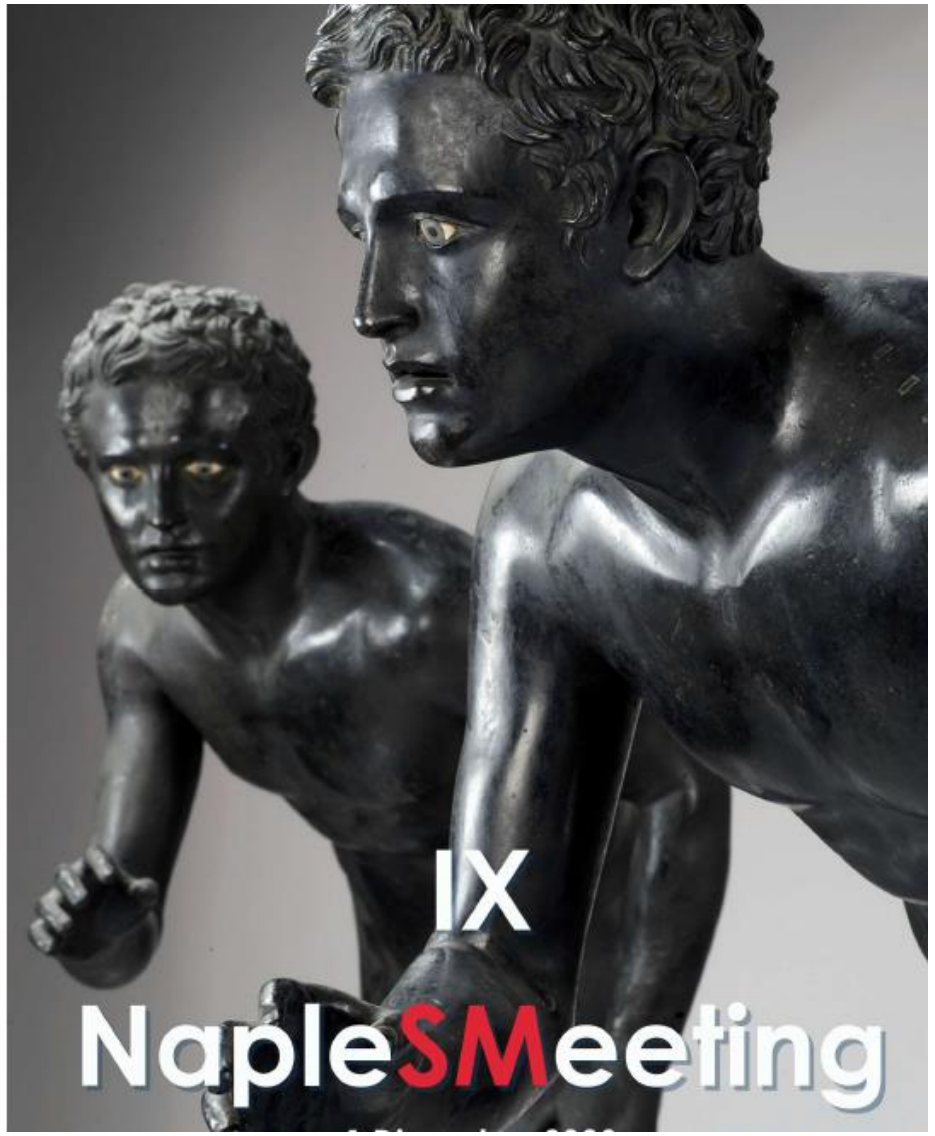
Towards new therapeutic strategies

DMT Stop



Dr. Pietro Annovazzi

UOC neurologia a indirizzo neuroimmunologico

Centro Sclerosi Multipla

ASST Valle Olona – PO di Gallarate (VA)

Sistema Socio Sanitario
Presidio Ospedaliero di Gallarate
Regione Lombardia
ASST Valle Olona

Disclosures

Dichiaro di aver ricevuto onorari per partecipazioni a congressi, attività scientifiche e/o advisory boards da:

- Almirall
- Biogen
- BMS
- Janssen
- Merck
- Novartis
- Roche
- Sanofi-Genzyme
- Teva
- Viatris

Di cosa parleremo

- Interruzione di terapia
  - Perché?
  - Si può fare?

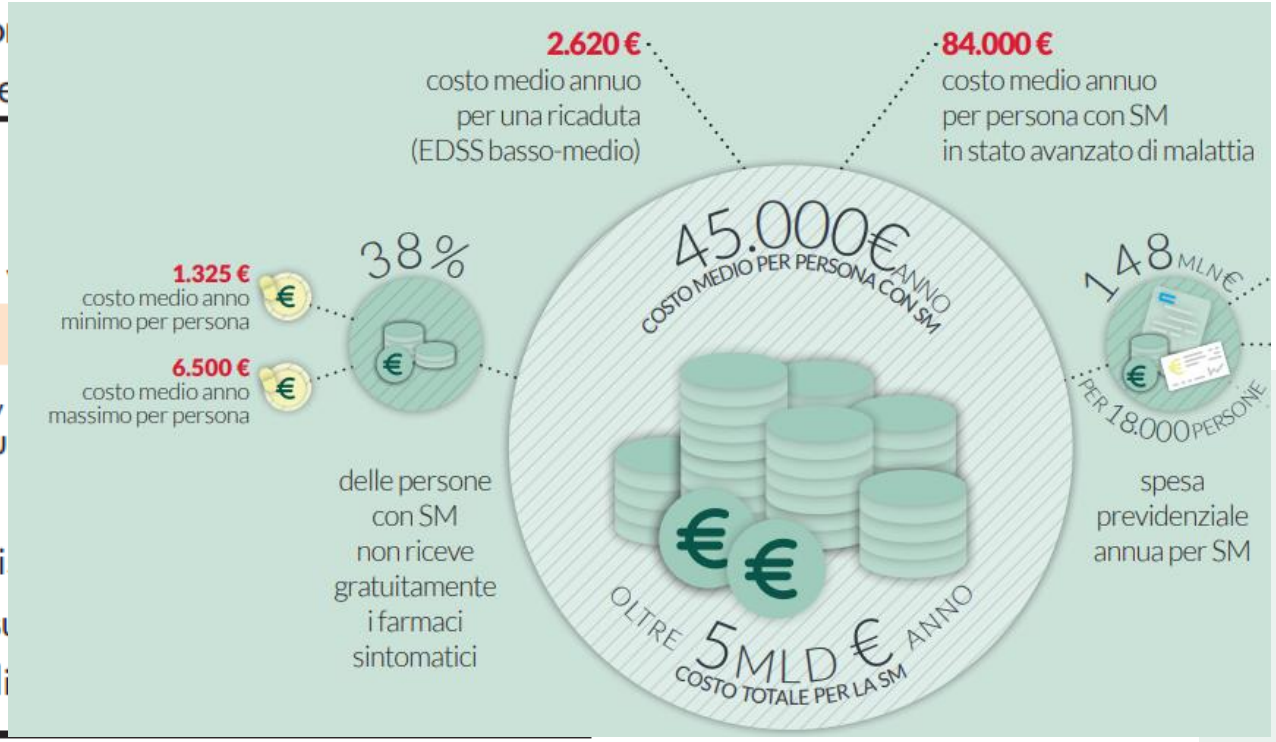
- De-escalation
  - Perché?
  - Si può fare?
  - Come

Perchè sospendere una terapia che apparentemente sta funzionando?

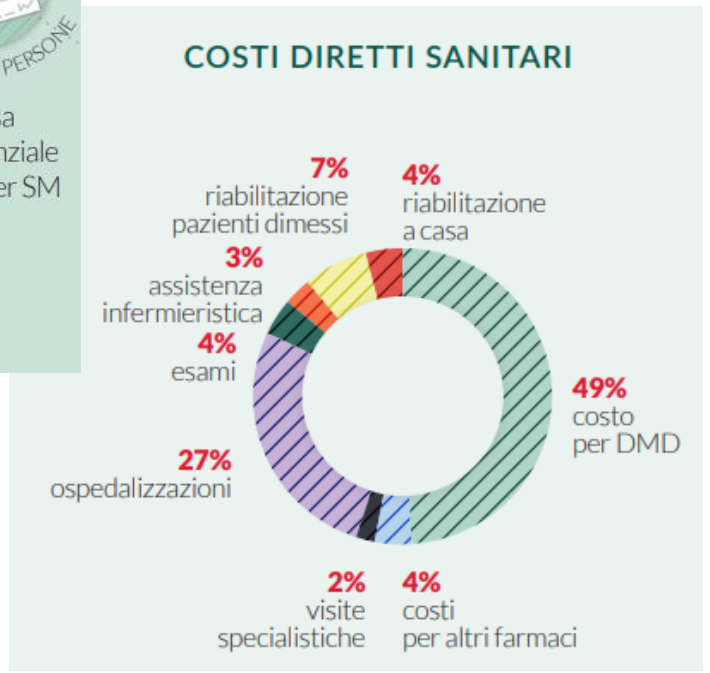
Table 1. Reasons for disco
treatments (DMTs) in multiple

Temporary suspension
• Planning pregnancy
• Switch of DMTS respecting
Permanent stopping
Disease related, patient related, (regulatory indication, reimbu
• Stable disease
• Serious adverse effects or ri
• Intolerability, adherence issu
• Perceived or documented di

Hartung et al Curr Op Neurol 2021



Barometro AISM 2019



Il punto di vista dei colleghi?

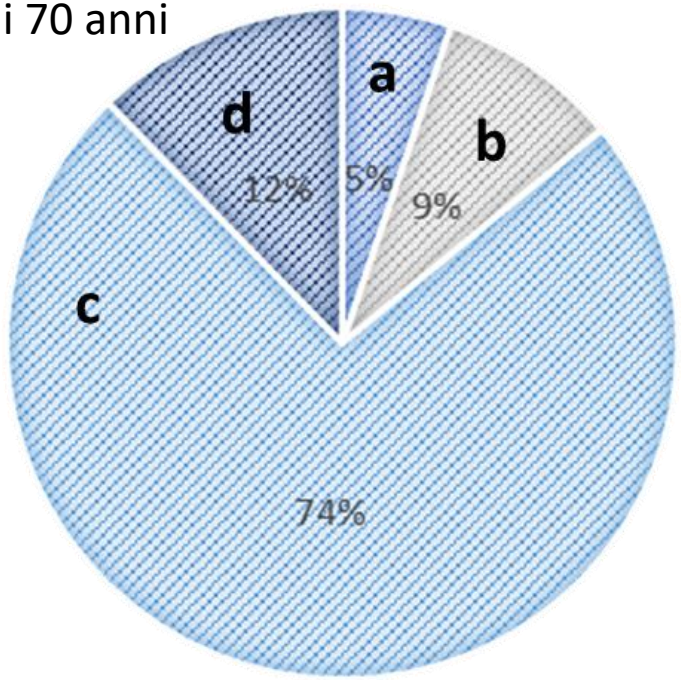
ITALIAN SURVEY ABOUT DMTs discontinuation

57 Neurologi di 31 Centri SM

100% prendono in considerazione una interruzione di terapia

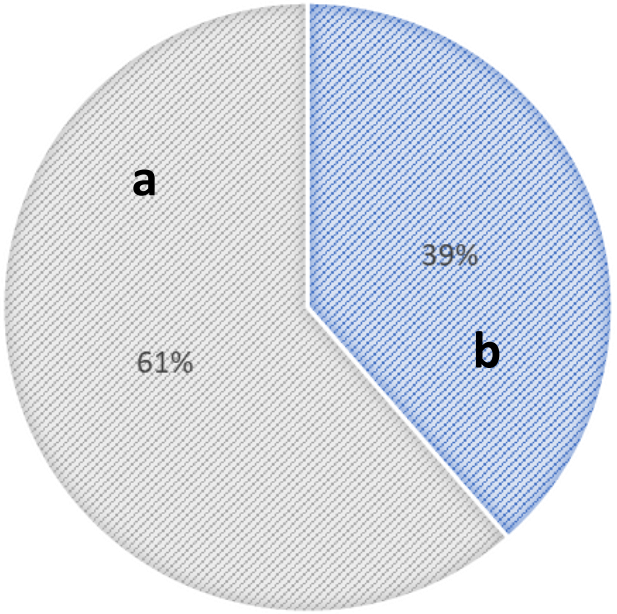
Se prendi in considerazione la sospensione della terapia dopo quale età?

a. Consideri solo se è stabile da 10 anni e non importa l'età
b. dopo i 50 anni
c. dopo i 60 anni
d. dopo i 70 anni



Prendi in considerazione la sospensione della terapia solo se si tratta di una prima linea o anche di una seconda linea?

a. solo prima linea
b. entrambe



Moiola 2023

Studi randomizzati

RCT	Follow-up (post-discontinuation)	Main eligibility criteria	Primary Endpoint
DISCOMS (USA) NCT03073603	2 years *from discontinuation of any DMT*	- Age: ≥55 years - RR, SP and PP phenotypes - No relapses in the last 5 years - No new MRI lesion in the last 3 years	Relapses or new MRI lesions
DOT-MS (Netherland) NCT03653273	2 years *from discontinuation of IFNB, GA, DMF or TRF*	- No age restriction - RR phenotype - No relapses in the last 5 years - No new MRI lesion in the last years	Relapses or new MRI lesions
STOP-I-SEP (France) NCT04260711	2 years *from discontinuation of any DMT*	- Age: ≥50 years - EDSS score ≥3.0 - SP phenotype since ≥3 years - No relapses in the last 3 years - No new MRI lesion in the last 3 years	Disability progression

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Studio DISCOMS

Studio randomizzato 1:1

- SM (RR, SP, PP)
- IFN, GA, TFU, DMF, FTY, NTZ, OCR
  - da almeno 2 anni (5 per TFU)
- No ricadute da almeno 5 anni
- No attività di RM da almeno 3 anni

NIH U.S. National Library of Medicine

ClinicalTrials.gov

ClinicalTrials.gov Identifier: NCT03073603

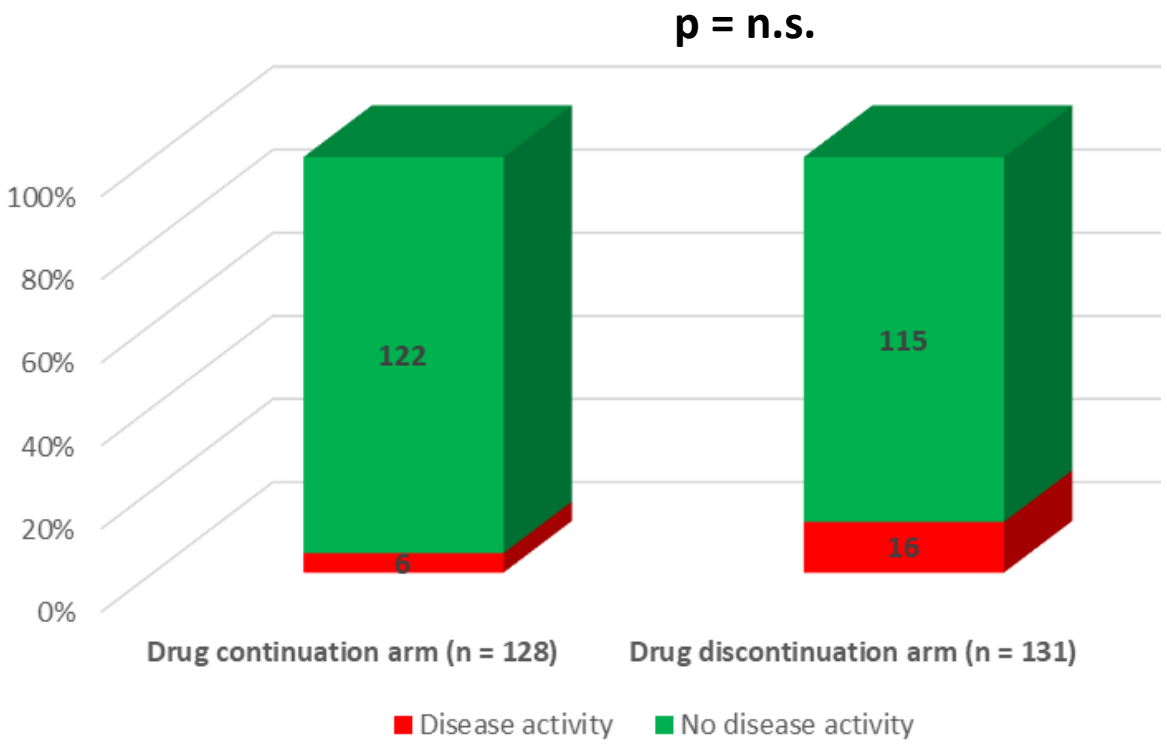
Recruitment Status : Completed
First Posted : March 8, 2017
Results First Posted : October 6, 2022
Last Update Posted : October 6, 2022

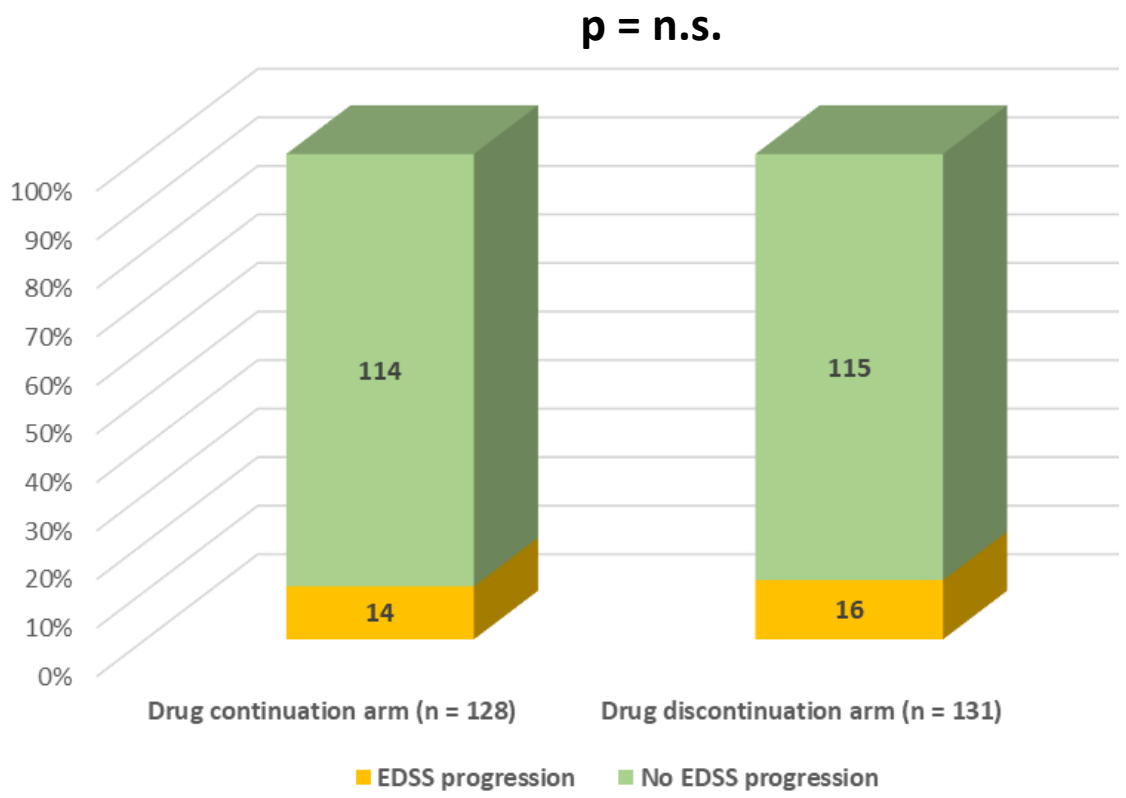
	Drug continuation arm (n = 128)	Drug discontinuation arm (n = 131)
Age	63 (± 5,2)	63,1 (± 4,9)
F/M	107/21	109/22
RR	108	108
SP	18	17
PP	2	6
didease duration (years)	20,9 (± 10,4)	23,4 (± 10,5)
time since last relapse (years)	13,2 (± 6,2)	14,5 (± 7,4)

Studio DISCOMS

Non inferiority trial

Margin of non-inferiority 8%





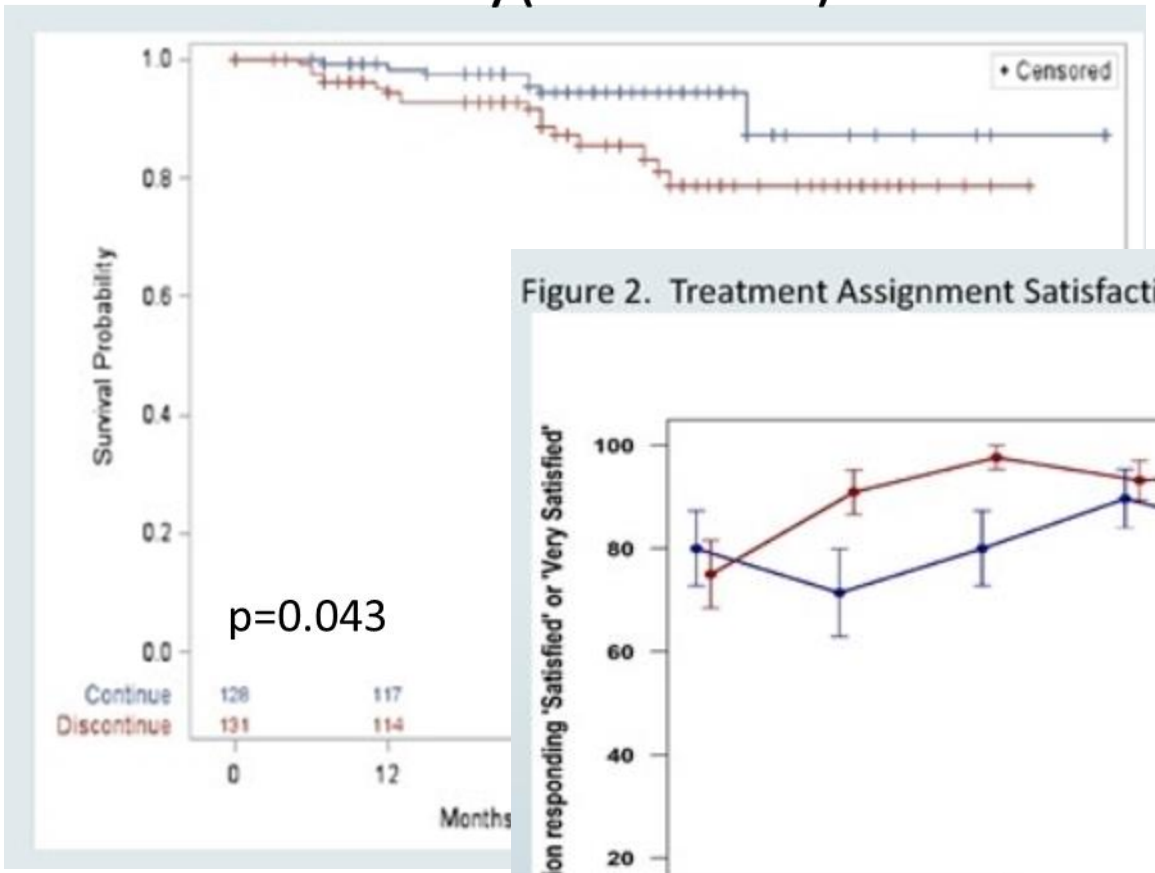
NIH U.S. National Library of Medicine

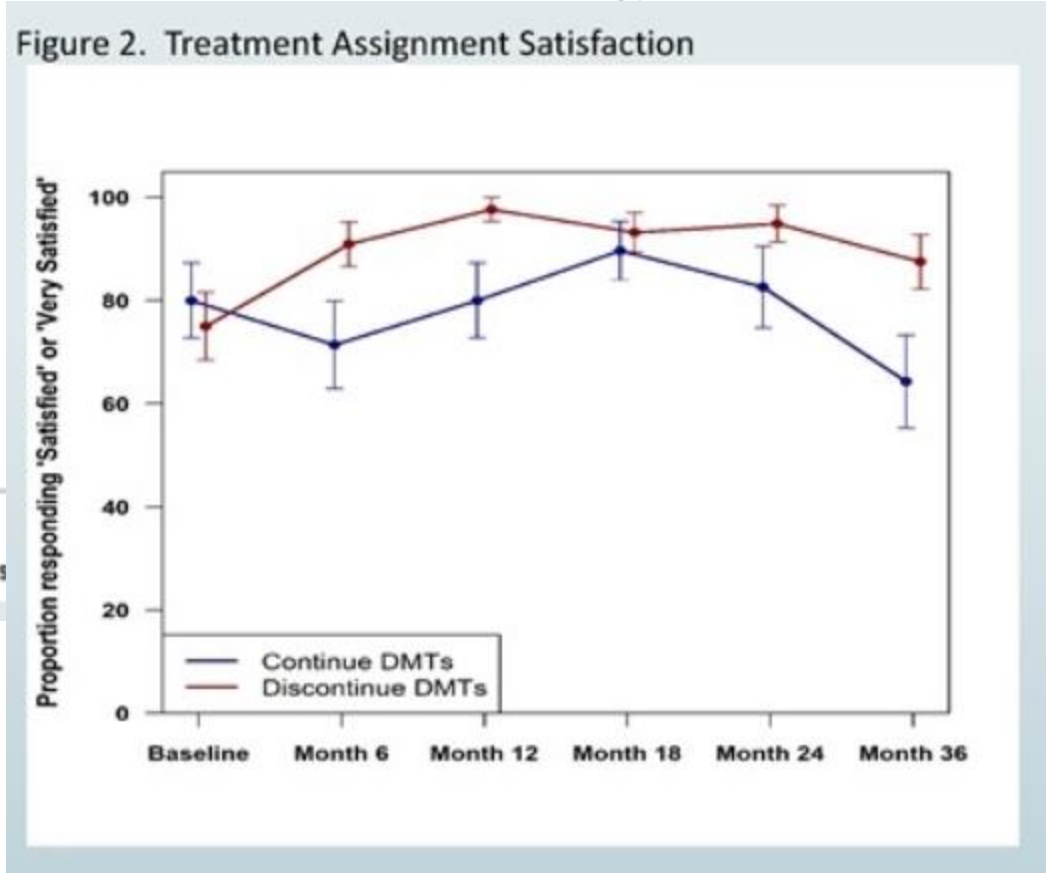
ClinicalTrials.gov

Estensione dello studio DISCOMS

		All Subjects (N = 74)	Continue DMTs (N = 30)	Discontinue DMTs (N = 44)
Ag1	Mean (SD)	62.2 (4.6)	61 (4.4)	63.1 (4.7)
Gender	N (%)			
Female		63 (85.1%)	25 (83.3%)	38 (86.4%)
Male		11 (14.9%)	5 (16.7%)	6 (13.6%)
Race/Ethnicity	N (%)			
Black or African American		7 (9.5%)	4 (13.3%)	3 (6.8%)
White		67 (90.5%)	26 (86.7%)	41 (93.2%)
Number of years since first onset of symptoms related to MS	Mean (SD)	21 (9.3)	17.1 (7.4)	23.7 (9.5)
Number of years since last documented relapse	Mean (SD)	13.3 (5.8)	11.5 (5.1)	14.5 (6)
EDSS	Mean (SD)	3 (1.6)	2.9 (1.5)	3 (1.6)
MS Phenotype	N (%)			
Relapsing-Remitting		69 (93.2%)	29 (96.7%)	40 (90.9%)
Secondary Progressive		5 (6.8%)	1 (3.3%)	4 (9.1%)

Time to disease activity (clinical or MRI)





Cutter et al. P309 ECTRIMS 2023

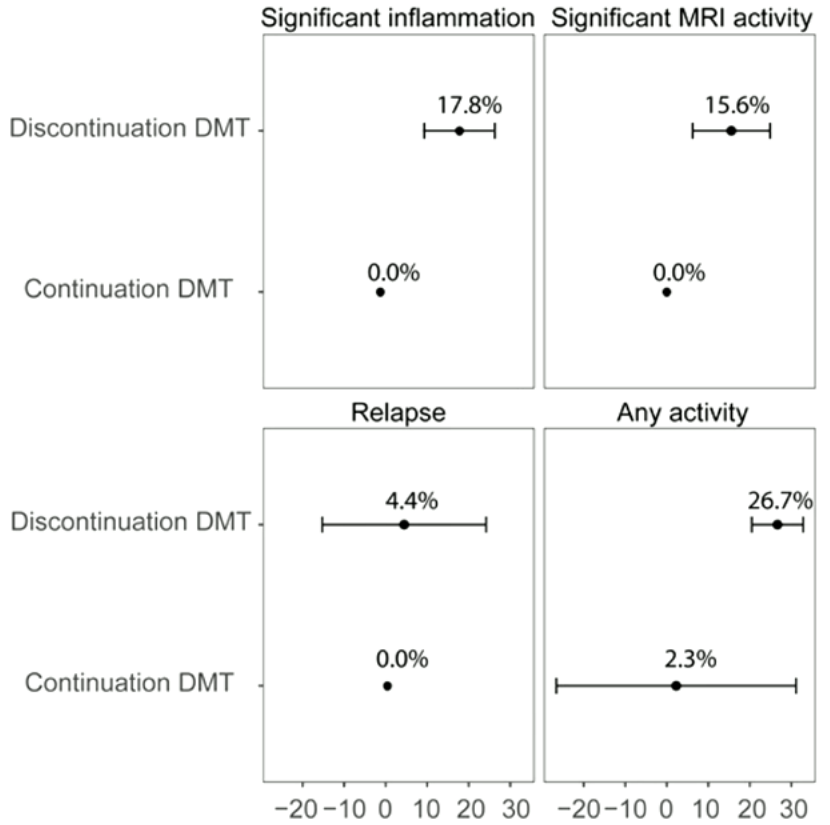
DOT-MS study

89 pz RR o SP in IFN, GA, DMF, TFU
Da almeno 5 anni no relapses, non Gd+/nuove lesioni
Randomizzati a STOP (45) o prosecuzione tp (44)
Interruzione anticipata -> campione non completo

	Discontinuation n=45	Continuation n=44
Female sex, n (%)	32 (71.1)	28 (63.6)
Age, years, mean (SD) *Range*	52.8 (8.5) *35 - 71*	54.3 (7.0) *39 - 68*
MS subtype, n (%) RRMS SPMS	 41 (91.1) 4 (8.9)	 39 (88.6) 5 (11.4)
Type of DMT used, n, % Interferon Glatiramer acetate Teriflunomide Dimethyl fumarate	 17 (37.8) 12 (26.7) 4 (8.9) 12 (26.7)	 18 (40.9) 11 (25.0) 8 (18.2) 7 (15.9)
Follow-up duration, median (IQR)	19.0 (13.0-24.0)	19.0 (15.0-24.0)

Significant MRI activity = > 3 newT2 or > 2 Gd+

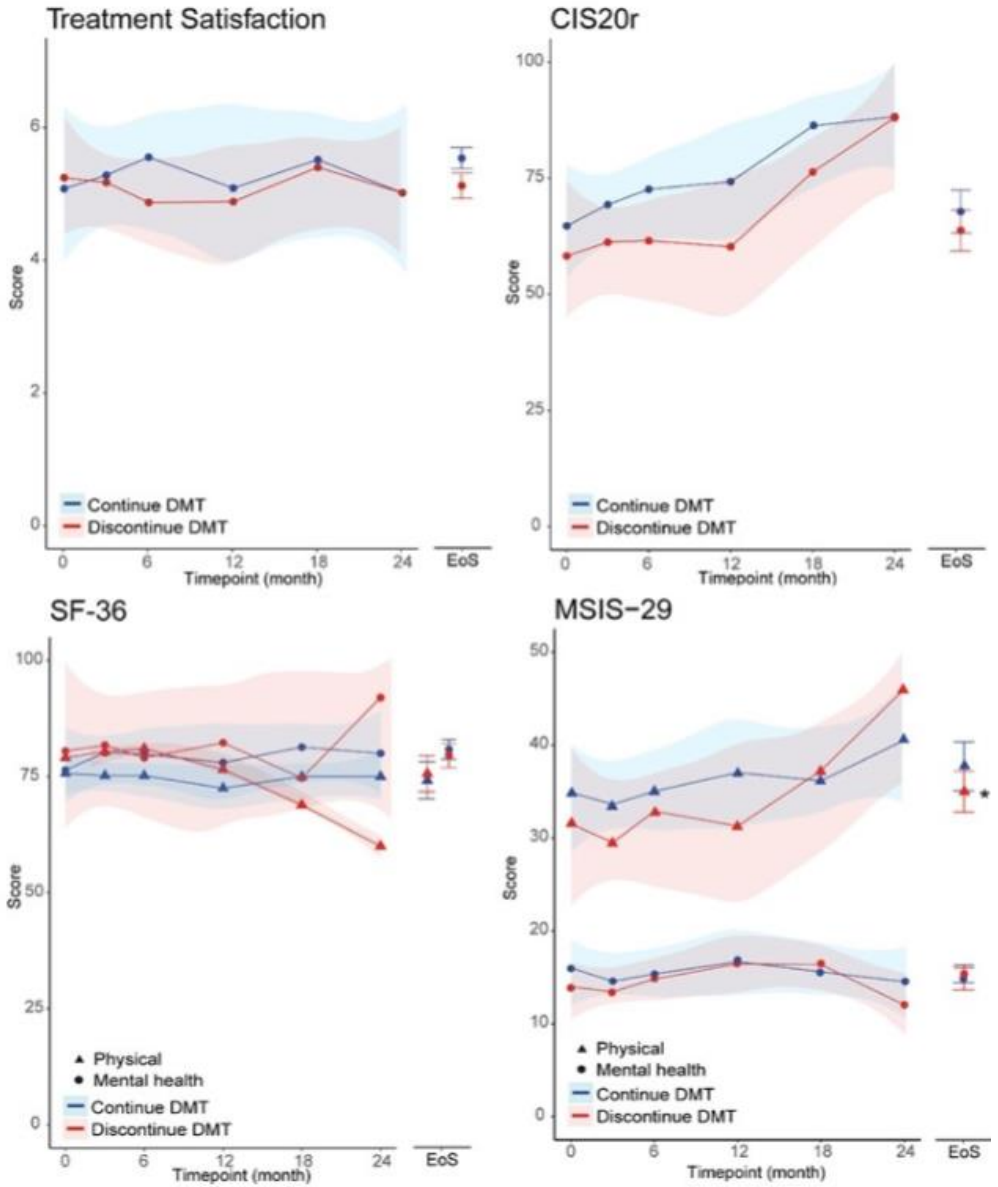
	Discontinuation n=45	Continuation n=44
Significant activity, n (%)	8 (17.8)	0 (0.0)
Relapses, n (%)	2 (4.4)	0 (0.0)
Significant MRI activity, n (%)	7 (15.6)	0 (0.0)
Any activity, n (%)	12 (26.7)	1 (2.3)



Coerver et al. DOT-MS study, ECTRIMS 2023

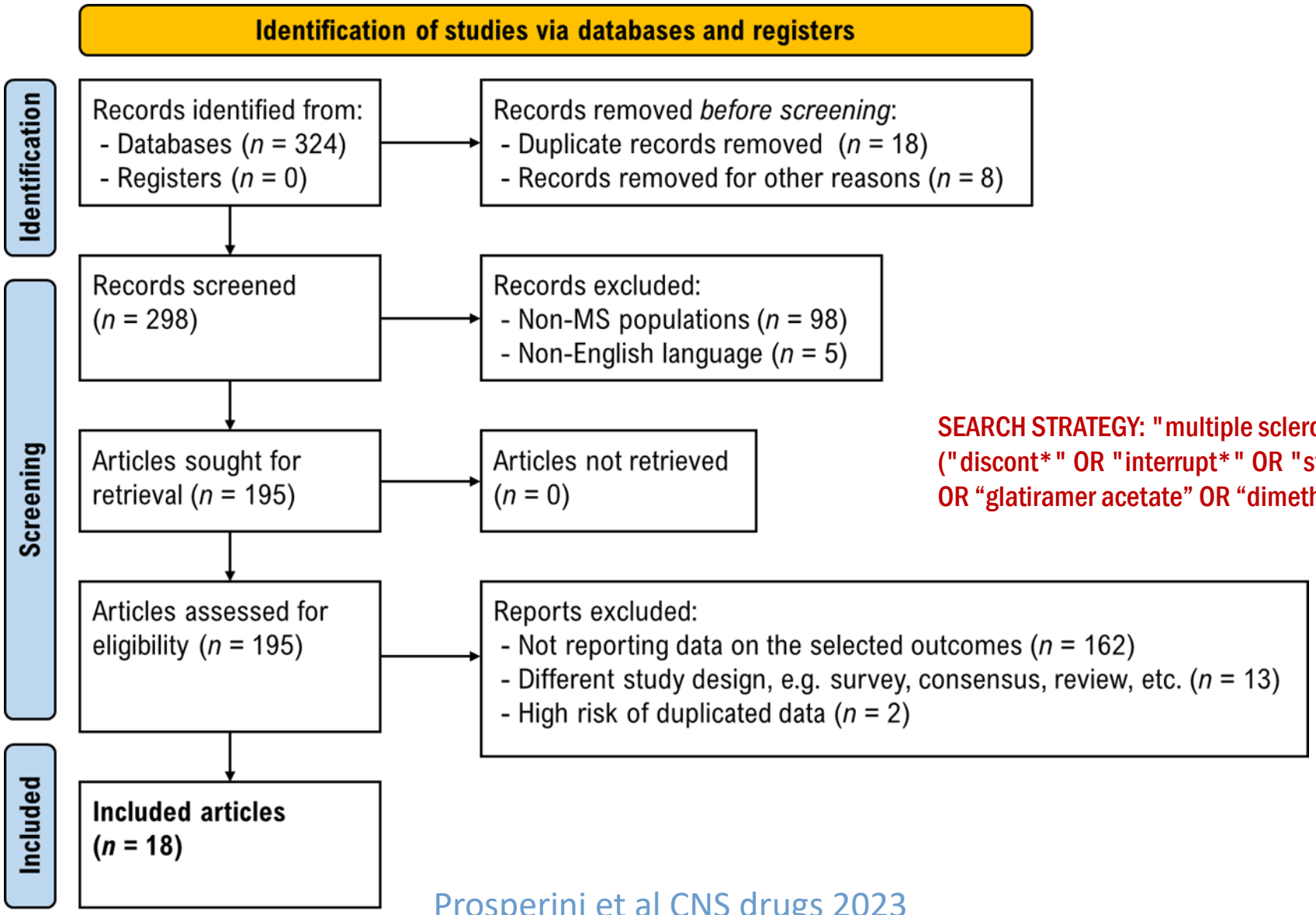
DOT-MS study

		Activity N=8	No activity N=81
Female sex, n (%)		5 (62.5)	55 (67.9)
Age, mean (SD)	n.s.	49.3 (9.1)	54.0 (7.6)
MS subtype, n (%) RRMS SPMS		 8 (100.0) 0 (0.0)	 72 (88.9) 9 (11.1)
Type of DMT used, n (%) Interferon Glatiramer acetate Teriflunomide Dimethyl fumarate	n.s.	 2 (25.0) 1 (12.5) 2 (25.0) 3 (37.5)	 33 (40.7) 22 (27.2) 10 (12.3) 16 (19.8)
Years since last relapse to BL, mean (SD)	n.s.	9.5 (4.1)	10.1 (5.3)
Follow-up duration, median (IQR)		23.5 (18.5-24.0)	18.0 (14.0-24.0)
Months to disease activity, median (IQR)		12.0 (6.0-16.5)	--



Coerver et al. DOT-MS study, ECTRIMS 2023
Fung et al. P791 ECTRIMS 2023

Metanalisi

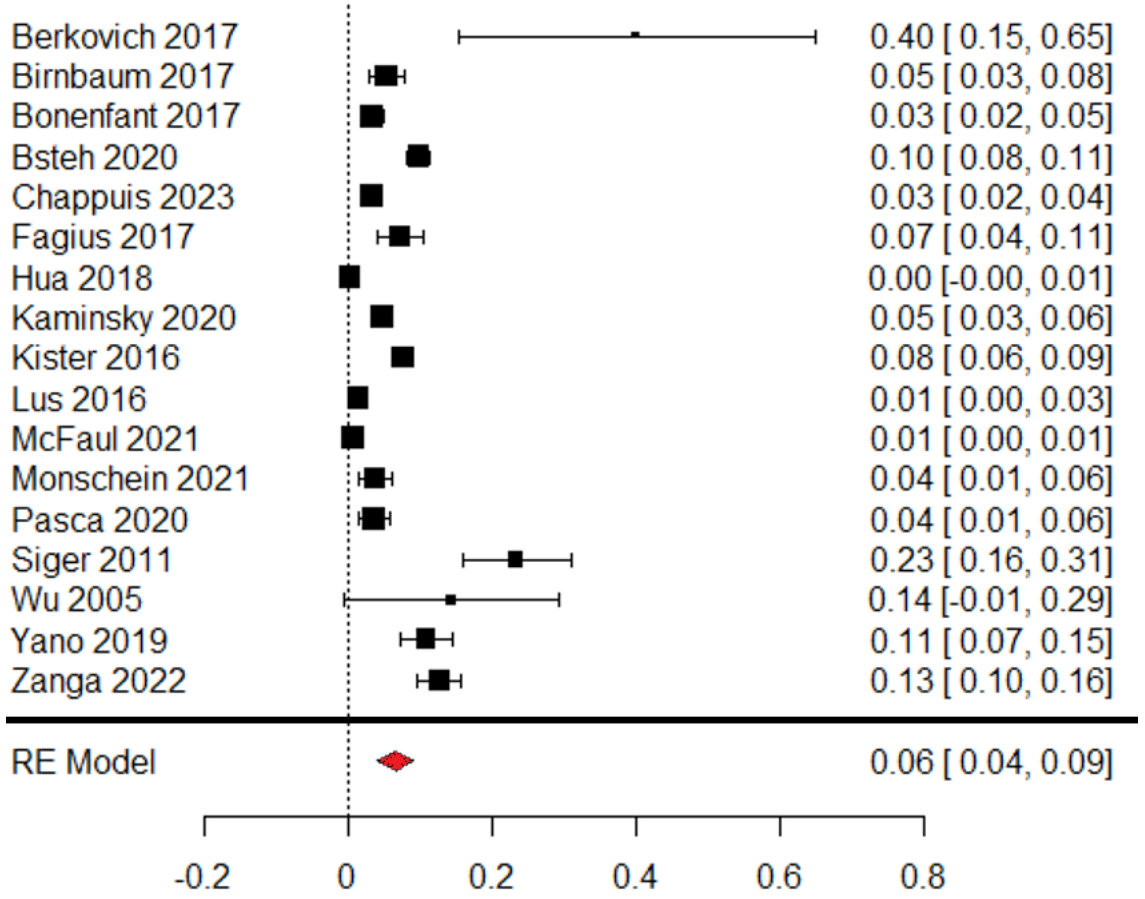


SEARCH STRATEGY: "multiple sclerosis" AND ("treatment" or "therap*") AND ("discont*" OR "interrupt*" OR "stop*" OR "withdraw*") AND (“interferon beta” OR “glatiramer acetate” OR “dimethyl fumarate” OR “teriflunomide”)

Prosperini et al CNS drugs 2023

Metanalisi

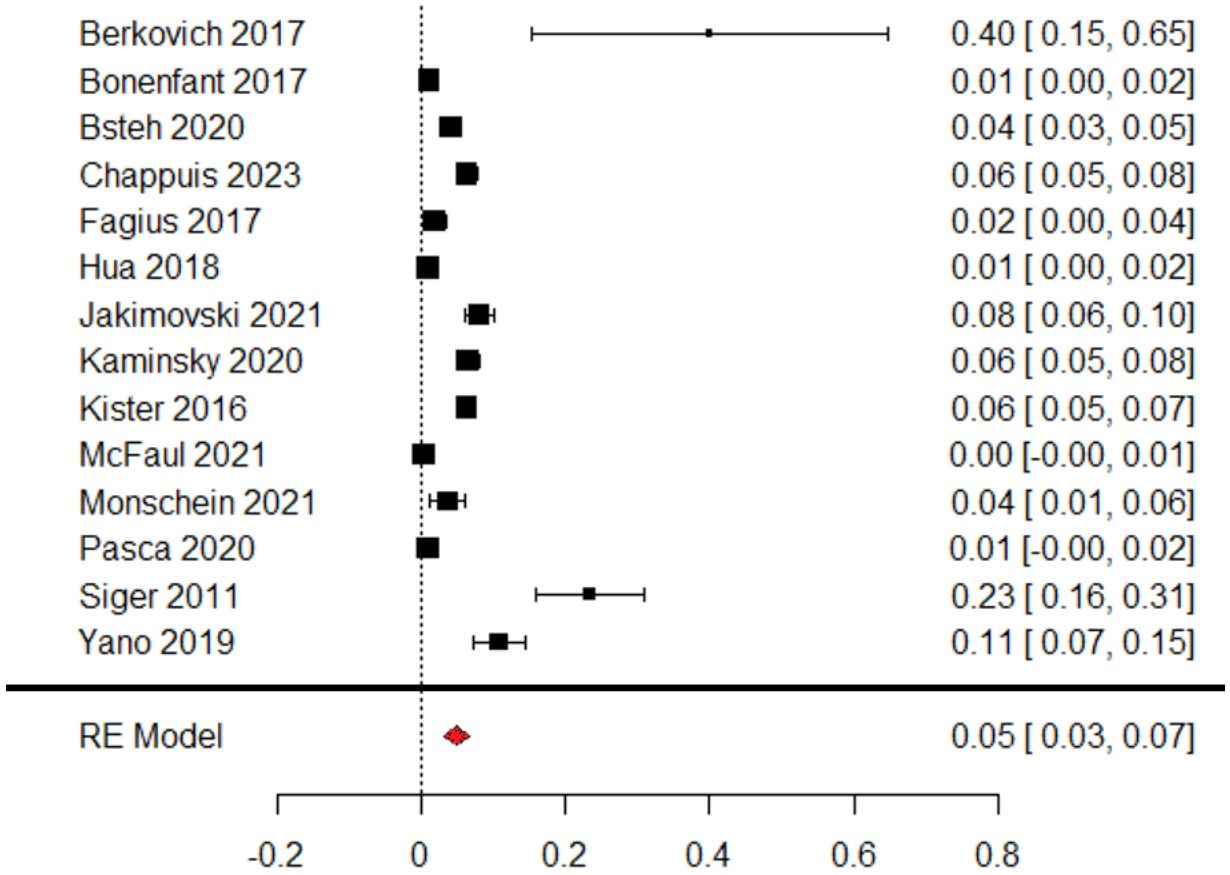
Post-discontinuation relapse-event rate



$Q_{16} = 204.3$, $p < 0.001$; $I^2 = 97.5\%$

Kendall's $\tau = -0.21$, $p = 0.27$; Egger's $Z = -1.60$, $p = 0.11$

Post-discontinuation disability accrual-event rate



$Q_{13} = 163.9$, $p < 0.001$; $I^2 = 97.8\%$

Kendall's $\tau = -0.27$, $p = 0.19$; Egger's $Z = -1.81$, $p = 0.08$

Prosperini et al CNS drugs 2023

Fattori di rischio associati ad attività di malattia e disabilità

	Post-discontinuation relapse (logit-transformed event rate)					Post-discontinuation disability accrual (logit-transformed event rate)			
	k	β	95% CIs	*p*-value		*k*	β	95% CIs	*p*-value
Sex ratio	17	2.30	−1.07 to 5.68	0.18		14	0.76	−4.10 to 5.63	0.76
Age (each 10 years)	17	−0.62	−1.19 to −0.06	**0.031**		14	−0.67	−1.34 to −0.01	**0.048**
Disease duration (each 10 years)	15	−1.36	−2.76 to 0.05	0.06		13	−1.39	−2.92 to 0.13	0.08
EDSS score (each point)	15	0.01	−0.40 to 0.41	0.97		12	−0.06	−0.60 to 0.48	0.83
RR versus SP phenotype	15	0.18	-1.48 to 1.11	0.78		13	-0.45	-2.01 to 1.17	0.57
Time of DMT exposure (each 10 years)	15	−2.10	−3.64 to −0.56	**0.008**		13	−2.55	−4.38 to −0.73	**0.006**
Time of stable disease course (each 10 years)	9	−3.32	−5.43 to −1.21	**0.002**		9	−3.38	−6.29 to −0.47	**0.023**

Prosperini et al CNS drugs 2023

Effetto dell'età

42 pazienti, non randomizzato

8 patients presented clinical and/or radiologic reactivation, 16 had EDSS progression and 5 required new DMT.

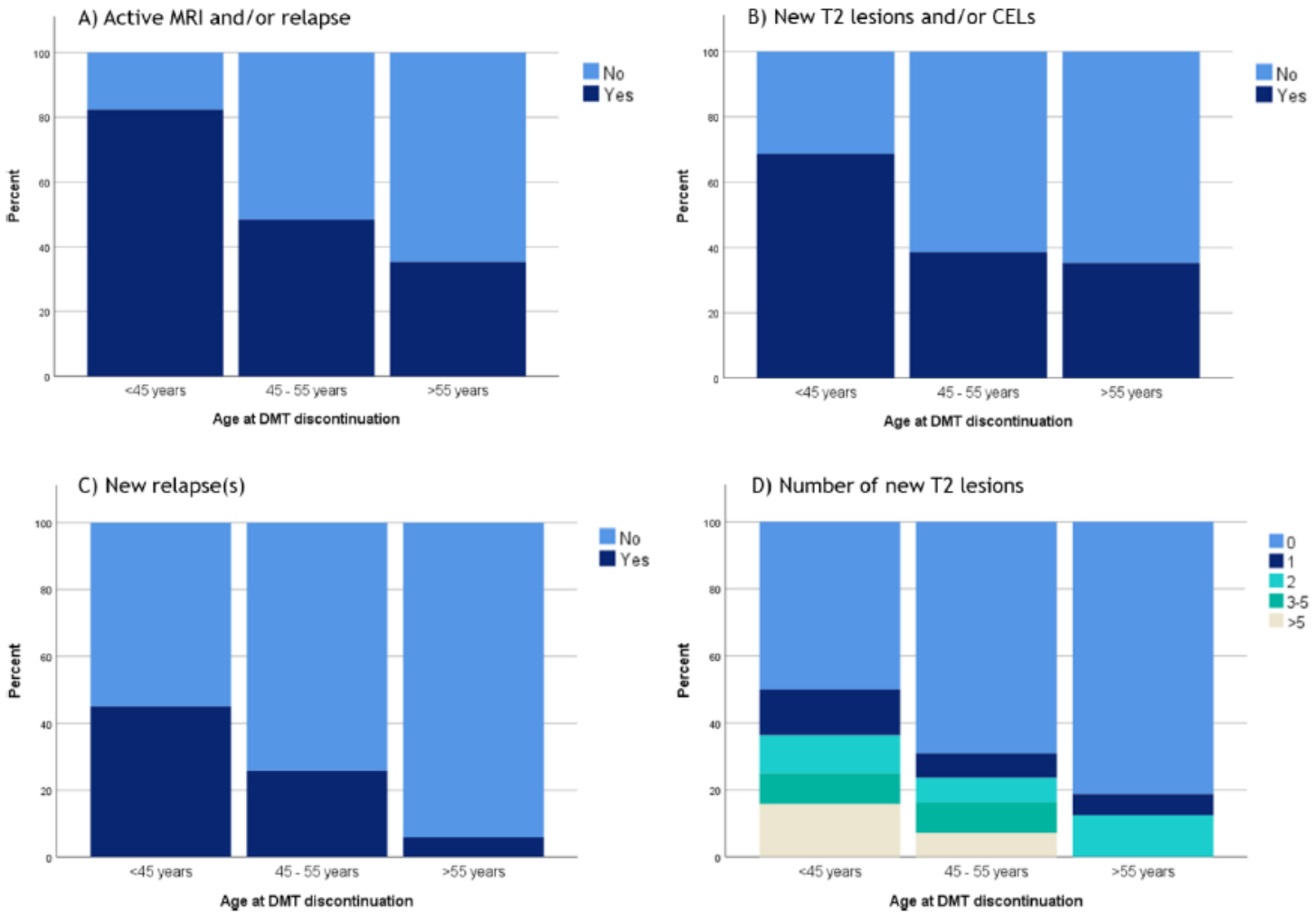
Table – Differences regarding clinical activity after discontinuation

Factor	No relapse	Relapse	*p value*
Gender Male (n=5) Female (n=37)	 2 (40.0%) 32 (86.5%)	 3 (60.0%) 5 (13.5%)	**0.040**
Age at discontinuation (years)	55.9 ± 12.5	42.9 ± 14.2	**0.014**
ARR on last DMT	0.08 ± 0.13	0.12 ± 0.09	0.363
Last EDSS	5.25 ± 2.6	3.75 ± 3.9	0.735
Last DMT - Interferon (n=23) - Dimethyl-fumarate (n=8) - Fingolimod (n=5)	 20 (86.9%) 7 (87.5%) 3 (60.0%)	 3 (13.1%) 1 (12.5%) 2 (40.0%)	0.541

Mean time until new relapse was 2.8 (± 1.4) years, in a 5 years mean time of follow-up.

Delgado-Soares et al. P1521 ECTRIMS 2023

130 pazienti, non randomizzato



Coerver et al. MSRD 2023

Rischio di progressione indipendente da attività di malattia

Dati da registro stato di NY

Criteri di inclusione

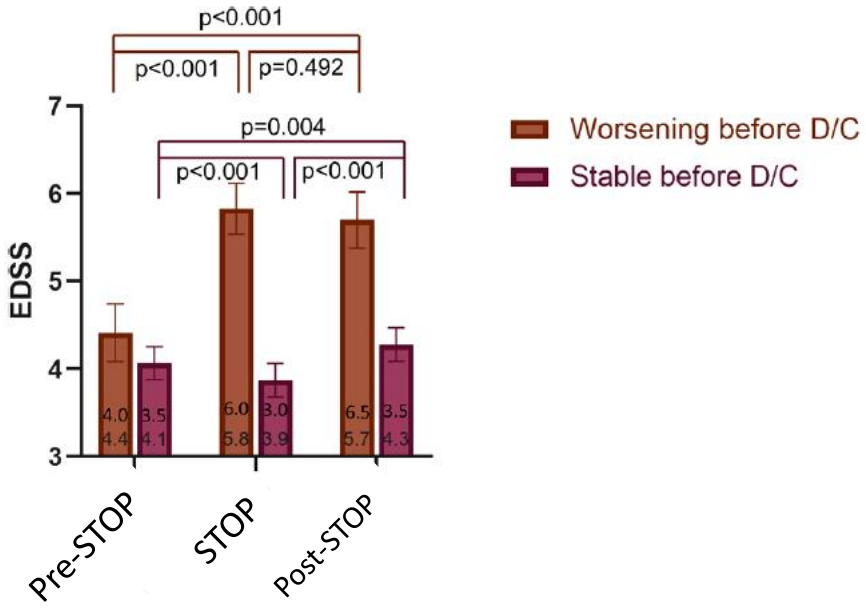
- SM RR o SP con stop tp
  - IFN 57%
  - GA 19%
  - NTZ 6%
  - Altro 18% (MTX, AZA, CFX...)
- In tp da almeno 6 mesi

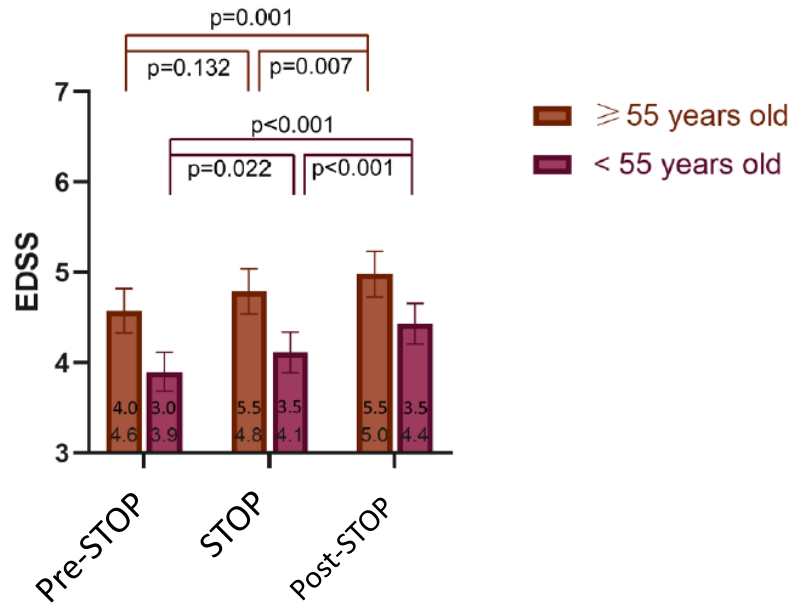
87/216 pz (40,3%): aumento EDSS (follow-up medio 4,5 anni)

- 29% dei pz RR stabili all'interruzione

Fattori di rischio per aumento EDSS:

- Forma progressiva
- EDSS > 6
- Non l'età





Jakimowski et al MSRD 2022

Rischio di progressione indipendente da attività di malattia

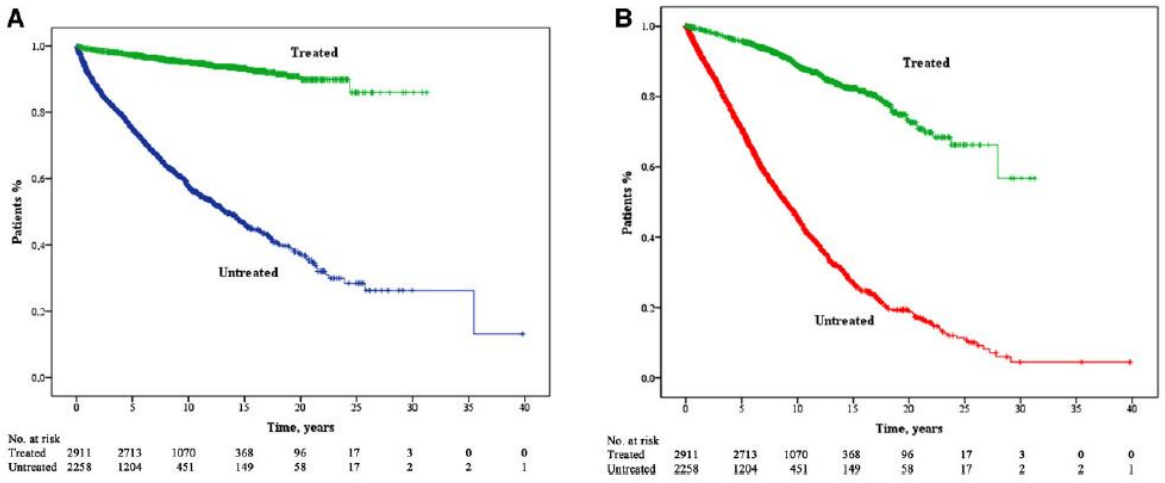


Figure 3 Risk of first RAW (A) and first PIRA (B) in DMT-treated and -untreated patients (Kaplan–Meier survival curves, log rank P < 0.001).

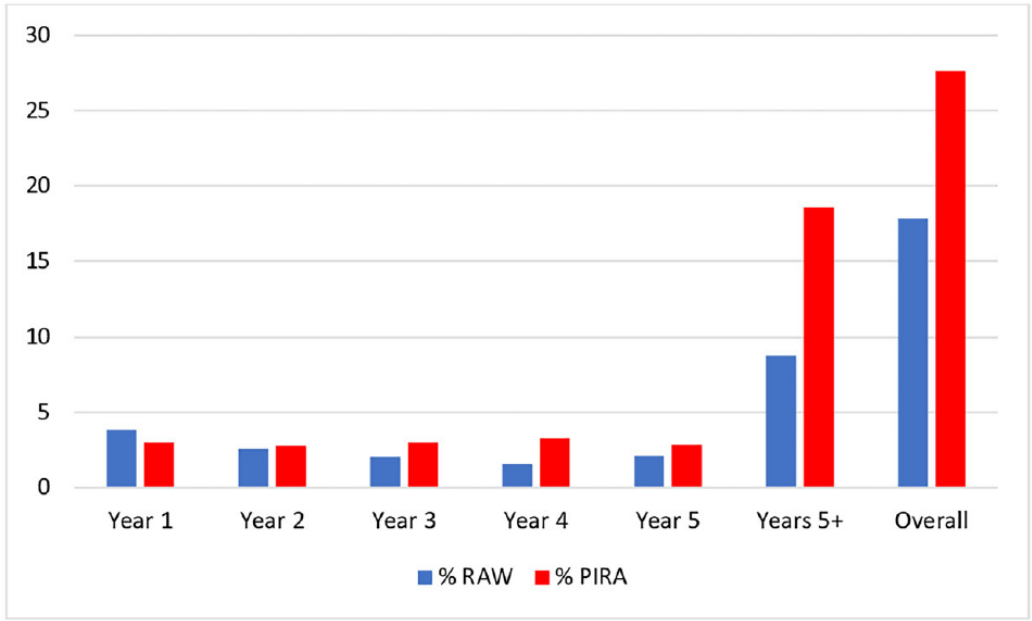


Figure 2 Percentage of RAW and PIRA events over the follow-up period.

Table 3 Factors associated with first PIRA event

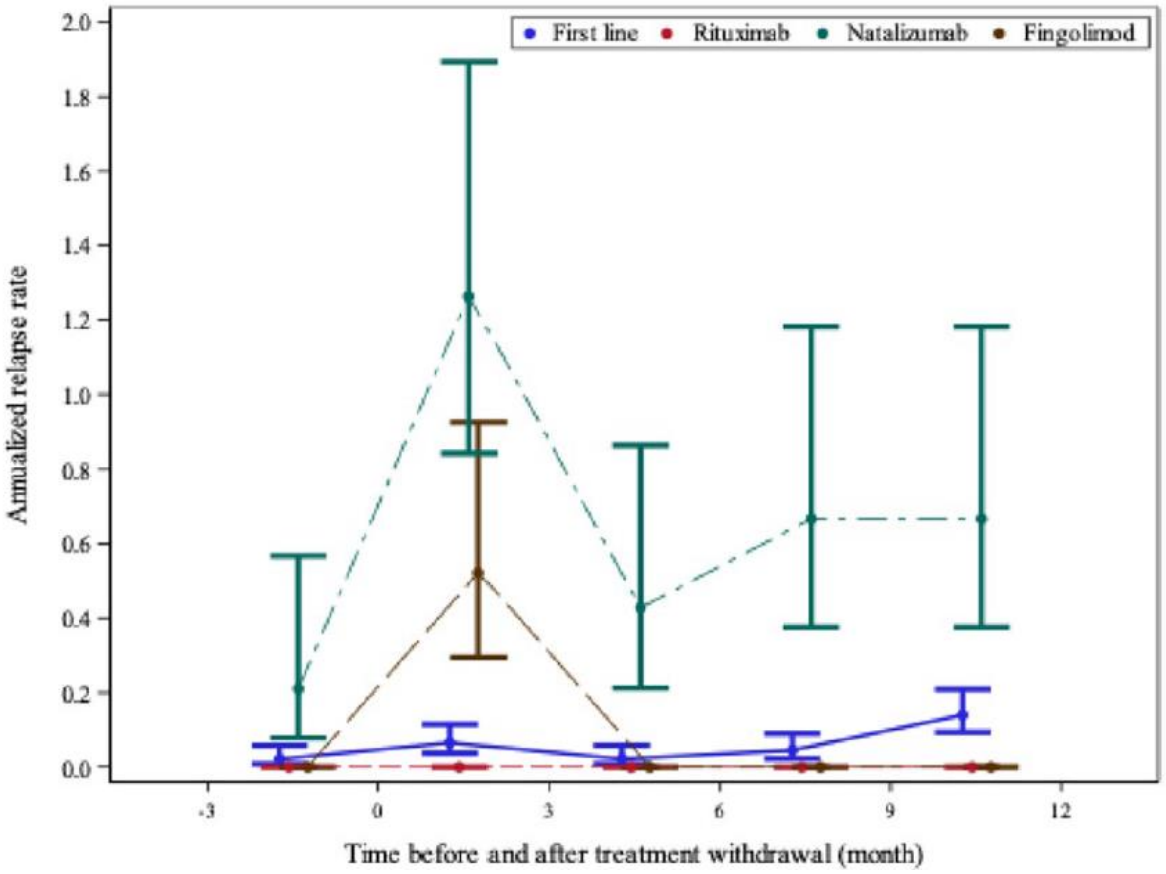
	HR	95% CI	P
Sex (female versus male)	0.99	0.89–1.11	0.857
Onset topography (multifocal versus unifocal)	1.02	0.89–1.18	0.763
Age at baseline	1.19	1.13–1.25	<0.001
Disease course at baseline (RR versus CIS)	1.44	1.28–1.61	<0.001
Disease duration at baseline	1.56	1.28–1.90	<0.001
EDSS at baseline	0.92	0.88–0.96	<0.001
Percentage of time spent on DMT before the event	0.18	0.15–0.22	<0.001
Number of relapses before the event[a]	0.76	0.73–0.80	<0.001
Number of EDSS evaluations before the event[a]	0.91	0.90–0.92	<0.001

[a]Adjusted for an interaction term with time.

Portaccio et al Brain 2022

Interruzione delle II linee

232 pazienti
- 183 platform
- 49 II linee (23 FTY, 17 NTZ, 9 RTX)



Fattori associati con attività di malattia
- Relapses nei 3 anni precedenti
- Durata del trattamento prima dell'interruzione
- Interruzione di NTZ

Fattori associati con accumulo di disabilità
- Attività RM nei 3 anni precedenti
- Interruzione di FTY

Chappuis et al. JOON 2023

De-escalation: razionale

Immunosenescenza

- Aumentata suscettibilità alle infezioni
- Ridotta risposta alle vaccinazioni
- Possibile aumento del rischio oncologico

Variazioni patofisiologiche legate all'aging

- Minore attività infiammatoria classica
- Maggiore probabilità di smouldering MS
- Aumentato rischio di PIRA

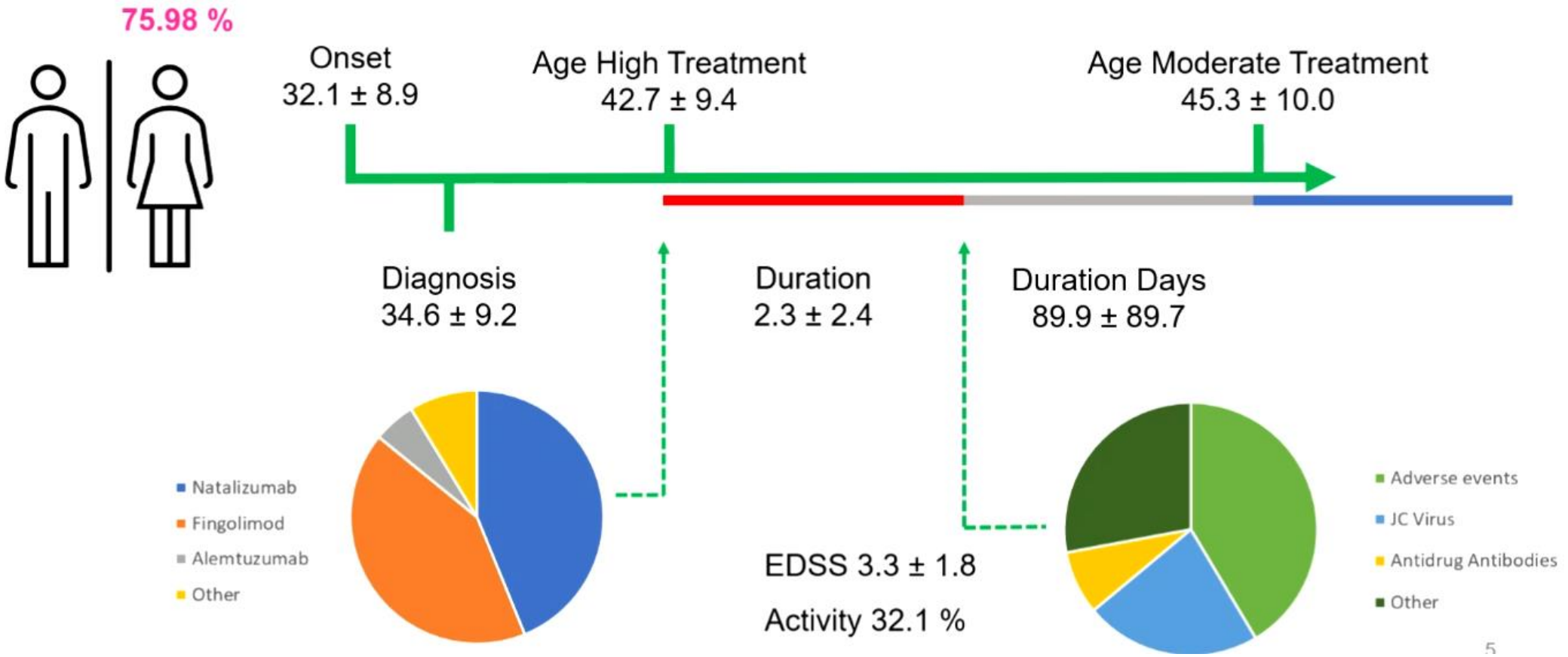
Diversa risposta ai farmaci legata all'aging

- Evidenze che attorno ai 45-50 c'è una minore differenziazione tra I e II linee
- Aumentato rischio oncologico con depletivi
- Comorbidità vascolare

Van Pesch ECTRIMS 2023

de-escalation: real world evidence

- Studio da registro danese: 333 pazienti
- De-escalation passaggio da ALZ/CLD/DAC/S1Pi/a-CD20/NTZ a DMF/GA/IFN/TFU



Elberling ECTRMS 2023

de-escalation: real world evidence

Duration – 1.9 ± 2.4

	Age
Escalation - 45.1%	44.9 (9.3)
Lateral switch - 25.8%	45.1 (10.4)
Continue - 18.0%	54.0 (10.1)
Stopping - 11.1%	49.9 (10.9)

75.7 % do not experience EDSS increase

- 58.6 % without relapse
- 51.4 % without relapse or MRI lesions

24.3 % experience EDSS increase ⇢ Escalation – 49.5%

Activity during HeDMT ⇢ Escalation – 51.4%

6

Fattori di rischio per relapse dopo de-escalation: sesso maschile (HR 0.63 95% IC 0.38-0.99) ed età (HR 0.96 95% IC 0.94-0.98)

Non valutato effetto del tipo di trattamento di de-escalation

Elberling ECTRMS 2023

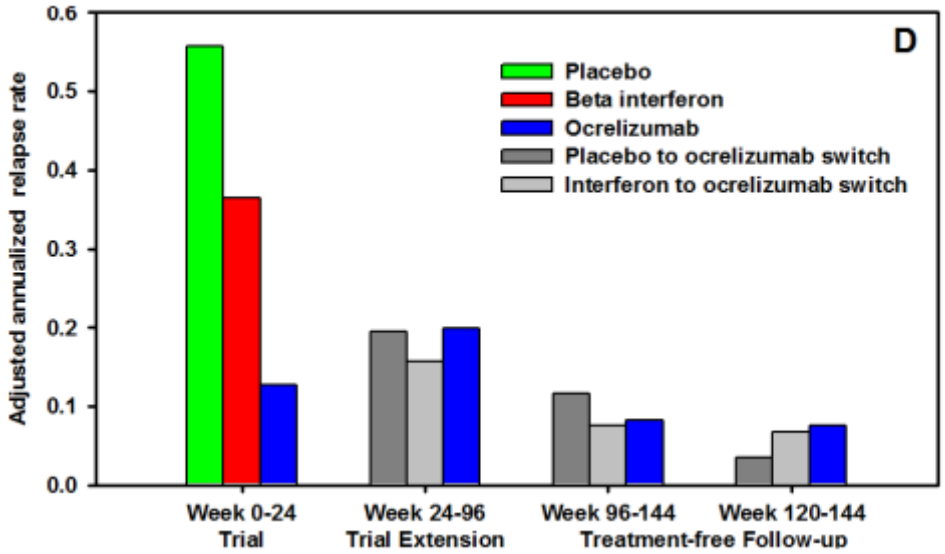
Strategie di de-escalation: terapie sequestranti

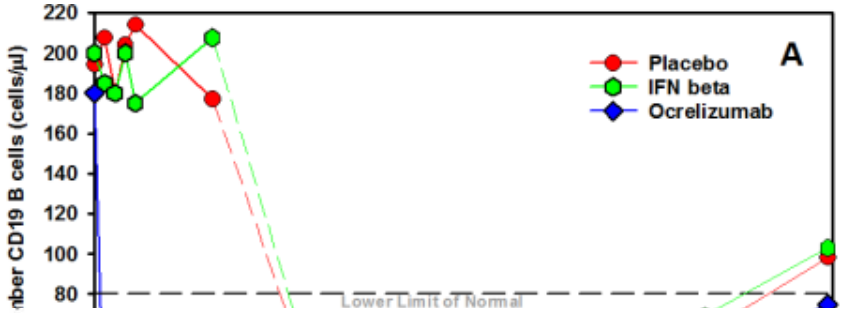
- Rischio di rebound
  - NTZ: 10-30%, 2-6 mesi dopo l'interruzione
    - Ruolo del BMI sulle tempistiche?
  - FTY 10-25%, 1-4 mesi dopo l'interruzione
  - Soprattutto in pazienti giovani, con elevata attività pre-tp e per passaggi a terapie di I linea
    - Descritto anche in pazienti over 50 e in pazienti in fase progressiva
- Washout breve
- Bridging con terapie ad elevata efficacia e rapido meccanismo di azione
  - Per quanto tempo?
- Successiva de-escalation a tp di I linea

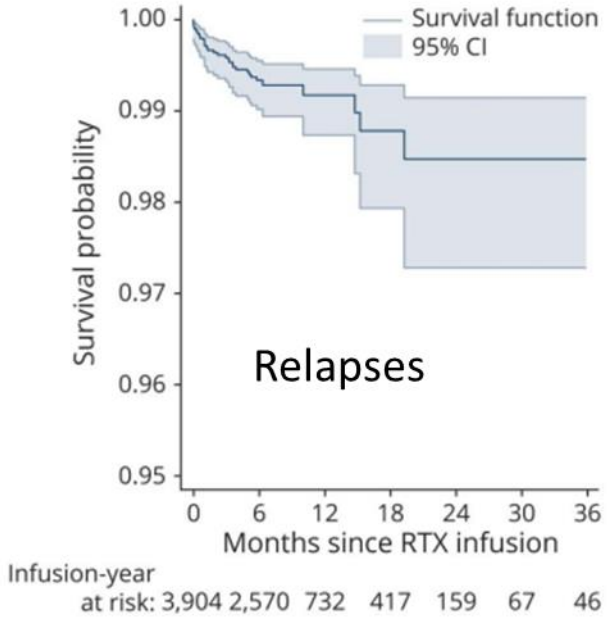
Van Pesch ECTRIMS 2023

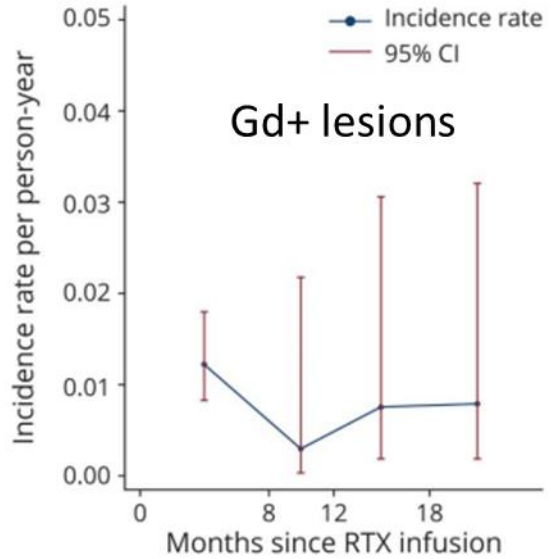
Strategie di de-escalation: antiCD20

- No evidenza di rebound, anzi
  - OCR studio di fase II: prevista estensione treatment-free (n = 133)







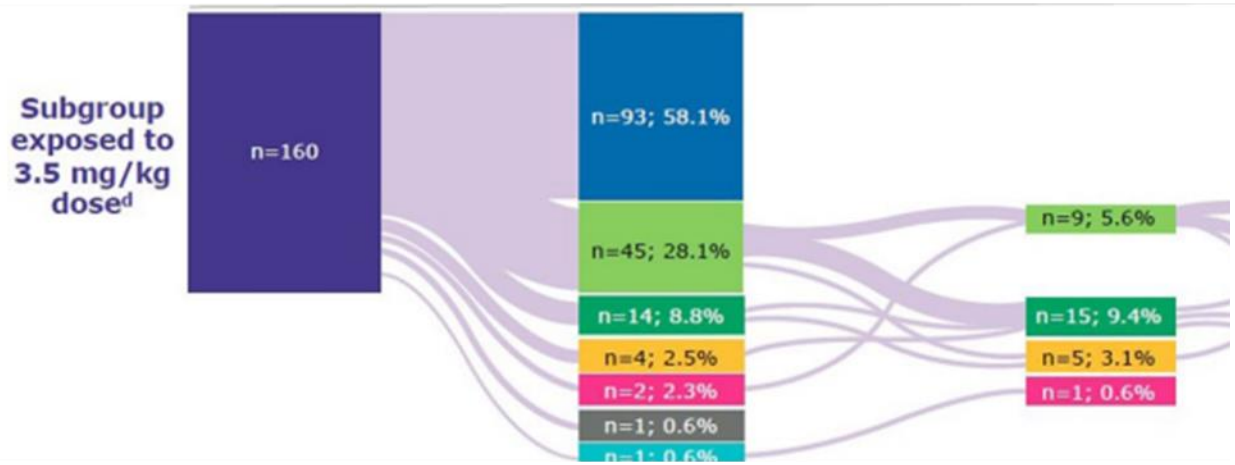


- Interruzione di RTX: 92 pz 3/92 relaps
- Extended dose RTX mantiene efficaci

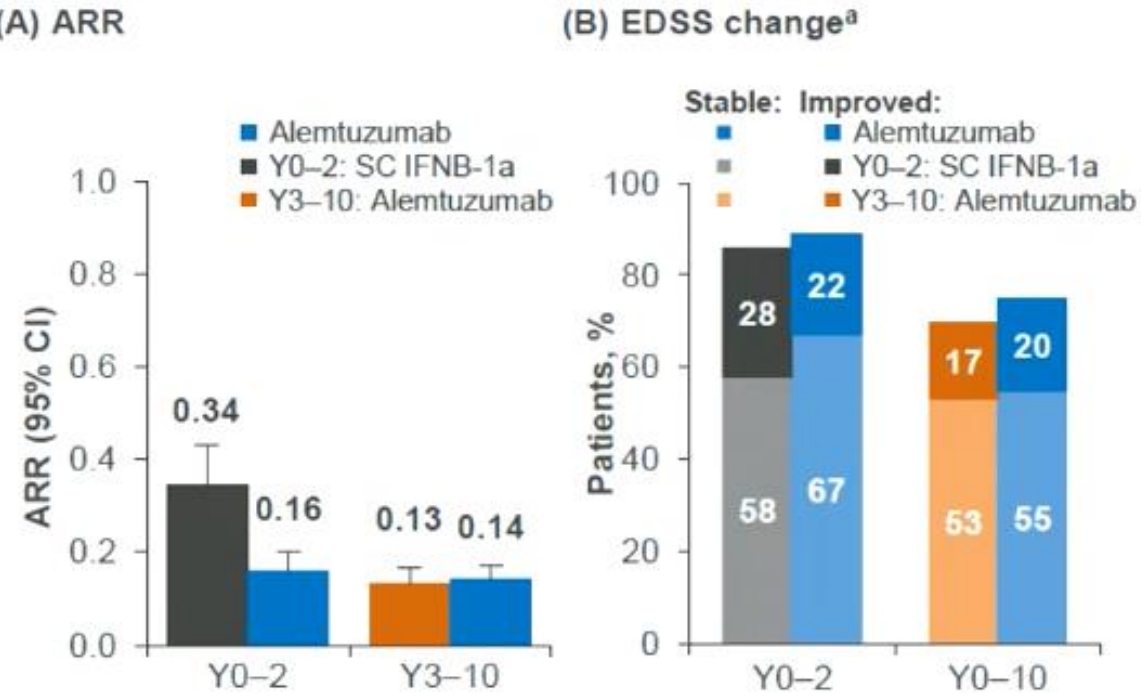
Baker et al 2020, Juto et al 2020, Starvaggi-Cucuzza et al 2022

Strategie di de-escalation: post tp pulsate

- Strategia più utilizzata: wait and see o cicli ulteriori di tp



Retention rate >70%
53% remain untreated at Y10



Giovannoni et al 2023, Coles et al 2021

Conclusioni

- L’interruzione del trattamento in un paziente con SM, anche se stabile, sembra comportare un lieve rischio di ripresa di malattia
- I principali predittori di stabilità di malattia dopo una sospensione sono età over 60, durata dell’esposizione al DMD e/o assenza di attività per molti anni prima della sospensione

- Resta da esplorare meglio il rischio di accumulo di disabilità alla sospensione
- Resta da valutare se riprendere una terapia al primo segno di attività può essere una strategia efficace

- Nell’inversione della piramide terapeutica, ad un approccio più aggressivo nelle fasi iniziali di malattia si può associare una de-escalation nelle fasi più avanzate
  - Dobbiamo condividere protocolli e raccogliere evidenze

Grazie per l’attenzione