazione nel SNC di nuove ondate di linfociti T non ancora attivati che, in presenza di segnali costimolatori, possono reagire a nuovi epitopi.

7) I linfociti T attivati e le cellule del sistema immunitario residente nel SNC promuovono la demielinizzazione attraverso meccanismi diretti e rilascio di fattori solubili infiammatori e neurotossici

Vanderlugt CL et al, Epitope spreading in immune-mediated diseases: implications for immunotherapy. Nat Rev immunol. 2002 Feb;2(2):85-95.

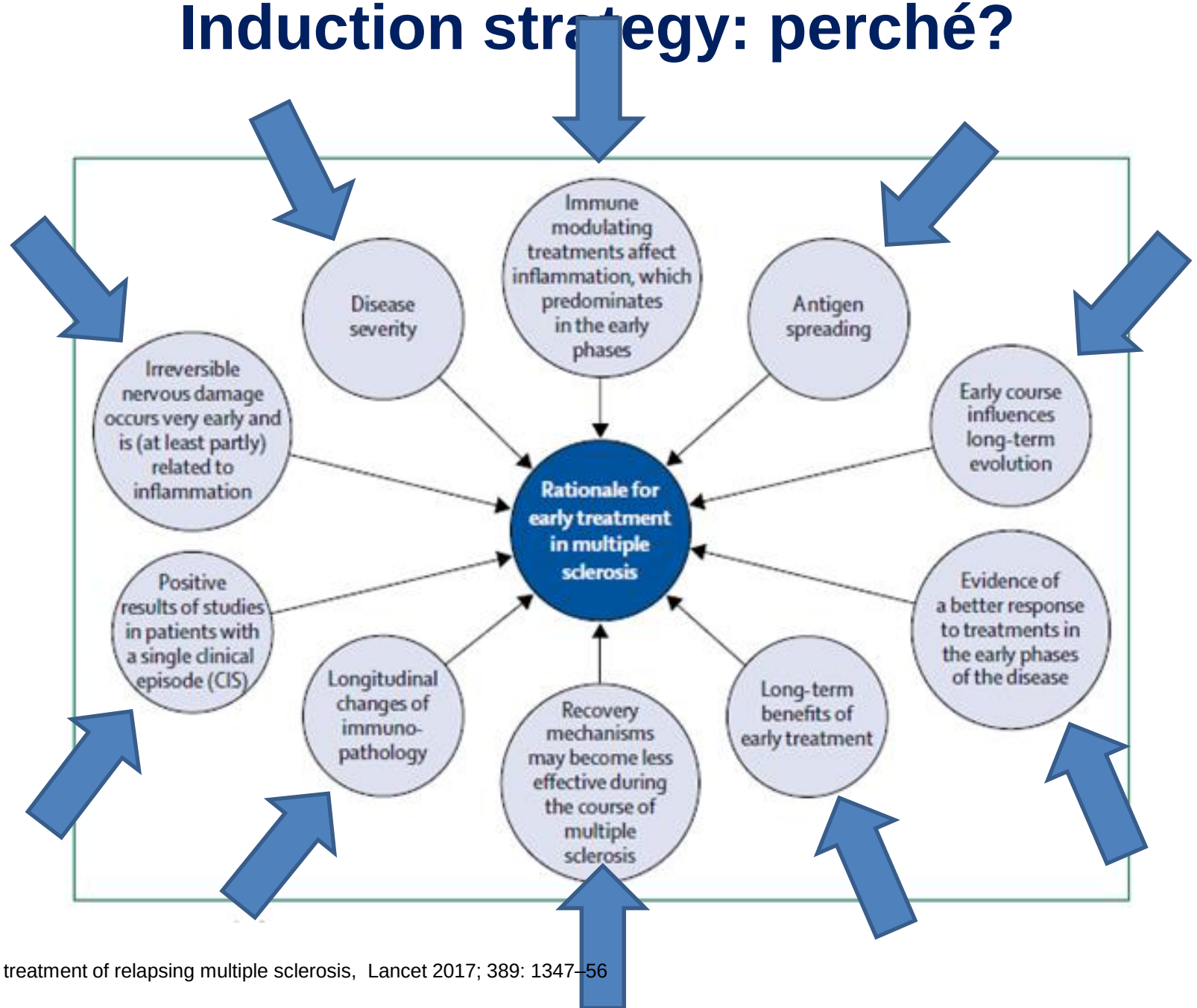
Induction strategy: perché?





Trapp et al, Axonal Transection in the lesions of Multiple Sclerosis, N Engl J Med 1998;338:278-85
Comi et al, Evolving concepts in the treatment of relapsing multiple sclerosis, Lancet 2017; 389: 1347–56

Induction strategy: perché?



Comi et al, Evolving concepts in the treatment of relapsing multiple sclerosis, Lancet 2017; 389: 1347–56

Induction strategy: con quale obiettivo?

- **A lungo termine: prevenire la disabilità fisica/cognitiva**

- **A breve termine: No Evidence of Disease Activity (NEDA)**

Migliore outcome clinico nel breve periodo

Ritardo nella progressione di disabilità nel lungo periodo

Il raggiungimento del NEDA a 2 anni ha un VPP del 78.3% per assenza di progressione (EDSS≤0.5) a 7 anni

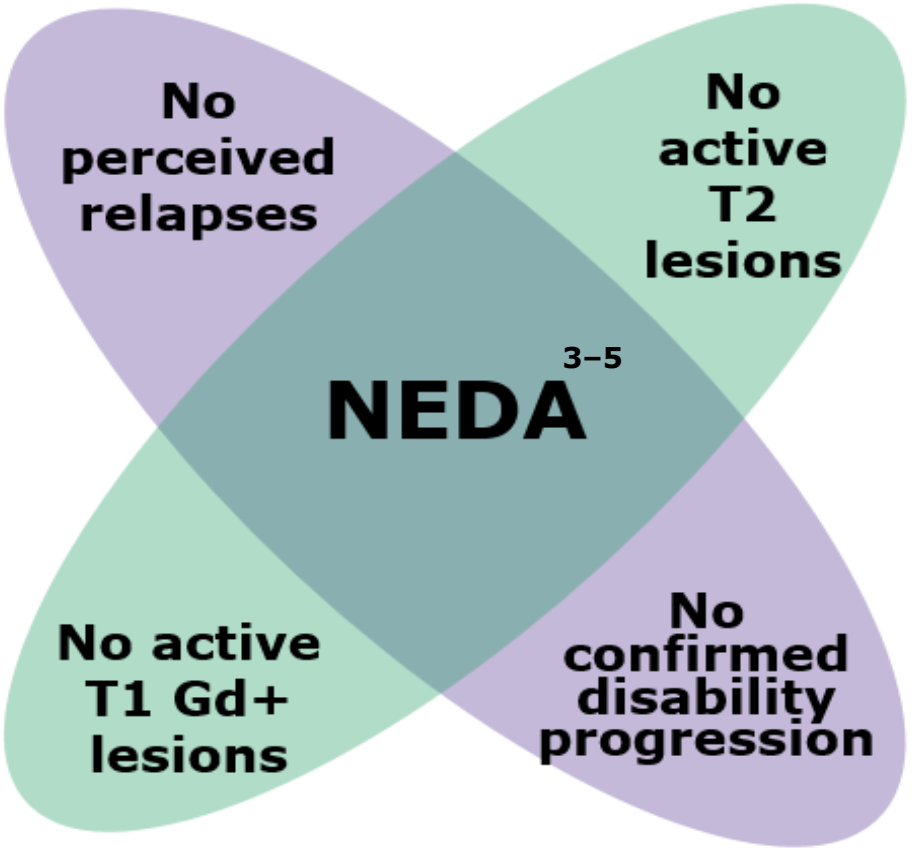
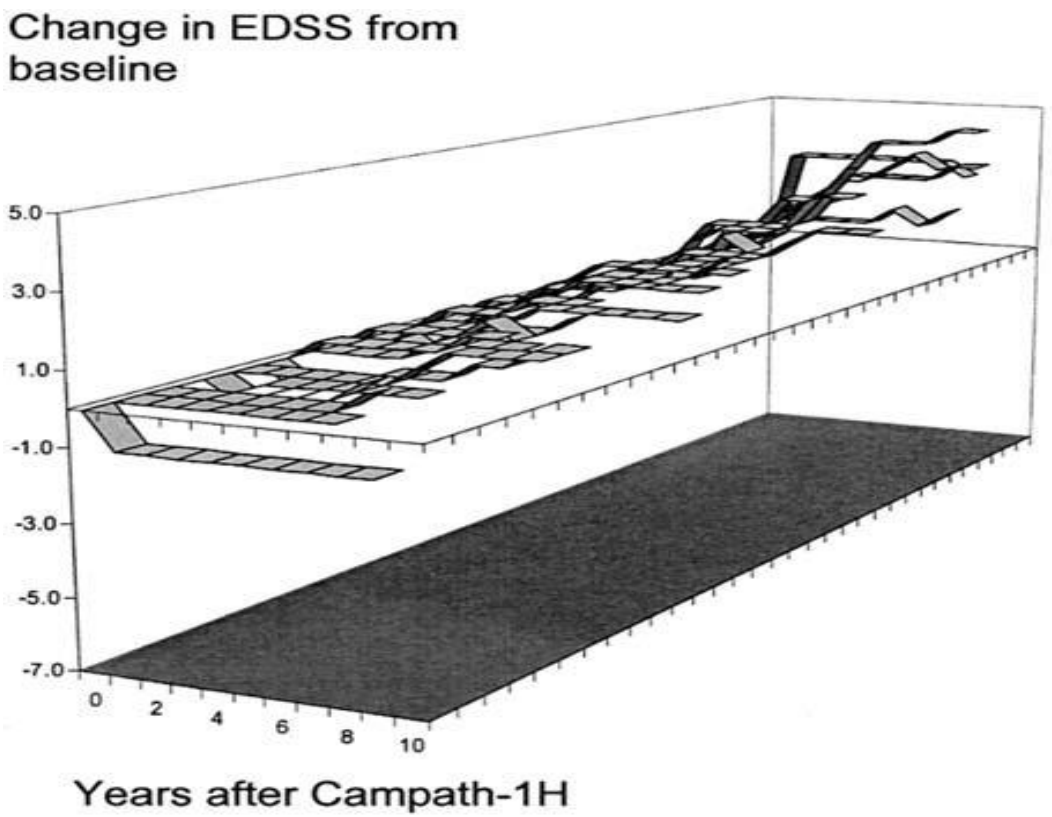


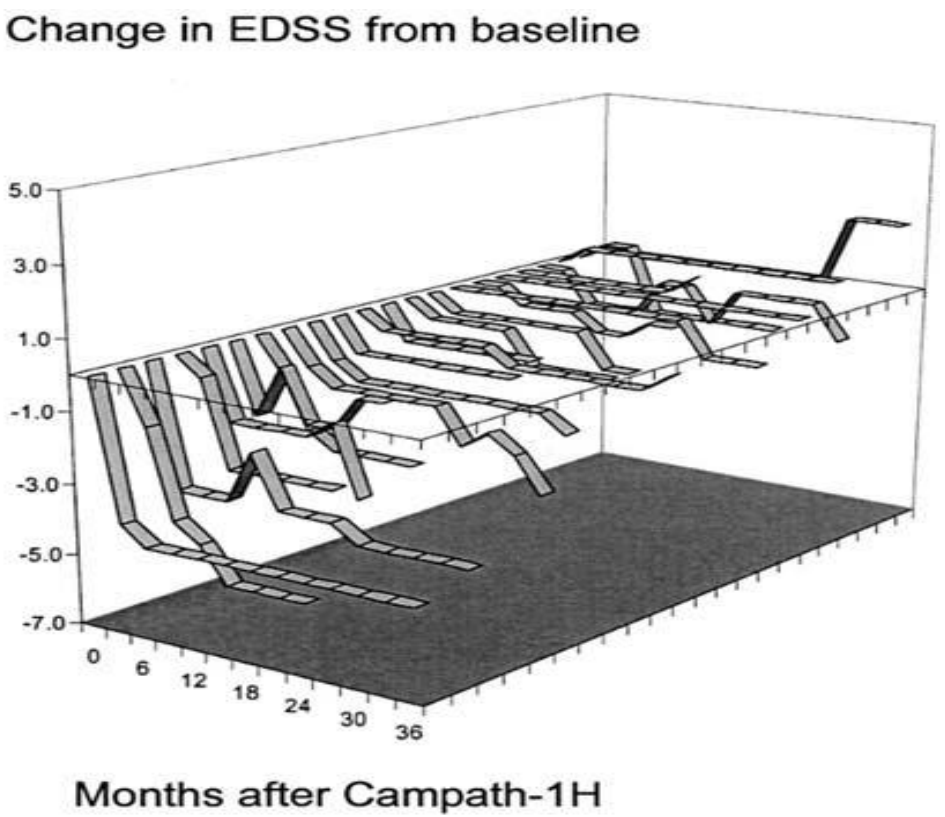
Figure developed from Giovannoni G et al. Lancet Neurol 2011;10:329–37
Rotstein D et al., Evaluation of No Evidence of Disease Activity in a 7-Year Longitudinal Multiple Sclerosis Cohort, JAMA Neurology (2015)72(2):152-158

Induction strategy: quando?

SMSP da 3 anni



SMRR elevata attività



Coles JA et al. The window of therapeutic opportunity in multiple sclerosis. Evidence from monoclonal antibody therapy. J Neurol (2006) 253 98–108

Induction strategy: per quali pazienti?

Table 1: Clinical and radiological factors suggestive of aggressive multiple sclerosis (MS)[8,9]

Clinical features	MRI features
Demographics Male sex Older age (>40 years) at onset African American African-Latin American	At onset High T2 lesion burden More than two gadolinium-enhancing lesions Presence of T1 lesions ('black holes') Early discernable atrophy Infratentorial lesions
Relapse severity ≥1-point change on EDSS, ≥2-points change on any individual functional system, or ≥1-point change on any two functional systems Steroid requirement Hospitalization	At follow-up Presence of new T2 lesions One or more new gadolinium-enhancing lesions
Type of attack Multifocal Partial or incomplete recovery Attack affects motor, cerebellar, sphincteric, or cognitive functions	
Relapse frequency Frequent relapses in the first 2-5 years Short inter-attack interval	
Disease course Rapid accrual of disability, e.g., EDSS score of 3.0 within 5 years, with superimposed relapses	

Adapted from Freedman et al. The Canadian J. of Neurological Science, 2018

Induction strategy: come attuarla?

- **Mitoxantrone seguito da interferone/copolimero**

  (T Vollmer et al Multiple Sclerosis 2008; 14: 663–670; Le Page et al. J Neurol Neurosurg Psychiatry 2008;79:52 6; Le Page et al. Neurology 2008;70(Suppl 1):A227)

- **Ciclofosfamide seguita da interferone/copolimero**

  (Harrison M et al. MSJ 2012 18:2 202-209; Ramtahal J, Boggild M. Mult Scler 2008;14:S175, Smith DR et al. Mult Scler 2005 Oct;11(5):573-82; *Patti F et al.J* Neurol Neurosurg Psychiatry. 2001 Sep;71(3):404-7;*)*

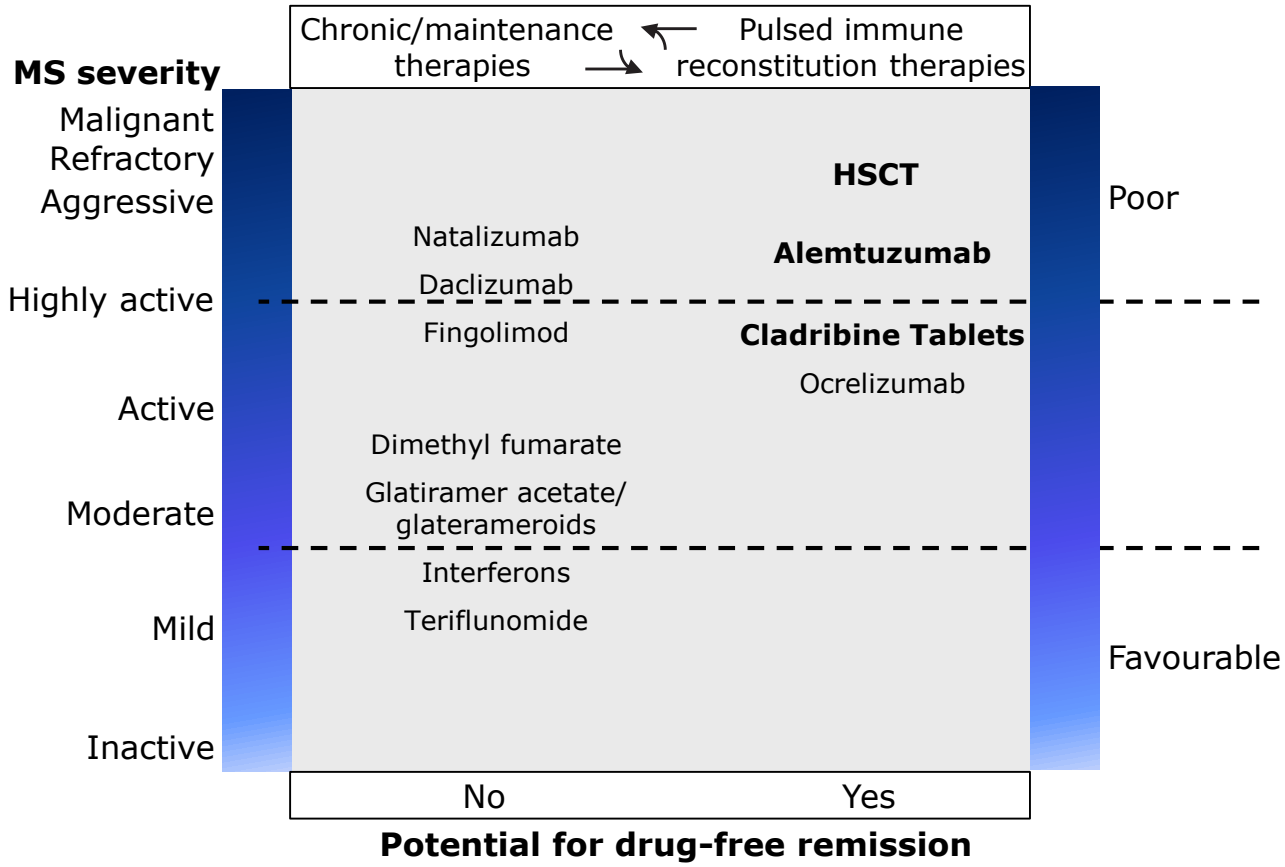
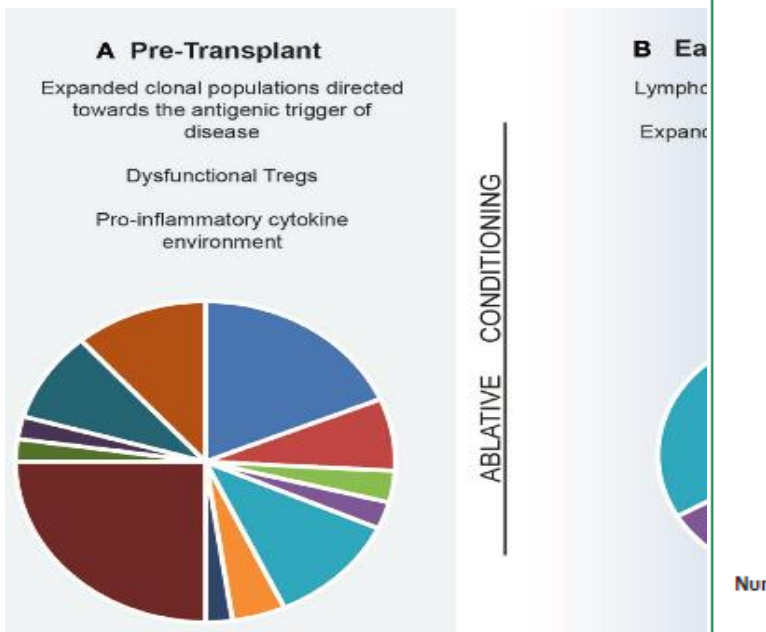


Figure adapted from Wiendl H, Nat Rev Neurol 2017, 13:573–4

Induction strategy: aHSCT

- **Mobilisation** (G-CSF with or without chemoterapy)
- **HSC collection** (cryopreservation with or without ex-vivo T-cell depletion)
- **Conditioning regimen** (chemotherapy with or without total body irradiation)
- **HSC infusion** (with or without in-vivo T-cell depletion)
- **Aplastic phase**
- **Recovery**



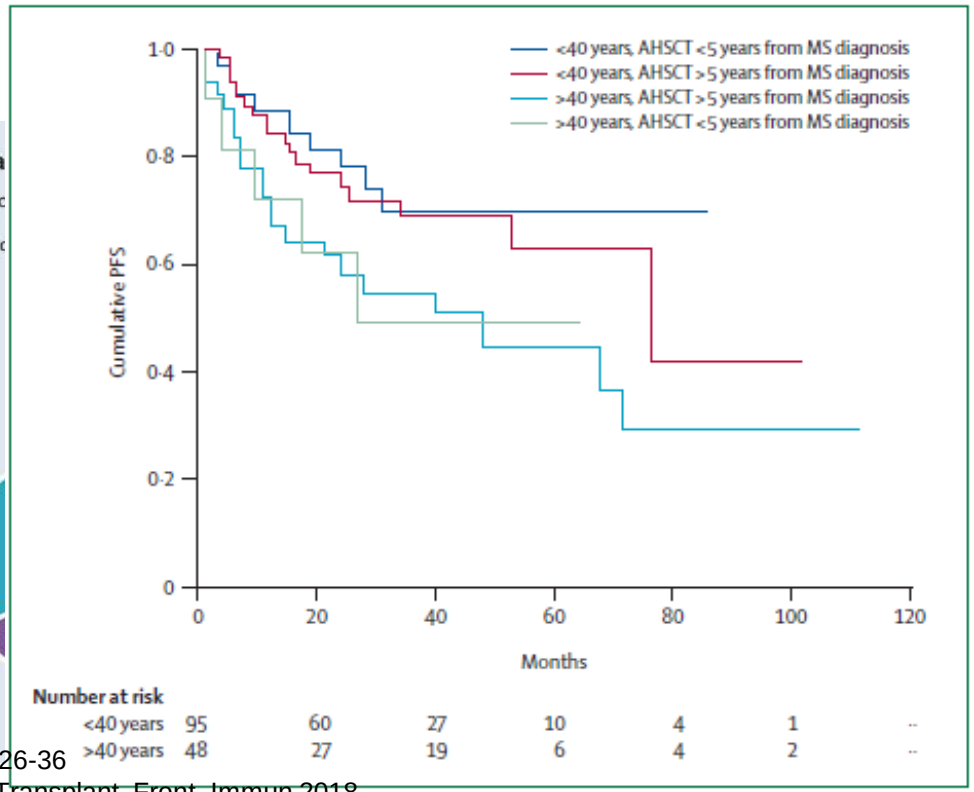


Figure 2: Kaplan-Meier curves of progression-free survival (PFS) according to age and years from diagnosis

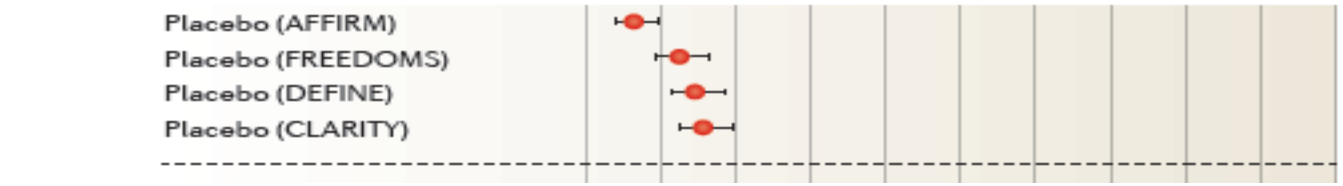
Mancardi et al, Autologous haematopoietic stem-cell transplantation in multiple sclerosis, Lancet Neurol 2008; 7:626-36
Massey JC et al, Regenerating Immunotolerance in Multiple Sclerosis with Autologous Hematopoietic Stem Cell Transplant, Front Immun 2018

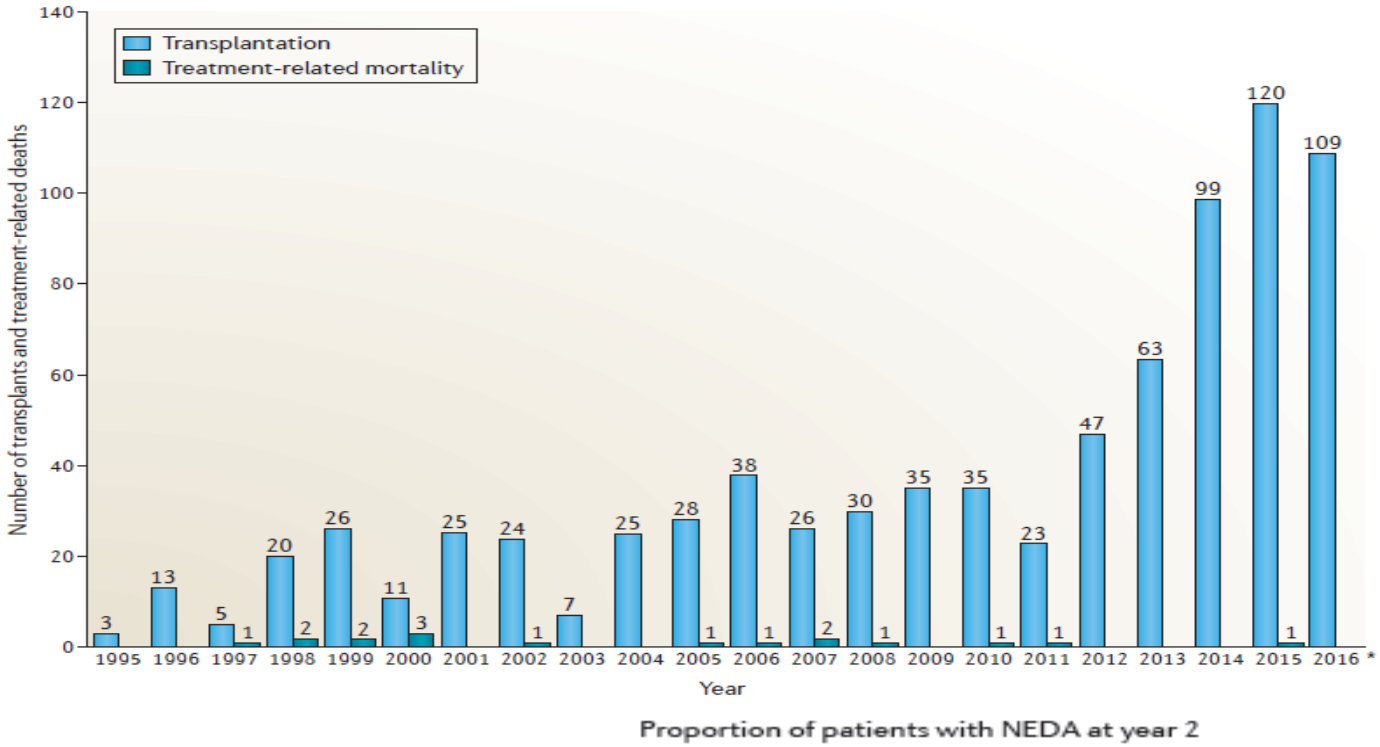
Induction strategy: aHSCT

IMMUNE RECONSTITUTION THERAPIES	
	AHSCT
Meccanismo di azione	Condizionamento con chemioterapia linfo/mieloablativa seguita da salvataggio di cellule staminali autologhe
Efficacia	
Ripopol	
Ripopol	
Ripopola	
Effetto su output timico	Aumento CD4+CD31+ e aumento T cell receptor excision circle

Adverse events

- TRM decreased from 7.3% (1995-2000) to 1.3% (2001-2007)
- In a 2017 meta-analysis of clinical trials for aHSCT in MS, TRM was 0.3% in patients transplanted after 2005
- Early toxic effects (56%): flares of disease, allergic reactions, fever, mucositis, engraftment syndrome
- Late toxic effects (6%): secondary autoimmune disorders, infectious risk (VZV)





Muraro et al., Nature Neurol Rev 2017

Induction strategy: Alemtuzumab

IMMUNE RECONSTITUTION THERAPIES	ALEMTUZUMAB
Meccanismo di azione	Lisi cellulare IgG3-mediata dei linfociti CD52
Efficacia nella SMRR	Remissione clinica e radiologica a 2 anni del 39% (Phase 3 treatment-controlled trials)
Ripopolazione linfociti T CD4+	Il 70–80% ritorna al baseline a 12 e 24 mesi
Ripopolazione linfociti T CD8+	Riduzione del 80-90% dopo la somminitrazione, raggiungendo il 50% del baseline a 12 e 24 mesi
Ripopolazione linfociti B	I linfociti CD19+ ritornano al baseline a 3-6 mesi, raggiungendo valori pari al 120–130% prima della successiva somministrazione
Effetto su output timico	Riduzione TREC

Adverse reactions

Infusion-associated reactions, thyroid disorders (42%), immune thrombocytopenia (2%), autoimmune nephropathies (0.3%), infection risk (HSV, VZV, Listeria), ischeamic or haemorrhagic stroke (13 cases), hemophagocytic lymphohistiocytosis (7 cases), alveolar haemorrhages (4 cases), autoimmune hepatitis (6 cases), myocardial infarction (10 cases).

- CD4+ and CD8+ T-cell counts were 30–40% of pre-treatment values 18 months after treatment
- CD8+ cytotoxic T-cells will reach the lower normal level after 9–12 months, while CD4+ T-cells repopulate at a slower rate, taking 1–2 years to reach the lower level of normal
- CD19+ B-lymphocytes repopulate within approximately 3–6 months and show an increase to 124–165% of baseline levels at 12 months.

Figure reproduced from Coles AJ et al. Lancet 1999;354:1691–5

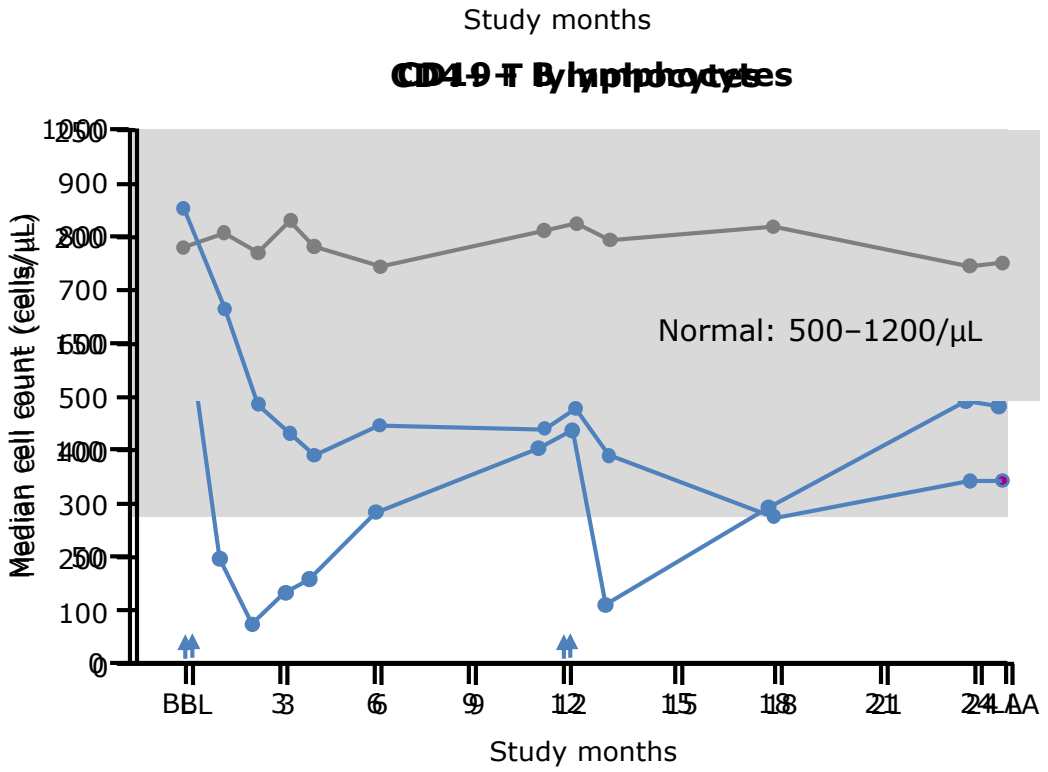
Zhang et al, Differential Reconstitution of T Cell Subsets following Immunodepleting Treatment with Alemtuzumab (Anti-CD52 Monoclonal Antibody) in Patients with Relapsing–Remitting Multiple Sclerosis J Immunol 2013, 191 (12) 5867-5874

Induction strategy: Cladribina

IMMUNE RECONSTITUTION THERAPIES	
	CLADRIBINA
Meccanismo di azione	Analogo purinico anti-proliferativo
Ripopolazione linfociti T CD4+	Riduzione del 40-60% (maggiormente cellule naïve rispetto alle cellule di memoria)
Ripopolazione linfociti T CD8+	Riduzione del 20-40% rispetto al baseline dopo somministrazione
Ripopolazione linfociti B	Riduzione del 90% dopo la somministrazione, valori prossimi al baseline prima della successiva dose a 12 mesi
Effetto su output timico	Non chiaro

Adverse reactions

Infection risk (HSV, VZV, PML, TB), risk of malignancies?



Comi et al, Effect of cladribine tablets on lymphocyte reduction and repopulation dynamics in patients with relapsing multiple sclerosis, Mult Scler Rel Disord 2019

Terapie di mantenimento vs IRTs

Maintenance Therapies

- Continuous treatment
  - Adherence potential problem
- Low to very high efficacy, only during active treatment
- Reversible
- It only blocks the immune system
- Perceived to be lower risk
  - Cumulative, or increased, risk with time
- Examples
  - GA, IFNβ, teriflunomide, BG12, fingolimod, natalizumab, anti-CD20
- Breakthrough disease
  - Suboptimal or failure to respond
  - NEDA reliable metric for efficacy
- Rebound activity
  - Highly likely
- Pregnancy
- No potential for a cure
  - Rebound
  - SPMS and progressive brain atrophy

IRTs

- Short courses or pulsed therapy
  - Adherence seldom a problem
- High to very high efficacy, extendend beyond period of active treatment
- Irreversible
- Radical changes in the lymphocyte repertoire and re-induction of self tolerance
- Perceived to be higher risk
  - Frontloading of risk or reduced risk with time
- Examples
  - Non-selective: mitoxantrone, alemtuzumab, HSCT-BMT
  - Selective: Cladribine Tablets
- Breakthrough disease
  - Marker for retreatment
  - NEDA unreliable to assess efficacy
- Rebound activity
  - Less likely
- Pregnancy

Figure adapted from Giovannoni G. Curr Opin Neurol 2018;31:233–43.

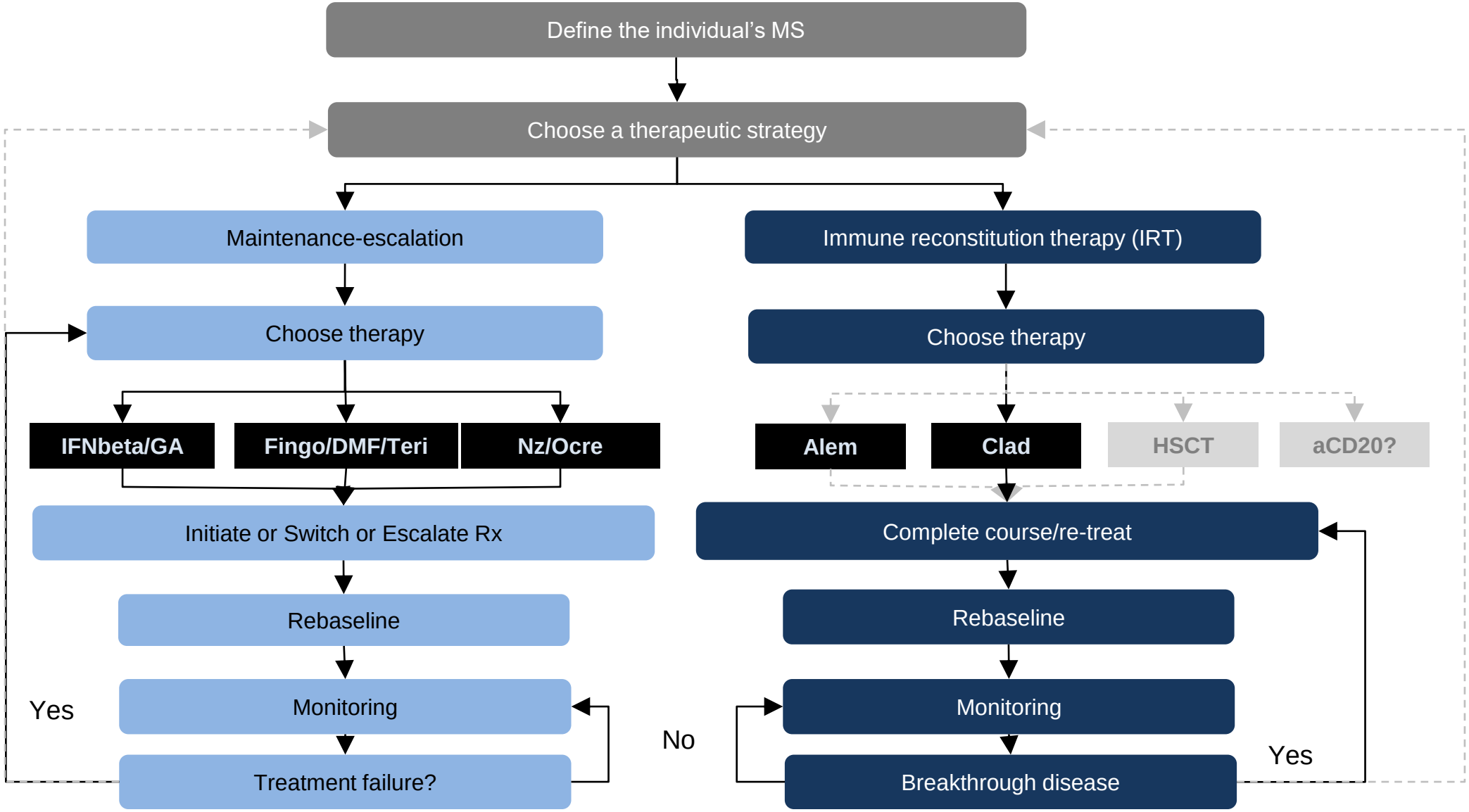


Figure adapted from Giovannoni G. Curr Opin Neurol 2018, 31:000–000