Universitätsmedizin Essen
Universitätsklinikum

WeltMSTag
DMSS
DEUTSCHE MULTIPLE SKLEROSE STIFTUNG NORDRHEIN-WESTFALEN

Refik Pul

Konzepte zur MS-Therapie und Ausblick

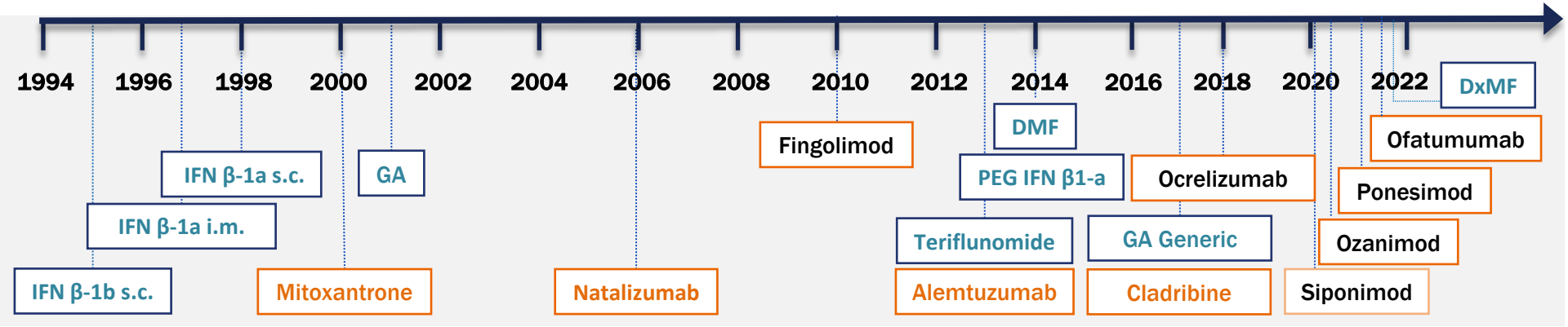
Klinik für Neurologie

Translational Neuro- and Behavioral Sciences

Interessenkonflikte

- Alexion
- Amgen/Horizon
- Bayer Healthcare
- Biogen
- Bristol Myers-Squibb
- Celgene
- Merck Serono
- Mylan/Viatris
- Novartis
- Roche
- Sanofi-Genzyme
- Sanofi-Aventis
- Stada
- Teva
- Janssen-Cilag

Disease Modifying Treatments



RRMS

Platform DMDs	HET DMDs
Interferon (IFN) β	*Mitoxantron*
Glatiramer acetate (GA)	Natalizumab
Teriflunomide	Fingolimod, Ozanimod, Ponesimod
Dimethyl fumarate (DMF) Diroximel fumarate (DxMF)	Alemtuzumab
	Cladribine
	Ocrelizumab

Eskalation

Induktion

Progressive MS

SPMS	PPMS
Interferon (IFN) β	Ocrelizumab
Siponimod *(Cladribine, Ocrelizumab, Ofatumumab,*	

31.05.2023 EMA Ublituximab
28.07.2025 Tegomilfumarat

PRISM-Studie Interferon β-1a s.c.

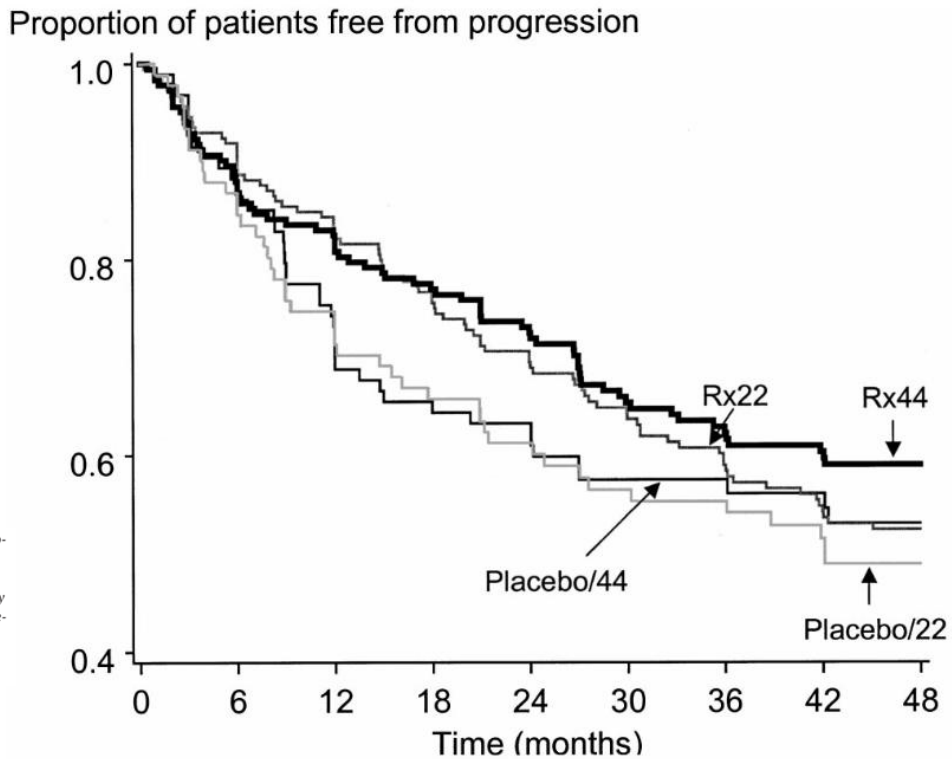


Figure 2. Kaplan–Meier curves for time to confirmed progression in disability for years 1 through 4 (all patients). Proportions of patients are those free from progression. The patients receiving highest cumulative dose of therapy have the lowest rate of progression as opposed to those receiving the lowest dose who had the highest rate of progression. Late treatment was not associated with a catch-up of benefit to early therapy.

PRISMS Study Group 2001 Neurology

Interferon β-1b s.c.

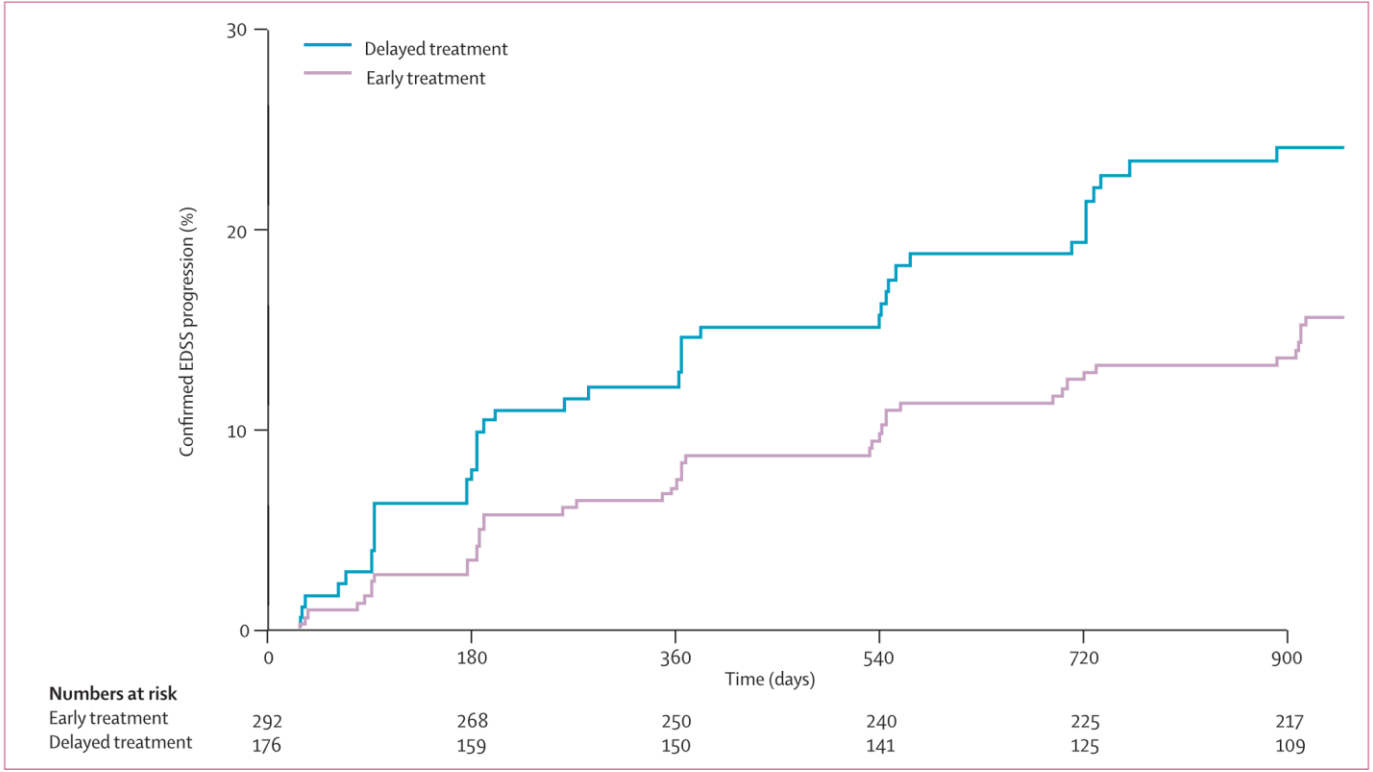
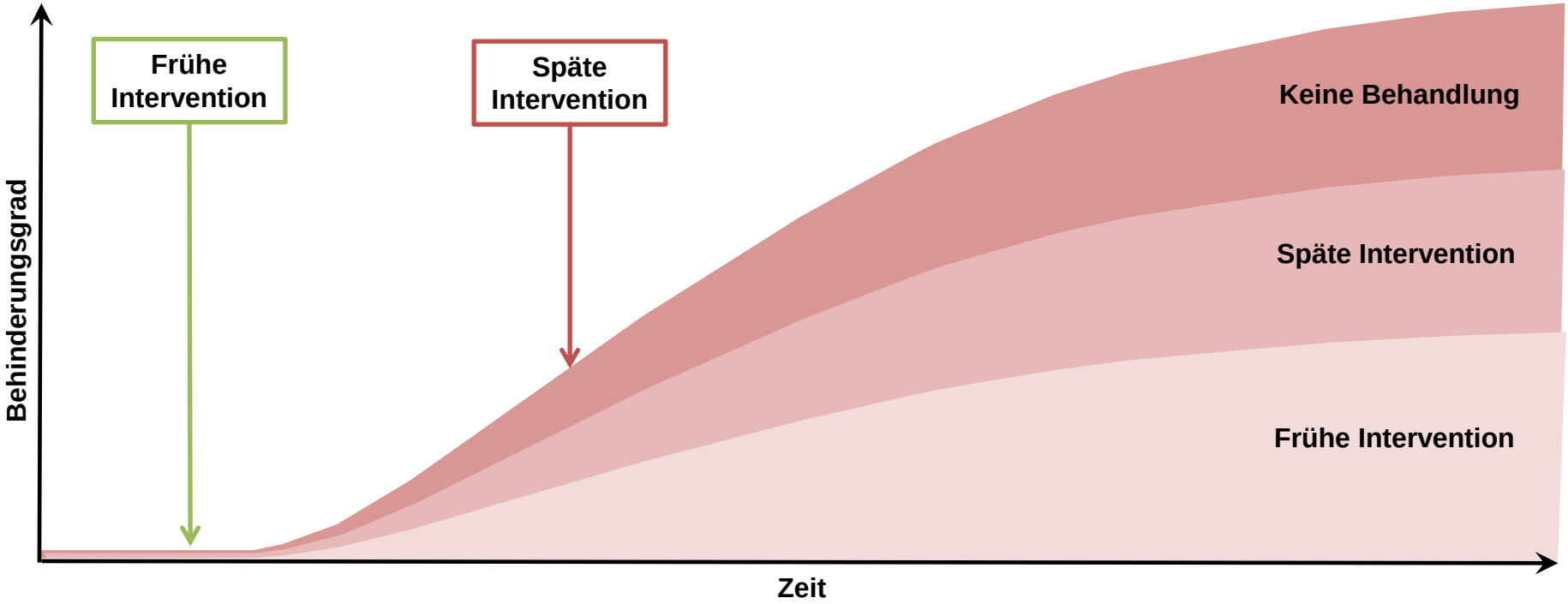


Figure 2: **Kaplan-Meier estimates for the probability of progression on the expanded disability status scale (EDSS) confirmed after 6 months within the 3-year period**

The cumulative probability of EDSS progression was lower in the early treatment group (p=0·022, log-rank test).

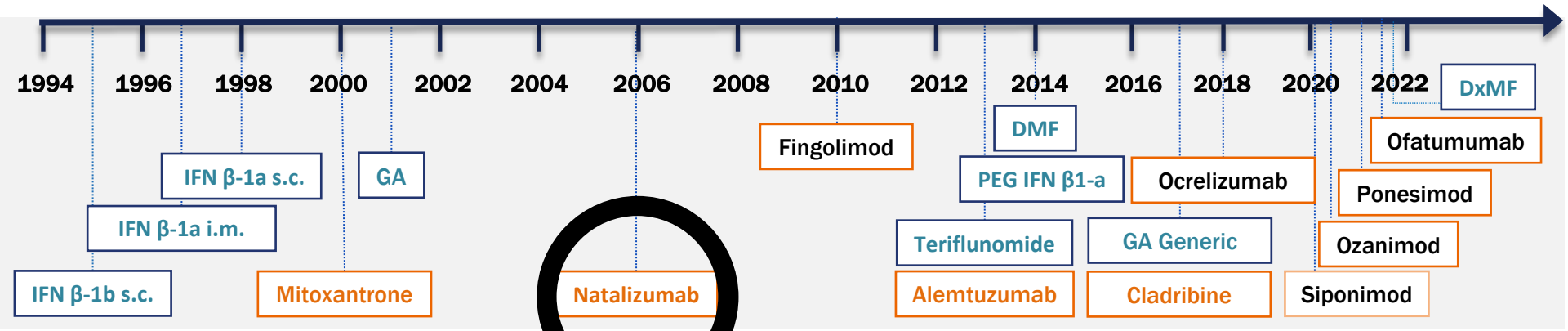
Kappos et al. 2007 Lancet

Konzepte zur Therapie



Konzept und Abbildung stammen von Miller et al 2004. Sie beruhen auf Überlegungen zu den Ergebnissen der CHAMPS/CHAMPION (Avonex®) und PRISM-4 (Rebif®).

Disease Modifying Treatments



RRMS

Platform DMDs

- Interferon (IFN) β
- Glatiramer acetate (GA)
- Teriflunomide
- Dimethyl fumarate (DMF)
  Diroximel fumarate (DxMF)

Induktion

Eskalation

HET DMDs

- *Mitoxantron*
- Natalizumab
- Fingolimod, Ozanimod, Ponesimod
- Alemtuzumab
- Cladribine
- Ocrelizumab

Progressive MS

SPMS

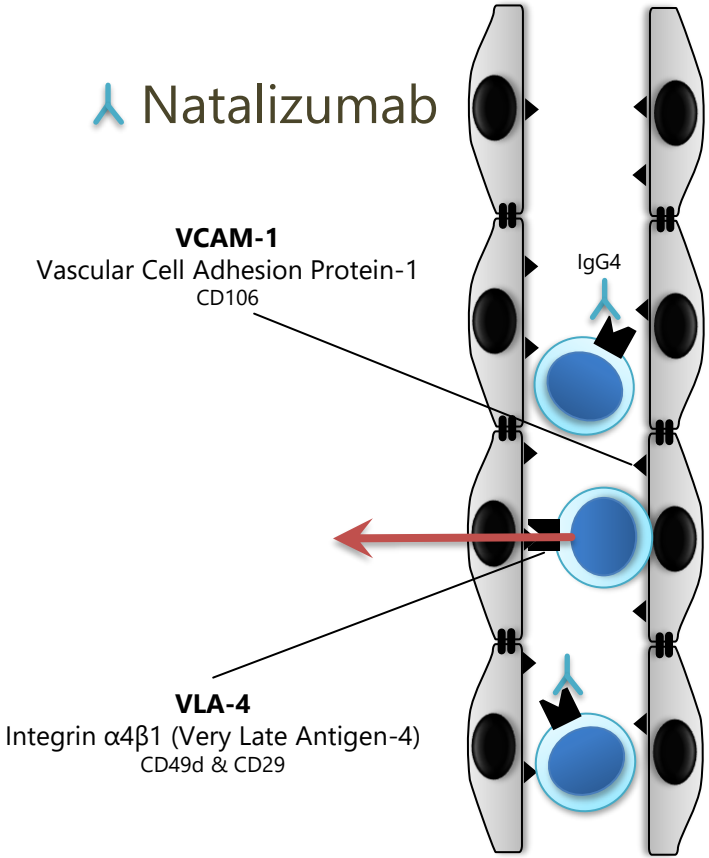
- Interferon (IFN) β
- Siponimod *(Cladribine, Ocrelizumab, Ofatumumab,*

PPMS

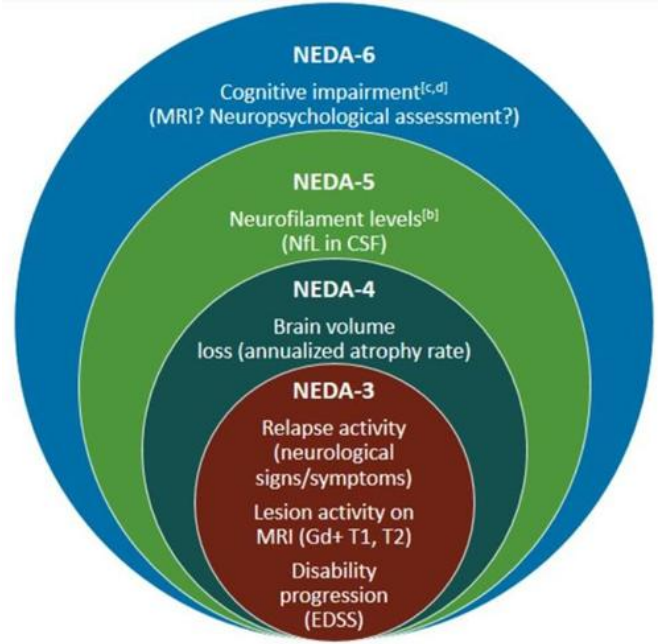
- Ocrelizumab

31.05.2023 EMA Ublituximab
28.07.2025 Tegomilfumarat

Kategorie 3: Natalizumab

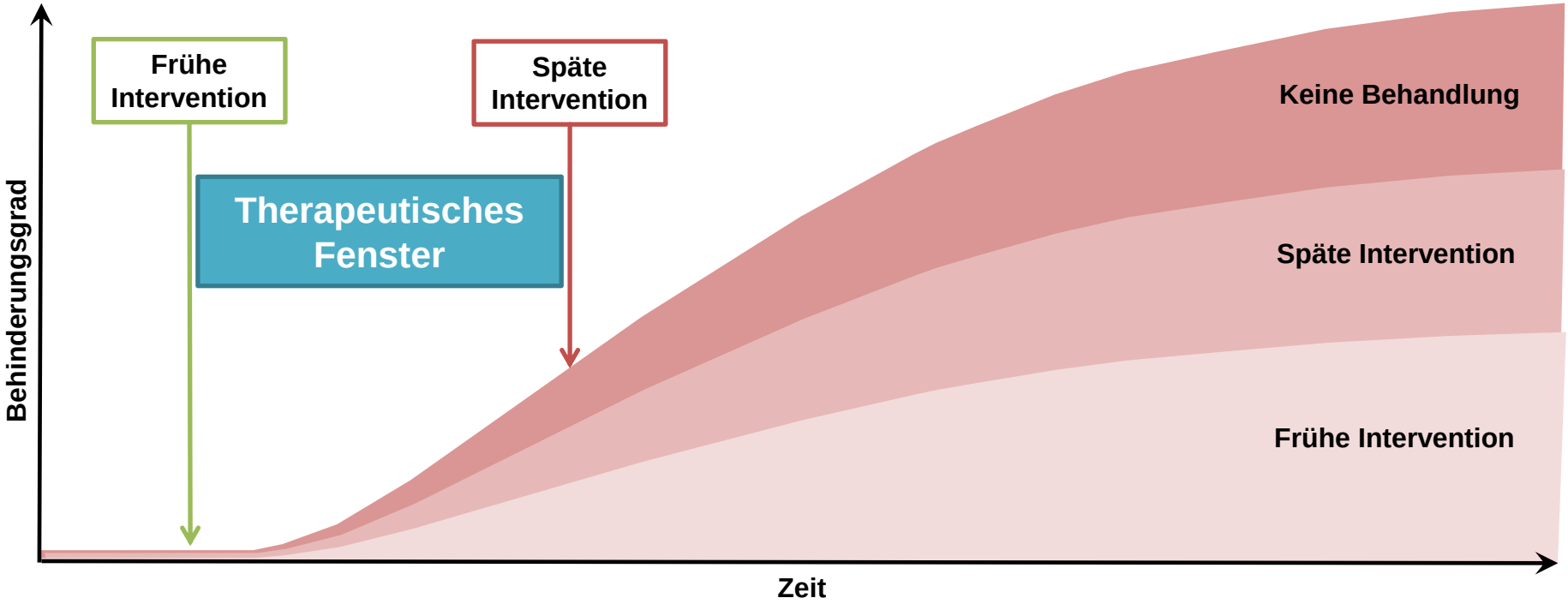


Konzept: Keine Evidenz für eine Krankheitsaktivität (NEDA)



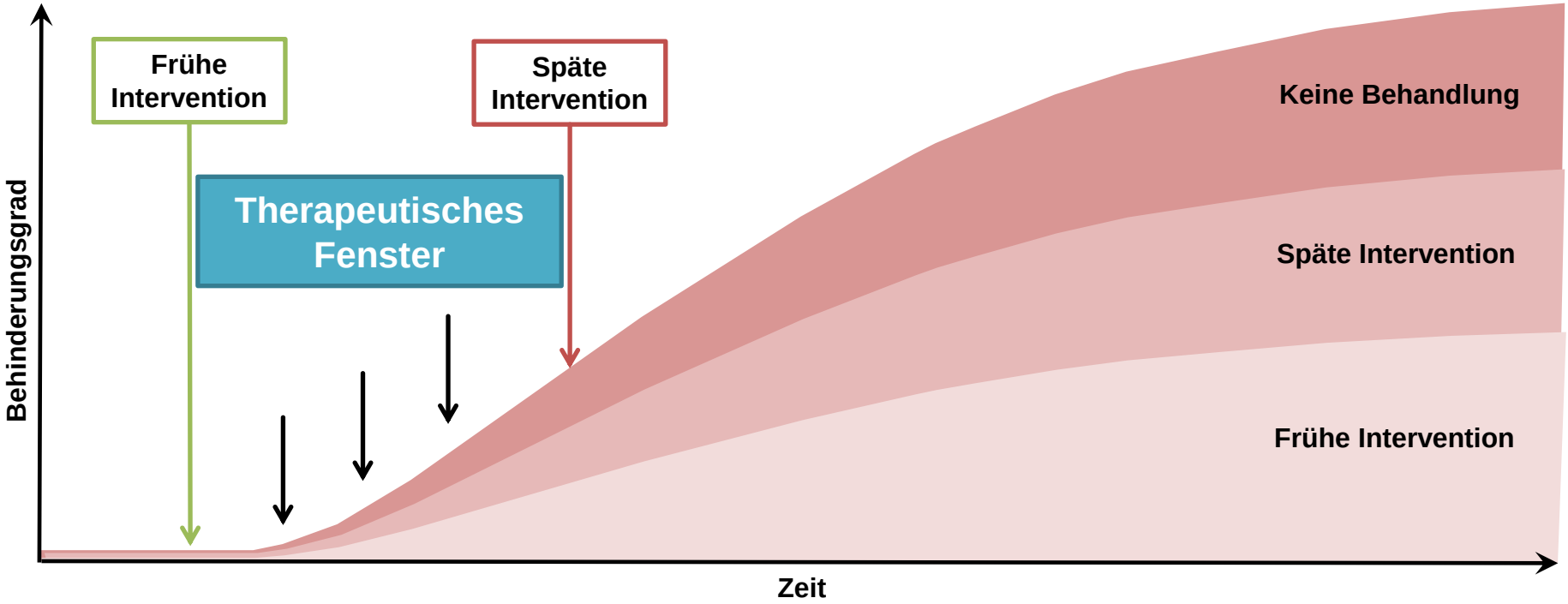
2009 Havdrova et al. Lancet Neurol
post-hoc Analyse AFFIRM-Studie
„Disease-Activity-Free" Status
2010 Havdrova et al. Neurology
„Freedom from Disease Activity"
2014 Nixon et al. Adv Ther
„No Evidence of Disease Activity"

Konzepte zur Therapie



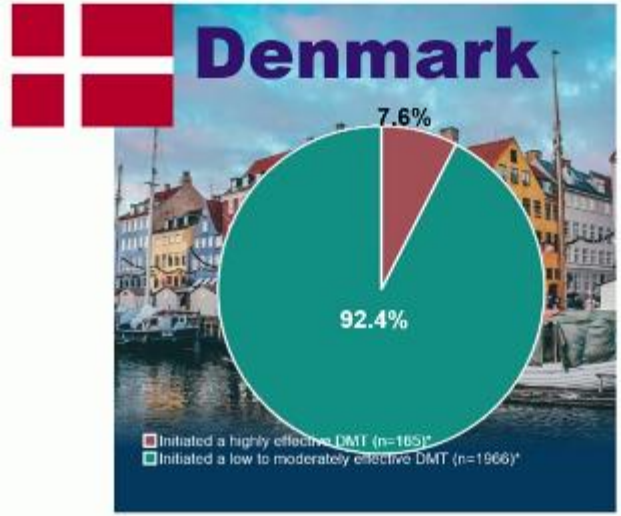
Der Begriff „window of therapeutic opportunity“ wurde von Alasdair Coles im Zusammenhang mit Alemtuzumab eingesetzt. 2016 gewann der Begriff mit Giovannoni Popularität (Giovannoni et al. 2016 MSARD).

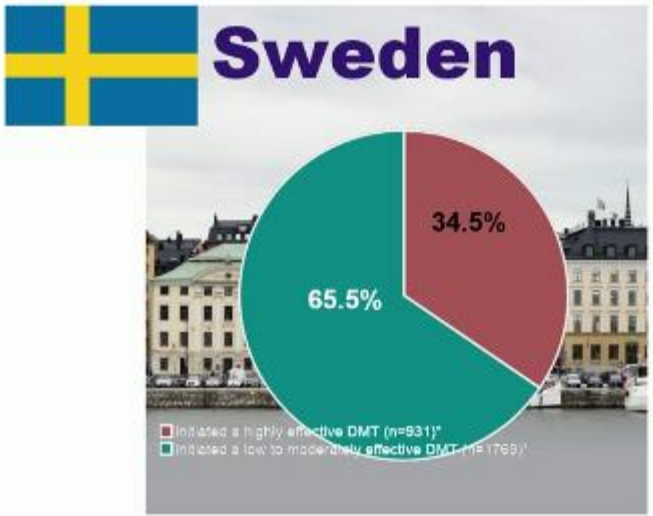
Konzepte zur Therapie



Optimierung der Therapie bis das Therapieziel NEDA (NEIDA) erreicht wird.

Evidenz

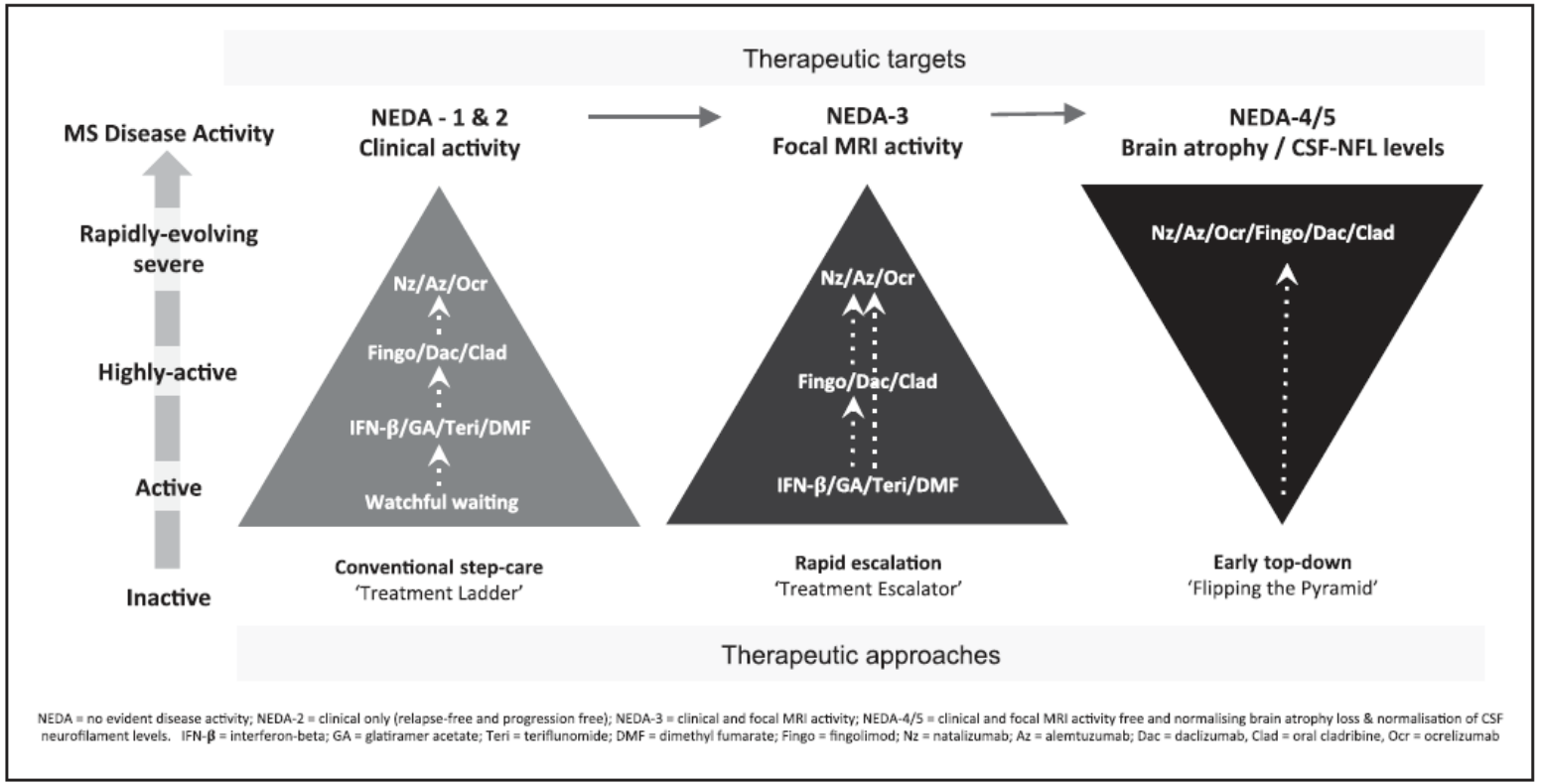




Data are from a retrospective cohort study of 4,861 patients with RRMS (Danish registry N= 2,161 and Swedish registry N=2,700) from Sweden and Denmark initiating their first DMT between 2013-2016†

Spelman et al. 2021 JAMA Neurology

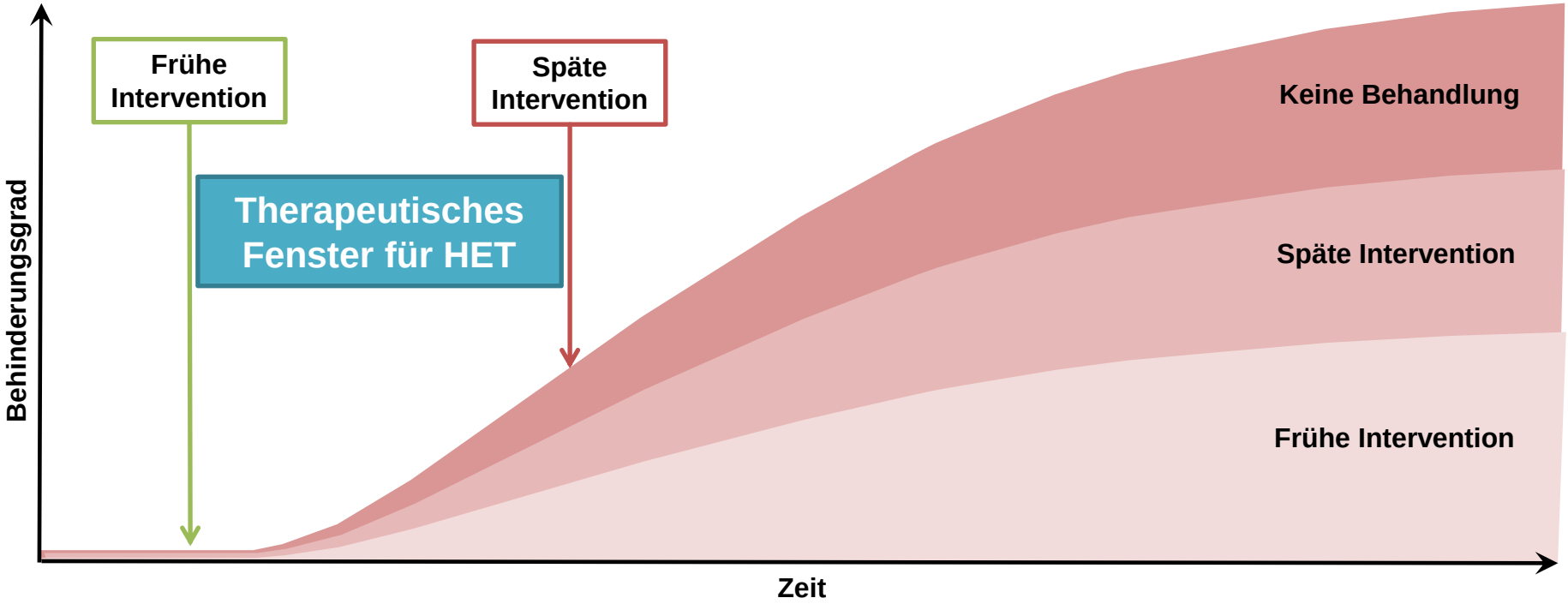
Umdrehen der Behandlungspyramide?



NEDA = no evident disease activity; NEDA-2 = clinical only (relapse-free and progression free); NEDA-3 = clinical and focal MRI activity; NEDA-4/5 = clinical and focal MRI activity free and normalising brain atrophy loss & normalisation of CSF neurofilament levels. IFN-β = interferon-beta; GA = glatiramer acetate; Teri = teriflunomide; DMF = dimethyl fumarate; Fingo = fingolimod; Nz = natalizumab; Az = alemtuzumab; Dac = daclizumab, Clad = oral cladribine, Ocr = ocrelizumab

AAN 2018, Abstract 005

Konzepte zur Therapie



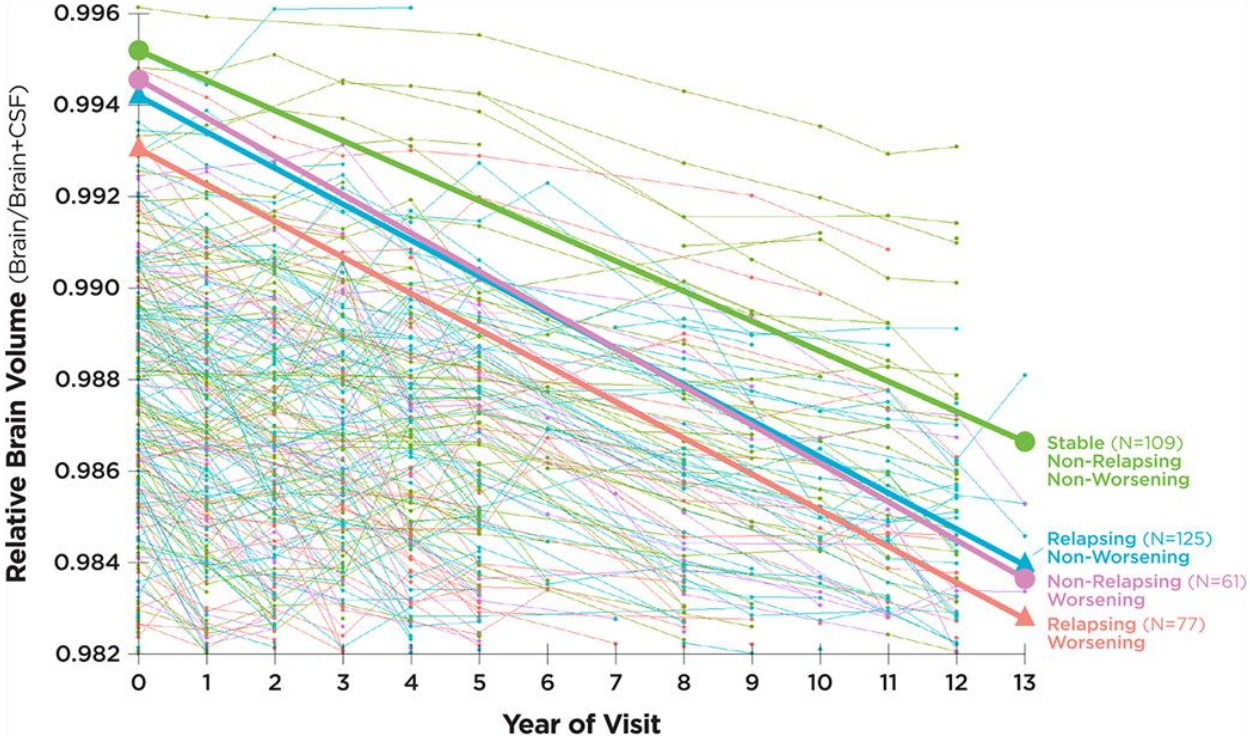
Aktuell: Diskussion über den frühen Einsatz von hocheffektiven Therapien.

Silent Progression in Disease Activity–Free Relapsing Multiple Sclerosis

University of California, San Francisco MS-EPIC Team, Bruce A. C. Cree, MD, PhD, MAS, Jill A. Hollenbach, PhD, MPH, Riley Bove, MD, MMSc, Gina Kirkish, MSc, Simone Sacco, MD, Eduardo Caverzasi, MD, PhD, Antje Bischof, MD, Tristan Gundel, Alyssa H. Zhu, MSc, Nico Papinutto, PhD, William A. Stern, Carolyn Bevan, MD, MS, Andrew Romeo, MD, Douglas S. Goodin, MD, Jeffrey M. Gelfand, MD, MAS, Jennifer Graves, MD, PhD, MAS, Ari J. Green, MD, MAS, Michael R. Wilson, MD, MAS, Scott S. Zamvil, MD, PhD, Chao Zhao, MSc, Refujia Gomez, Nicholas R. Ragan, Gillian Q. Rush, Patrick Barba, Adam Santaniello, Sergio E. Baranzini, PhD, Jorge R. Oksenberg, PhD, Roland G. Henry, PhD, and Stephen L. Hauser, MD

Trotz NEDA „Silent Progression“

Silent progression in disease activity–free relapsing multiple sclerosis



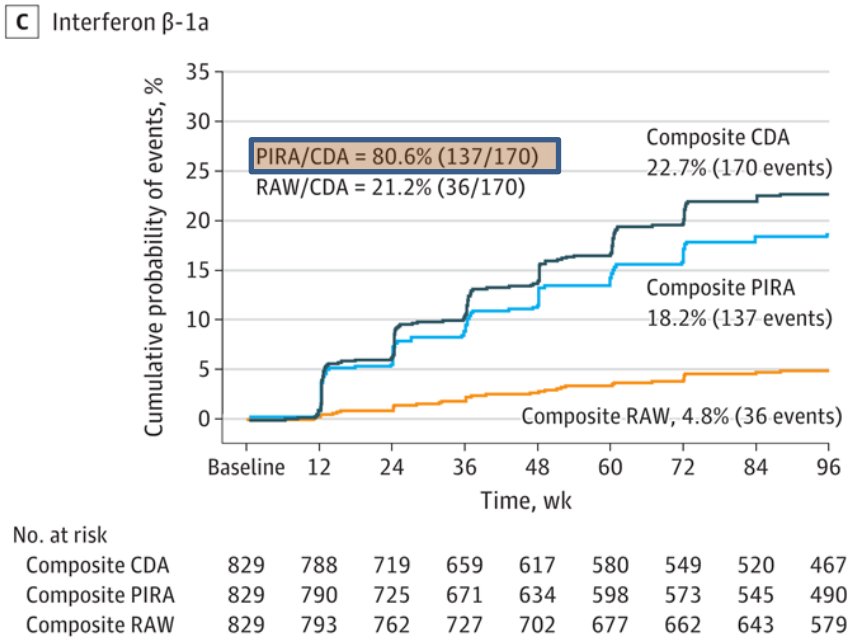
Cree et al. 2019 Ann Neurol, Silent progression

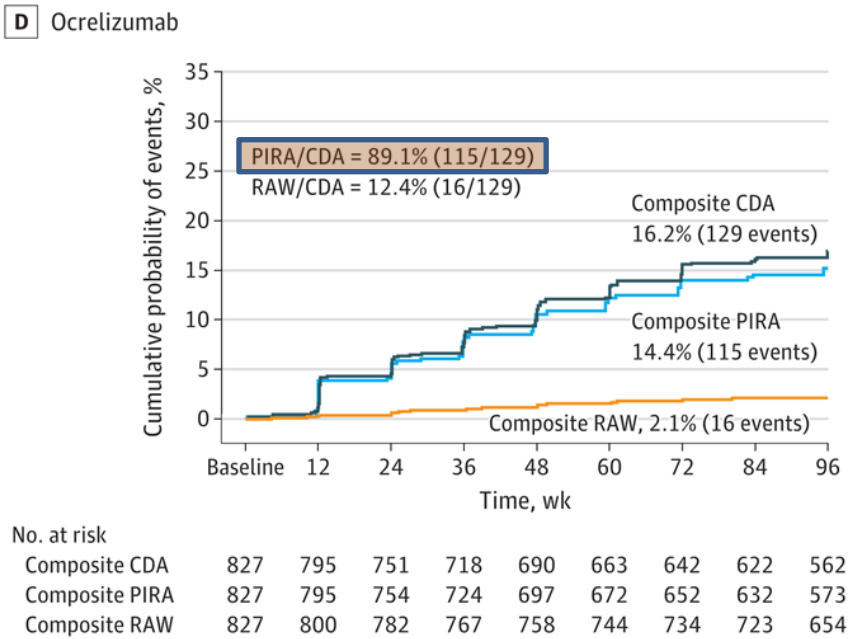
JAMA Neurology | Original Investigation

Contribution of Relapse-Independent Progression vs Relapse-Associated Worsening to Overall Confirmed Disability Accumulation in Typical Relapsing Multiple Sclerosis in a Pooled Analysis of 2 Randomized Clinical Trials

Ludwig Kappos, MD; Jerry S. Wolinsky, MD; Gavin Giovannoni, PhD; Douglas L. Arnold, MD; Qing Wang, PhD; Corrado Bernasconi, PhD; Fabian Model, PhD; Harold Koendgen, MD; Marianna Manfrini, MD; Shibeshih Belachew, MD; Stephen L. Hauser, MD

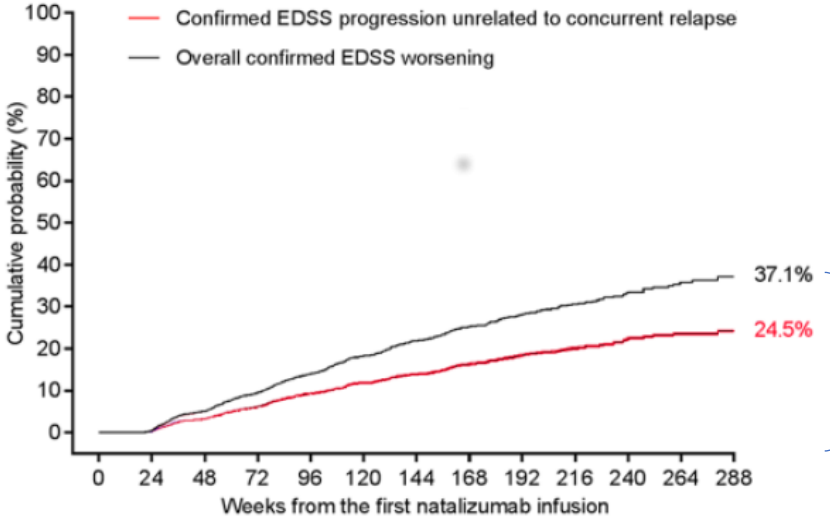
Konzept: Schubassoziierte und schubunabhängige Progression





Kappos et al. 2020 JAMA Neurol, RAW/PIRA

Auswertung von 5562 Patienten im Tysabri Observational Programme (TOP)



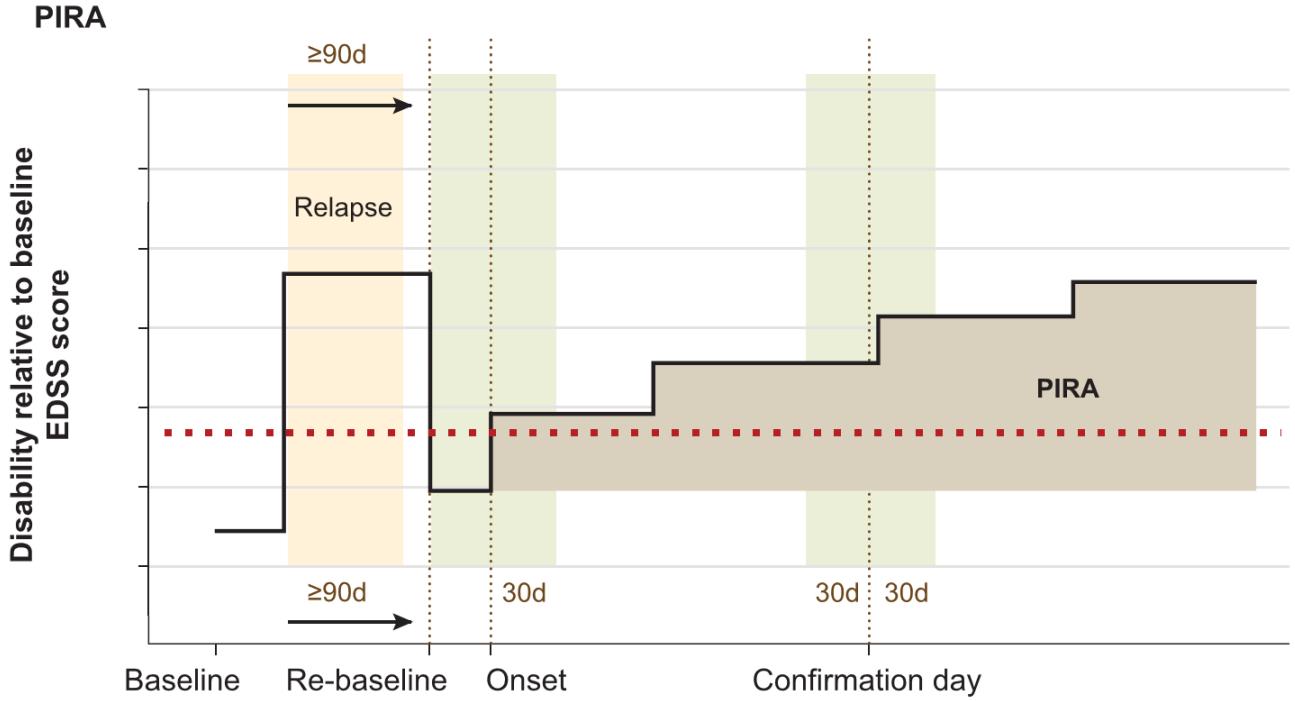
2/3 der Behinderungs-zunahme tritt schubunabhängig auf

Number of patients at risk

Confirmed EDSS progression unrelated to concurrent relapse	5562	4904	4163	3497	2822	2115	1608	1183	819	520	284	174	92
Confirmed EDSS progression	5562	4904	4164	3500	2825	2118	1609	1187	822	522	285	175	92

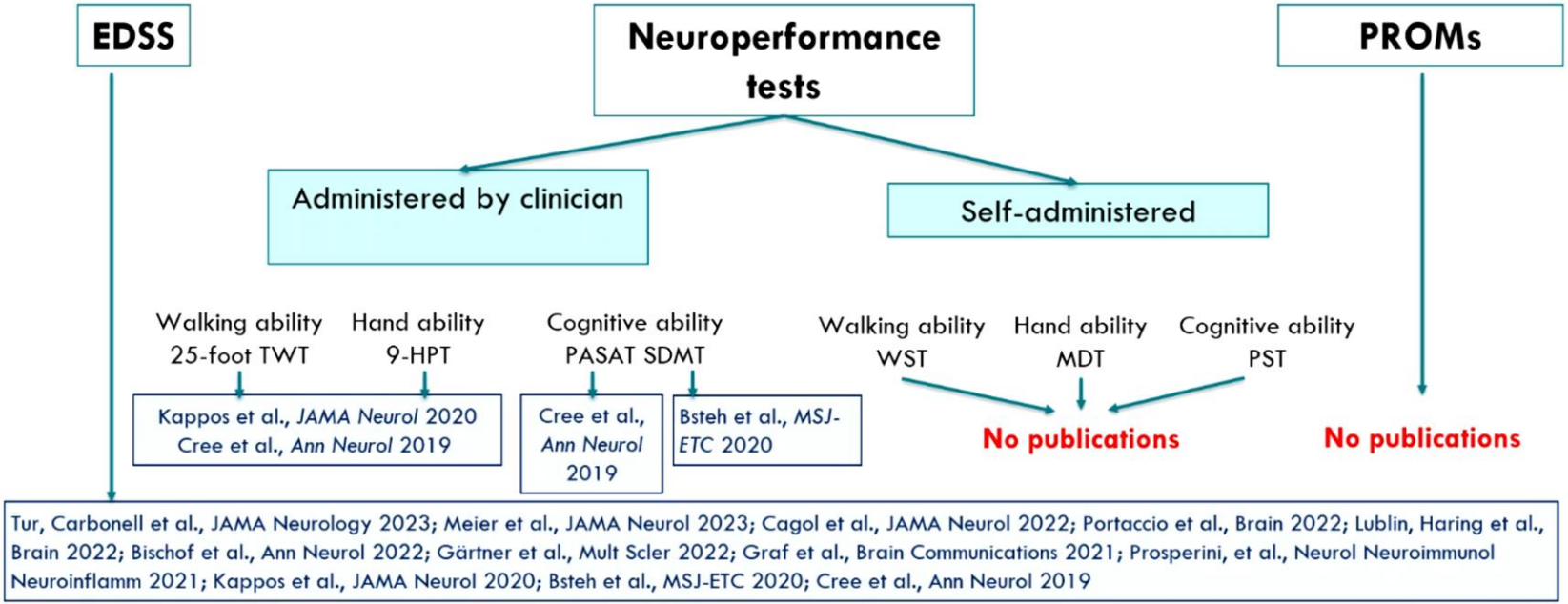
Baseline-Wert wurde ausgehend von einem beweglichen Referenzsystem neu bestimmt.
Schubassoziierte Verschlechterung: Schub trat innerhalb von 30 Tagen vor oder nach der zugehörigen EDSS-Bestimmung auf.

Modif. Kappos et al. MS J. 2018;24:963–973. DOI: 10.1177/1352458517709619



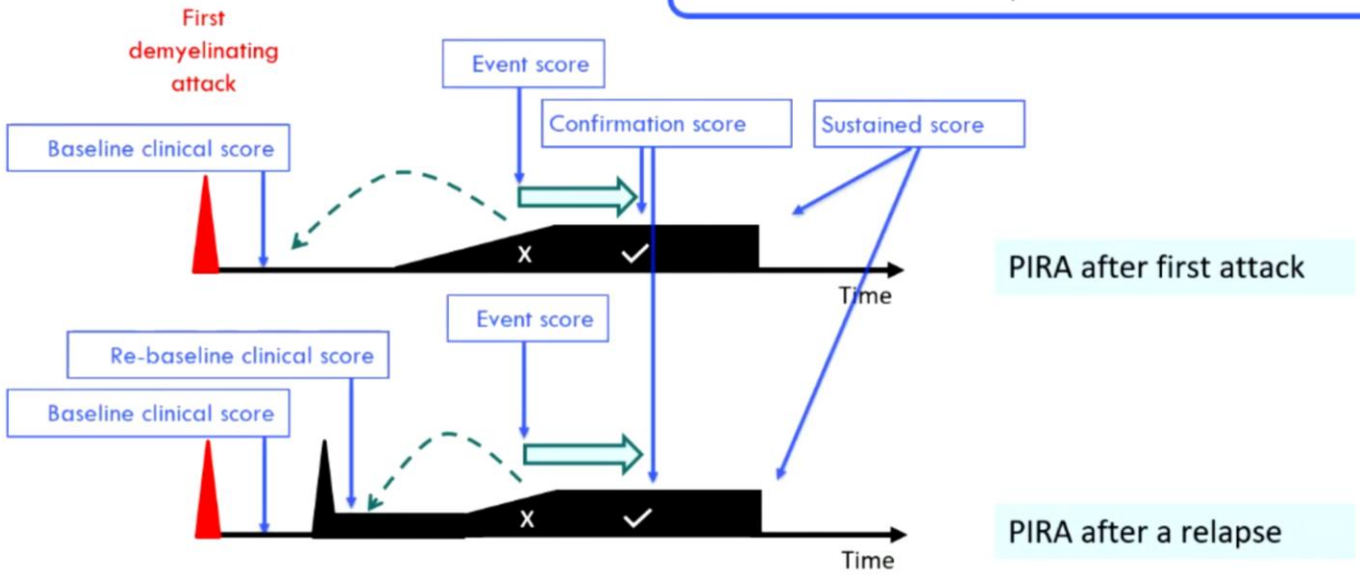
Lublin et al. 2022 Brain

Definition der PIRA



Definition der PIRA

Nomenclature:
Müller et al., JAMA Neurol 2023

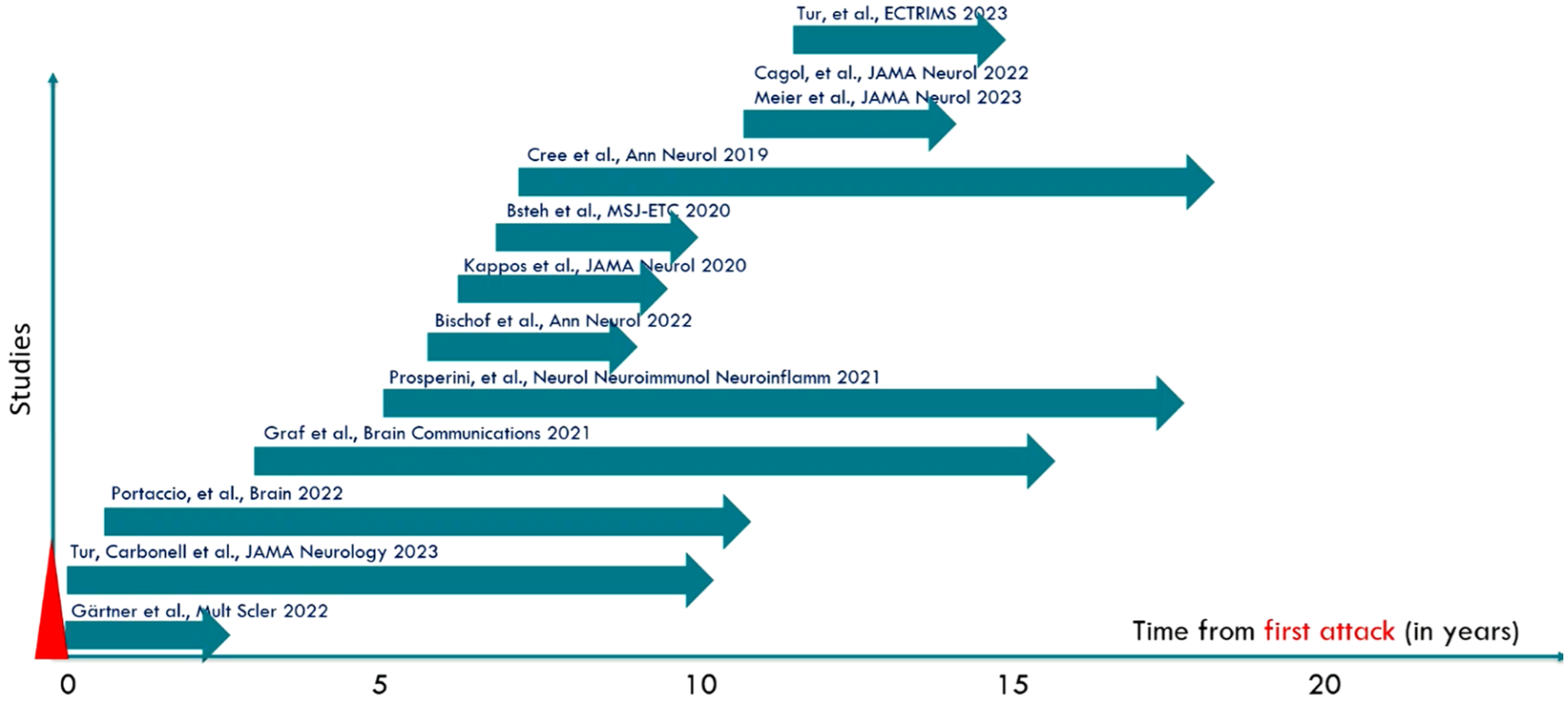


Legend

X Detection of disability accumulation with respect to baseline/re-baseline EDSS

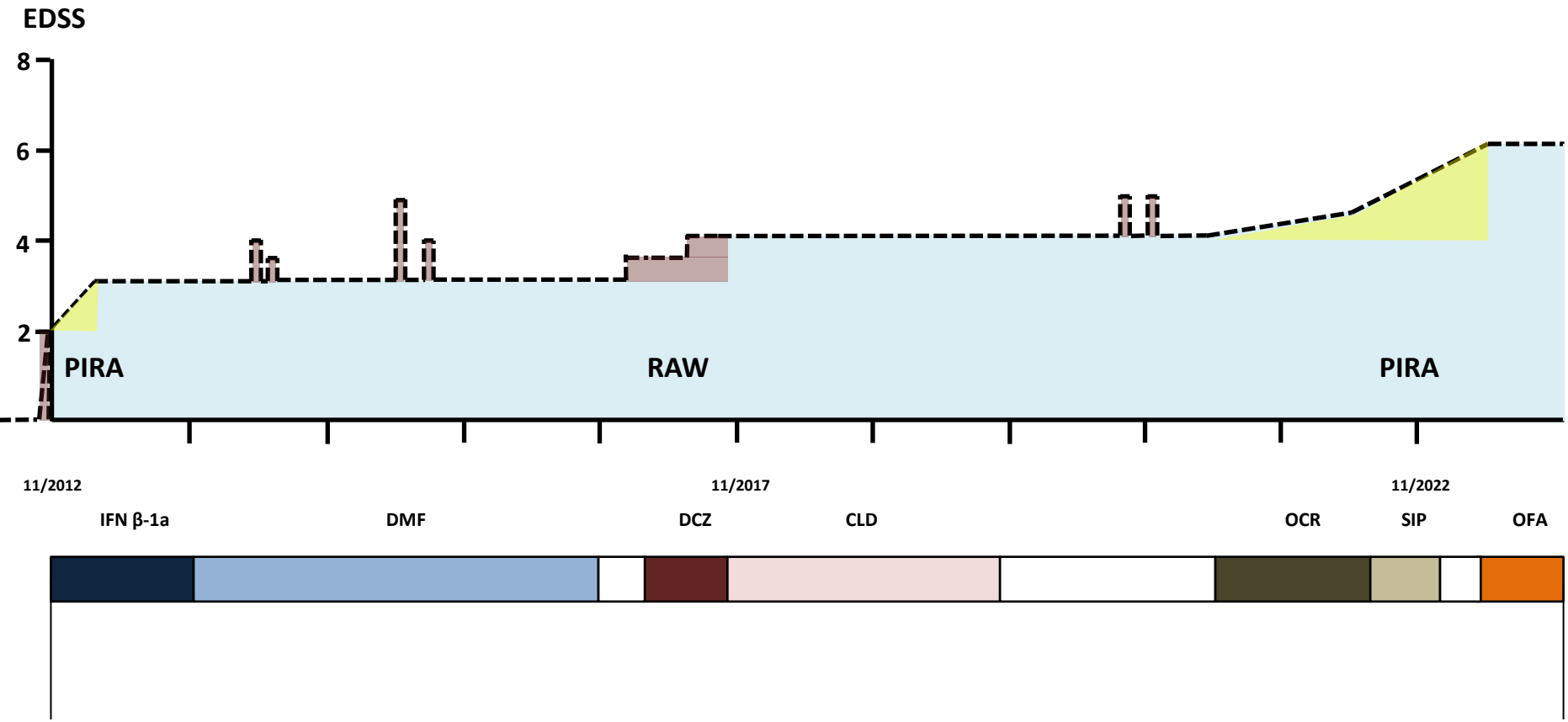
✓ Confirmation of disability accumulation 6 months later

Frequency of PIRA – 3 – 4% per year



Carassiti et al. 2018 Neuropathol Appl Neurobiol

Fallbeispiel

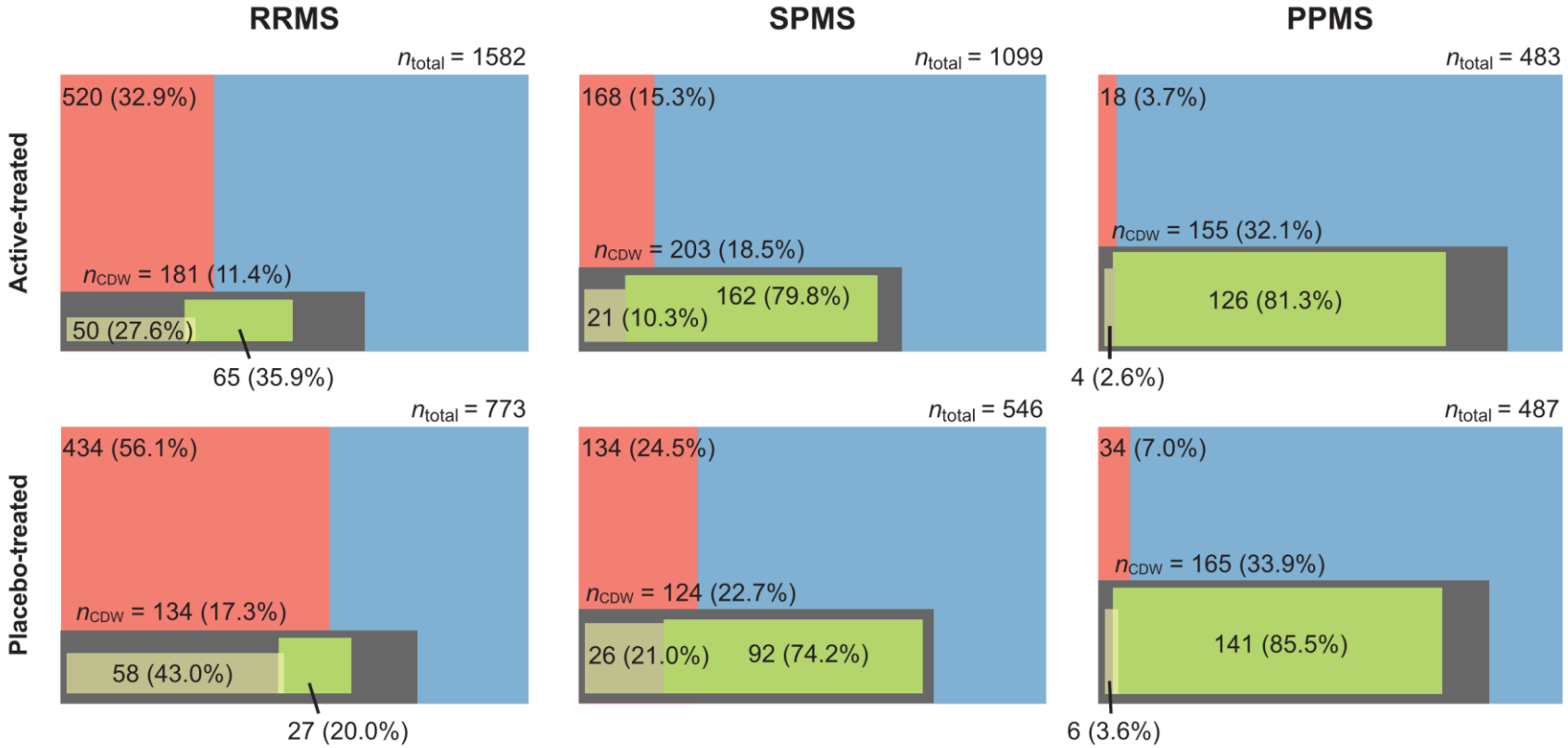


BRAIN
ORIGINAL ARTICLE

How patients with multiple sclerosis acquire disability

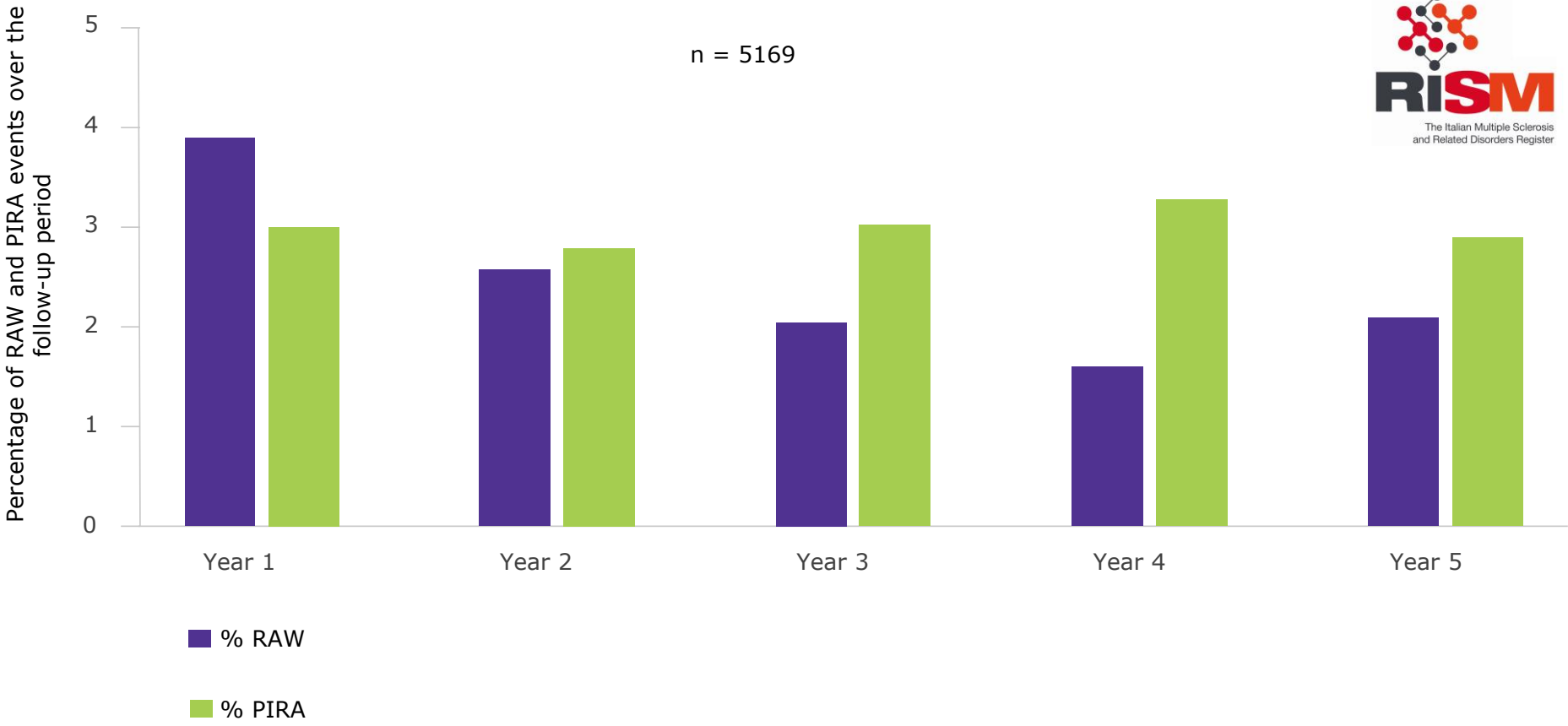
Fred D. Lublin,[1,†] Dieter A. Häring,[2,†] Habib Ganjgahi,[3] Alex Ocampo,[2] Farhad Hatami,[3] Jelena Čuklina,[2] Piet Aarden,[2] Frank Dahlke,[2] Douglas L. Arnold,[4] Heinz Wiendl,[5] Tanuja Chitnis,[6] Thomas E. Nichols,[3] Bernd C. Kieseier[2] and Robert A. Bermel[7]

Konzept: Schubabhängige und -unabhängige Progression



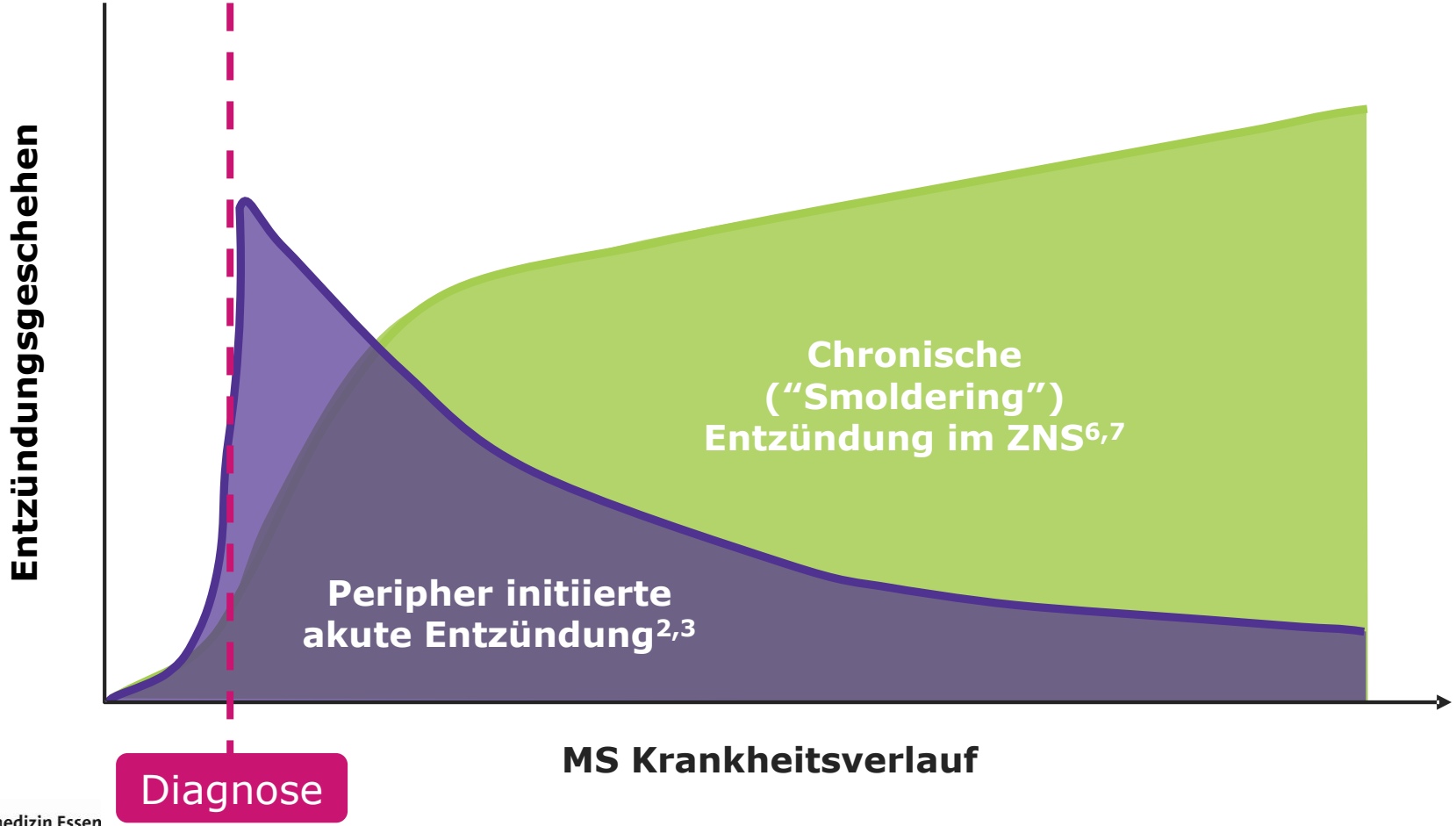
Lublin et al. 2022 Brain

PIRA and RAW



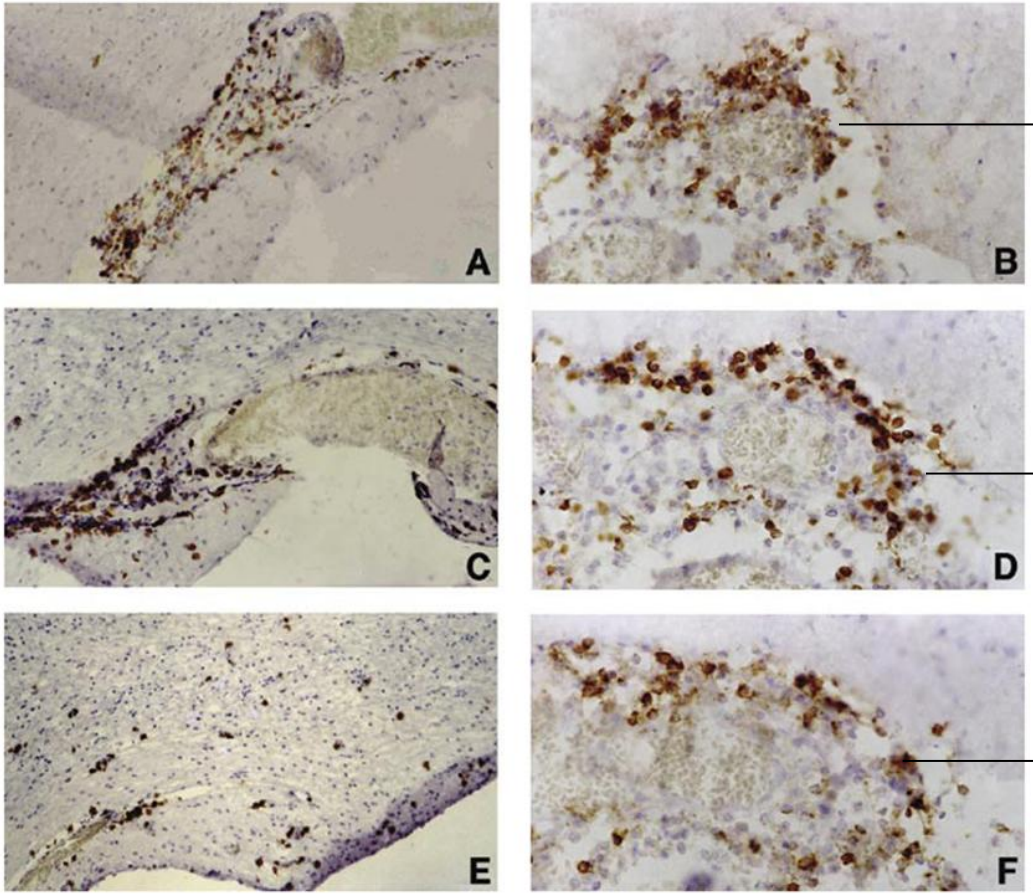
Portaccio et al. 2022 Brain

Konzepte zur Therapie

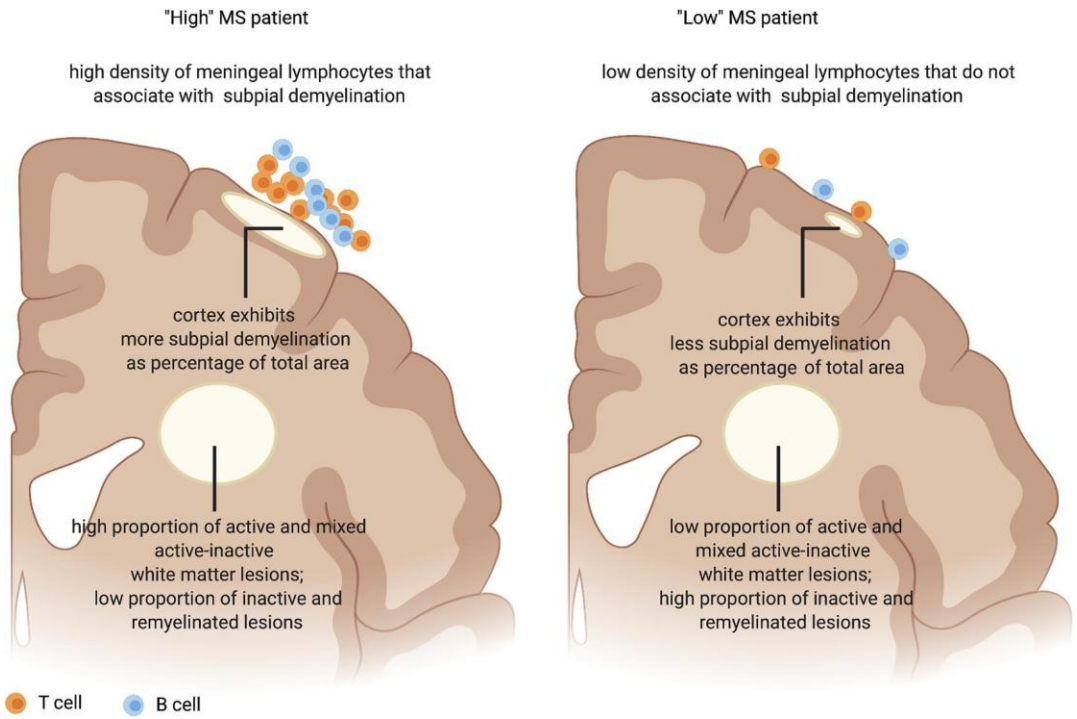


Lublin et al. 2022 Brain

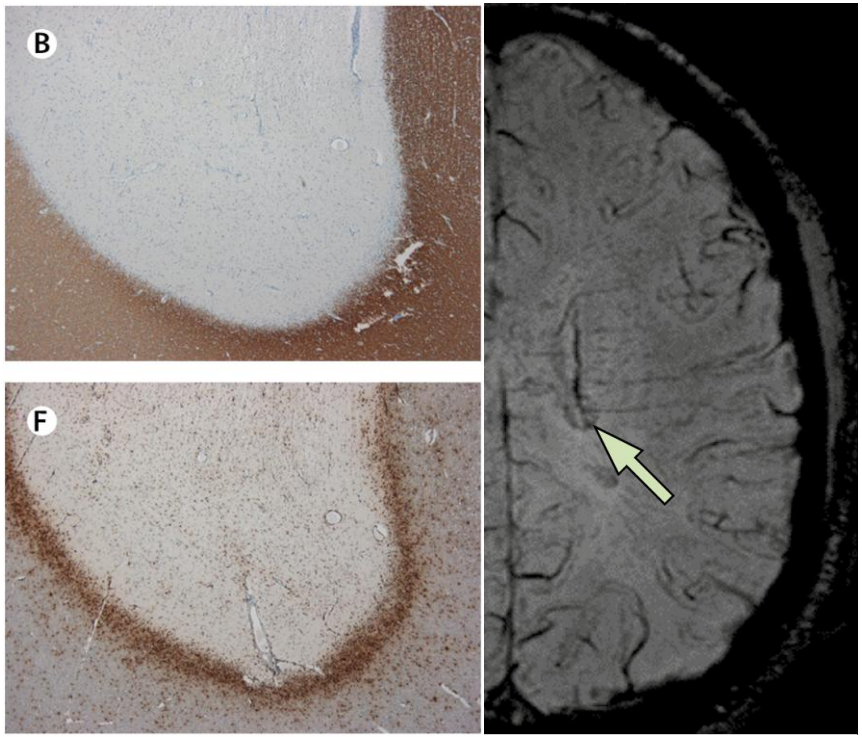
Entzündungsaktivität auch von den Leptomeningen her



Konzepte zur Therapie



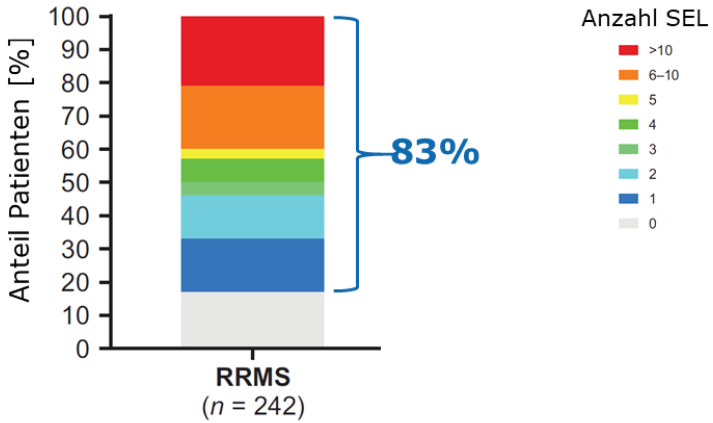
Ahmed et al. 2023, JCI Insight



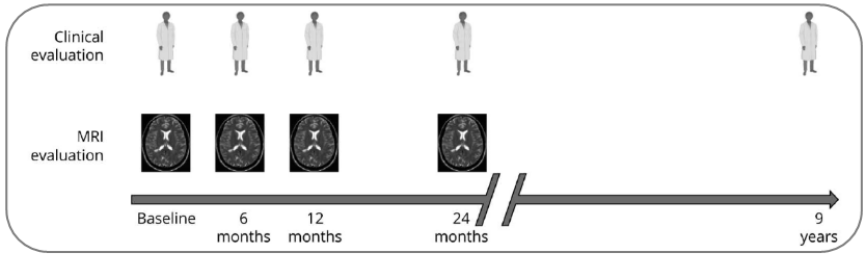
Filipi et al. 2019 Lancet Neurol

SEL treten bei bis zu 83% der RRMS-Patienten auf und sind mit langfristiger Krankheitsprogression assoziiert

SEL bei RRMS-Patienten[1]



Langzeitbeobachtung von RRMS-Patienten[2]



- Medianes follow-up **9,1 Jahre**
- **52 RRMS-Patienten** unter NTZ or FTY-Therapie
- Klinische Verlaufskontrolle und MRT-Untersuchung über 2 Jahre, gefolgt von einer einmaligen langfristigen klinischen Nachuntersuchung

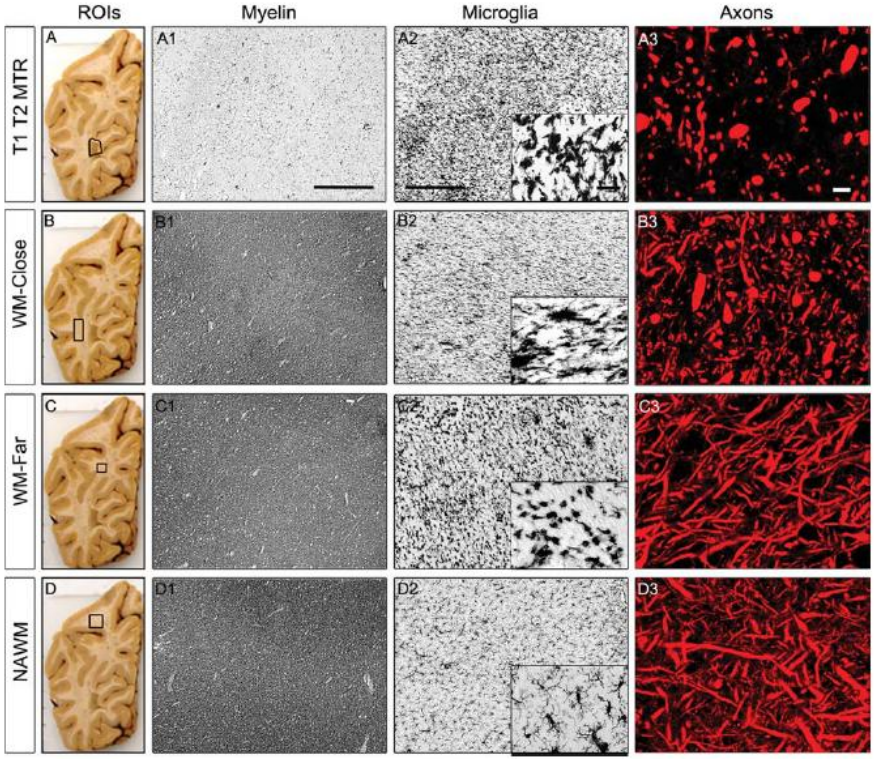
SEL treten bei bis zu **83 % der RRMS-Patienten auf**[1]

SEL sind mit langfristiger **EDSS-Verschlechterung und SPMS-Konversion** verbunden[2]

NTZ, Natalizumab; FTY, Fingolimod

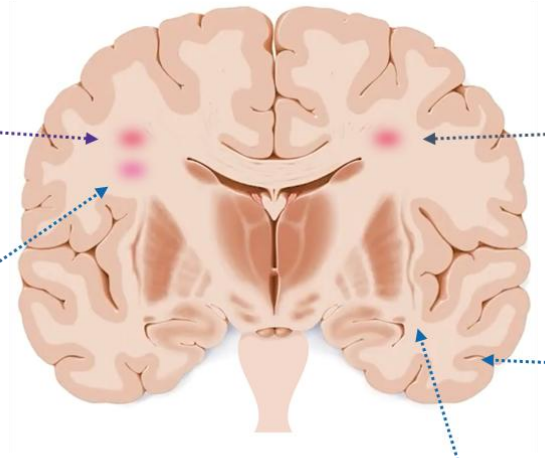
1. Elliott C, et al. AJNR, 2020;41(9):1584-1591; 2. Preziosa P et al., Neurol Neuroimmunol Neuroinflamm 2022, 9:e1139

Konzepte zur Therapie



Moll et al. 2011 Ann Neurol

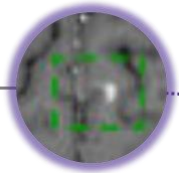
Biologische Mechanismen, die dem Fortschreiten der MS-Erkrankung zugrunde liegen[1–3]



Fokale Läsionen[4,5]

Gd Enhancement

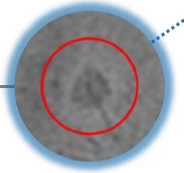
Evo: PhII und OLE



SELs und PRLs[6]

(Erweiterte) Bildgebung

Evo: PhII SEL

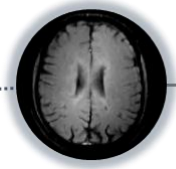


Akute axonale Schäde/ De- und Re-myelinisierung[8-10]

Blut und Liquor NfL

Erweiterte Bildgebung

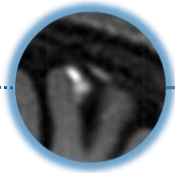
Evo: Präklinisch und PhII NfL



Meningeale Entzündung[7]

Leptomeningeales Enhancement

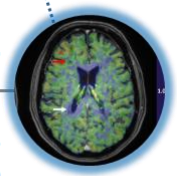
Evo: Präklinisch (Mausstudie)



Diffuse Entzündung der weißen Substanz[7]

PET oder Standardbildgebung

Evo: Geplante PhIIb PET-Studie



- Akute peripher initiierte Entzündung
- Chronische ZNS-kompartimentierte Entzündung
- Peripher initiiert und ZNS-kompartimentiert

Konzept - Funktionelle Reserve

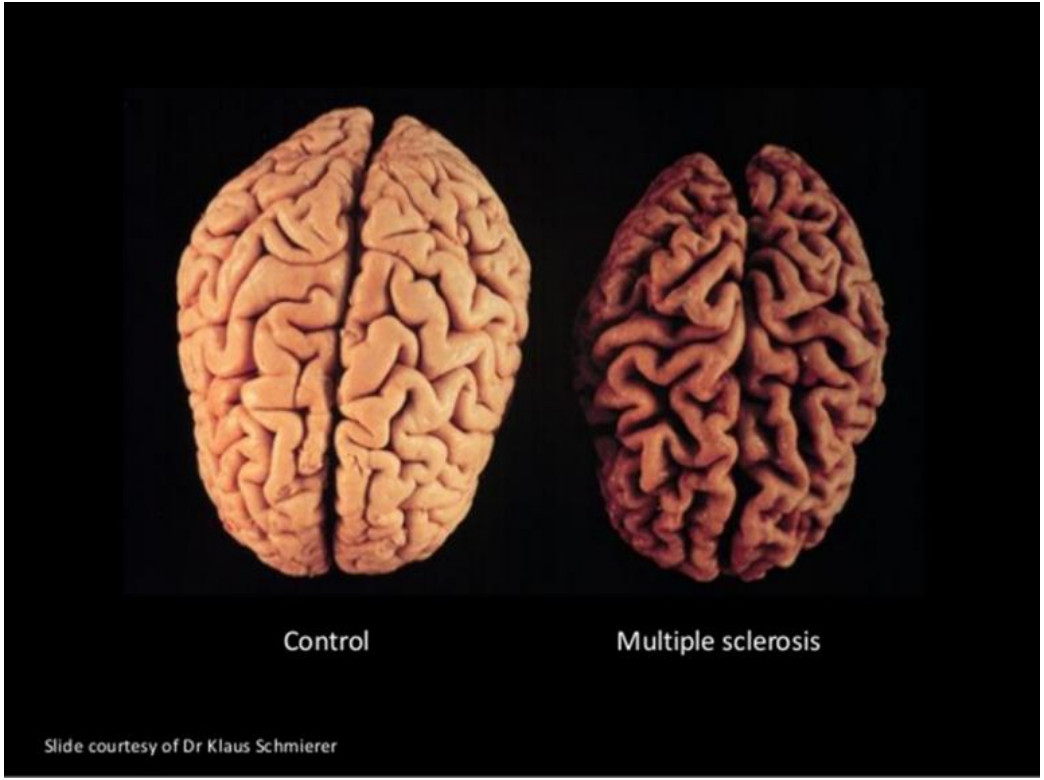
Zum Hirnvolumen tragen bei

Neurone	46%
Myelin	24%
Glia- und andere Zellen	30%

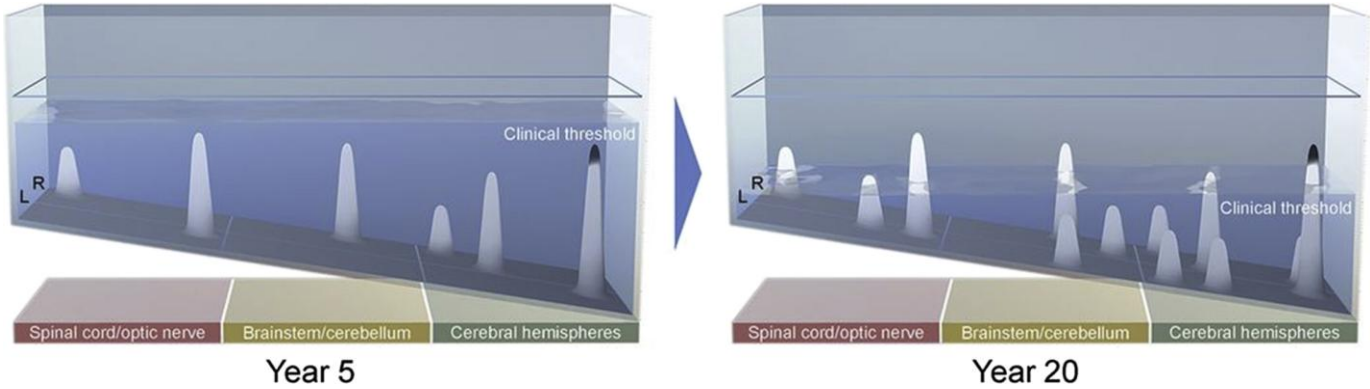
MS-Hirnatrophie: Folge des axonalen Untergangs und der Demyelinisierung

Lycklama et al. Journal of the Neurological Sciences 2005

Konzepte zur Therapie

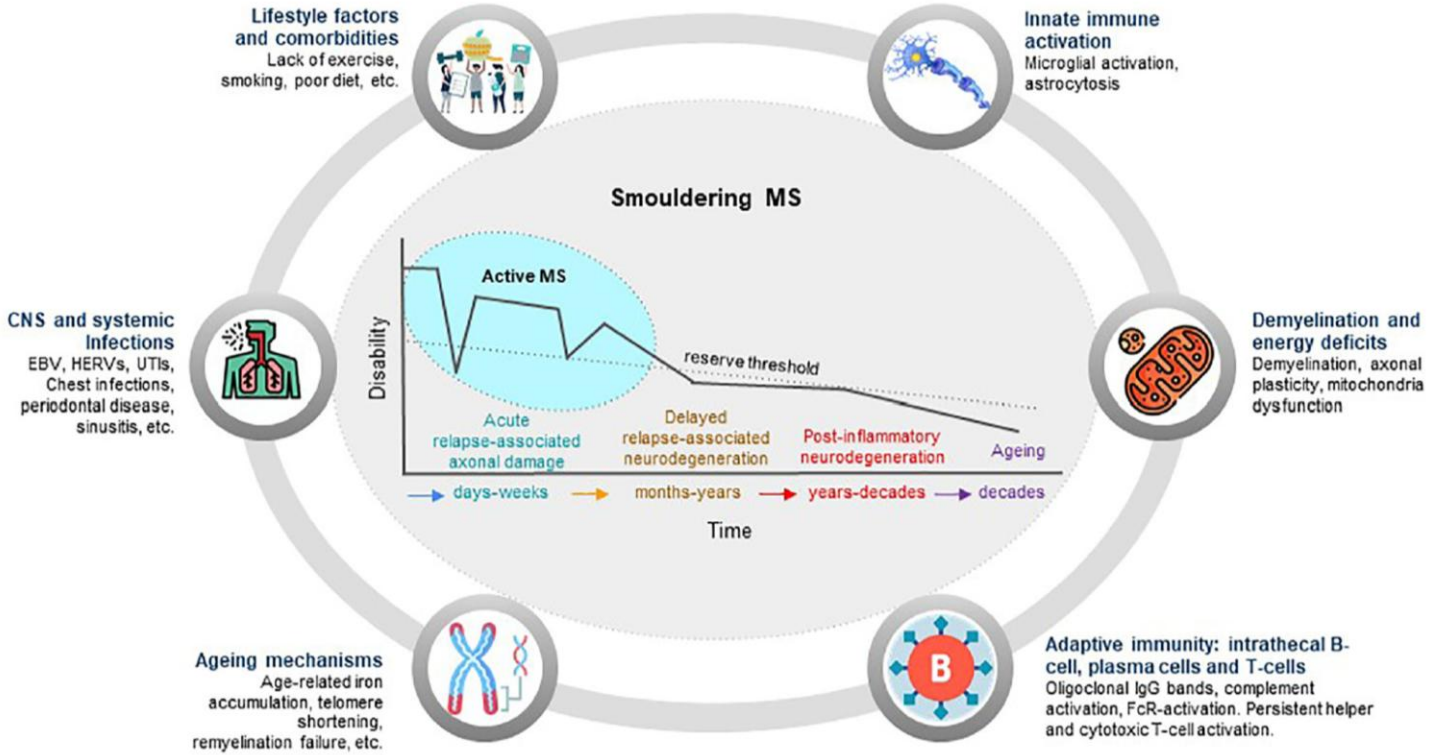


Konzept - Funktionelle Reserve



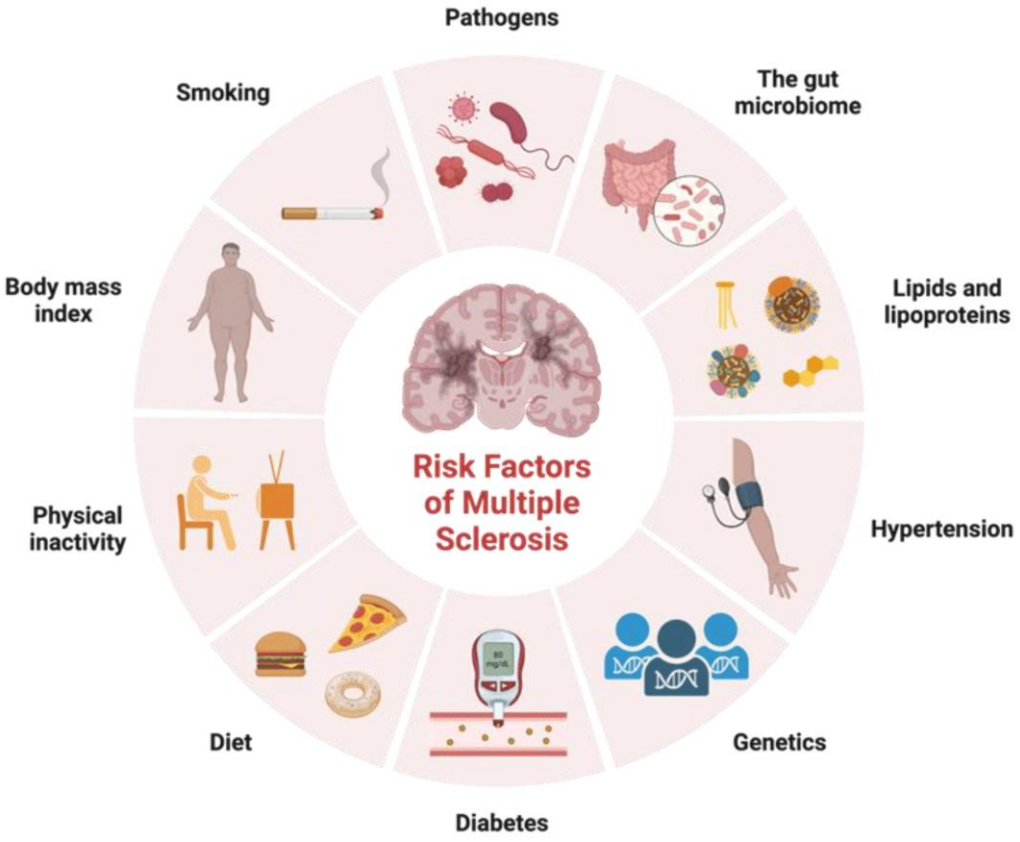
Krieger et al. 2018 Neurologic Clinics

Konzept: Smouldering MS



Giovannoni et al. 2022 TAND

Lifestyle



Landry et al. 2023 NeuroSci

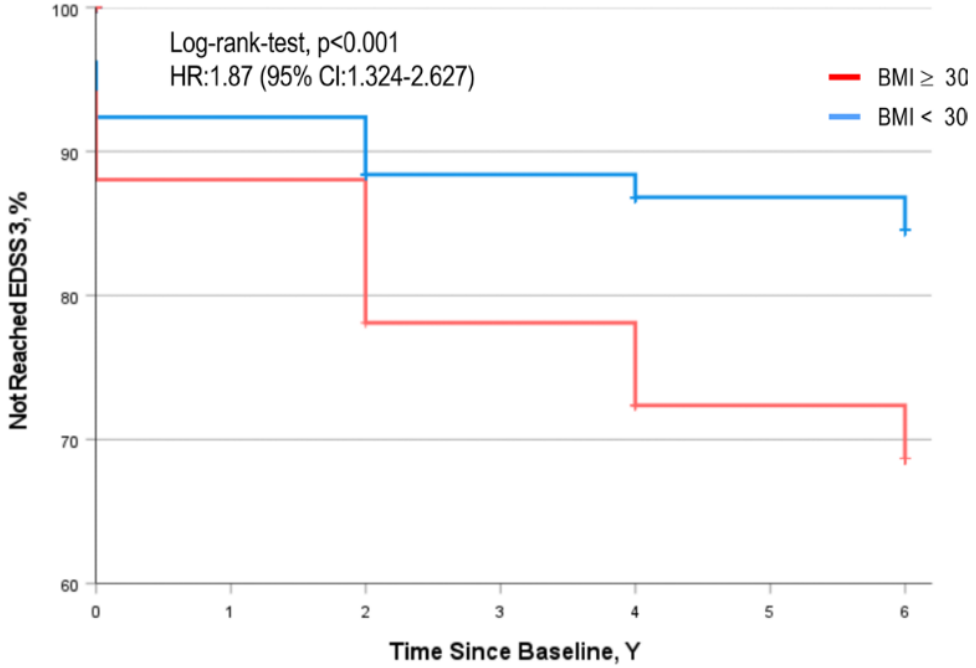
OPEN ACCESS

Original research

Association of obesity with disease outcome in multiple sclerosis

Isabel Lutfullin,[1] Maria Eveslage,[2] Stefan Bittner,[3] Gisela Antony,[4] Martina Flaskamp,[5] Felix Luessi ,[3] Anke Salmen ,[6,7] Barbara Gisevius,[6] Luisa Klotz,[1] Catharina Korsukewitz,[1] Achim Berthele,[5] Sergiu Groppa ,[3] Florian Then Bergh,[8] Brigitte Wildemann,[9] Antonios Bayas,[10] Hayrettin Tumani ,[11] Sven G Meuth,[12] Corinna Trebst,[13] Uwe K Zettl,[14] Friedemann Paul,[15] Christoph Heesen,[16] Tania Kuempfel,[17] Ralf Gold,[6] Bernhard Hemmer ,[5,18] Frauke Zipp,[3] Heinz Wiendl,[19] Jan D Lünemann ,[19] on behalf of the German Competence Network Multiple Sclerosis (KKNMS)

N=1066



No. at Risk

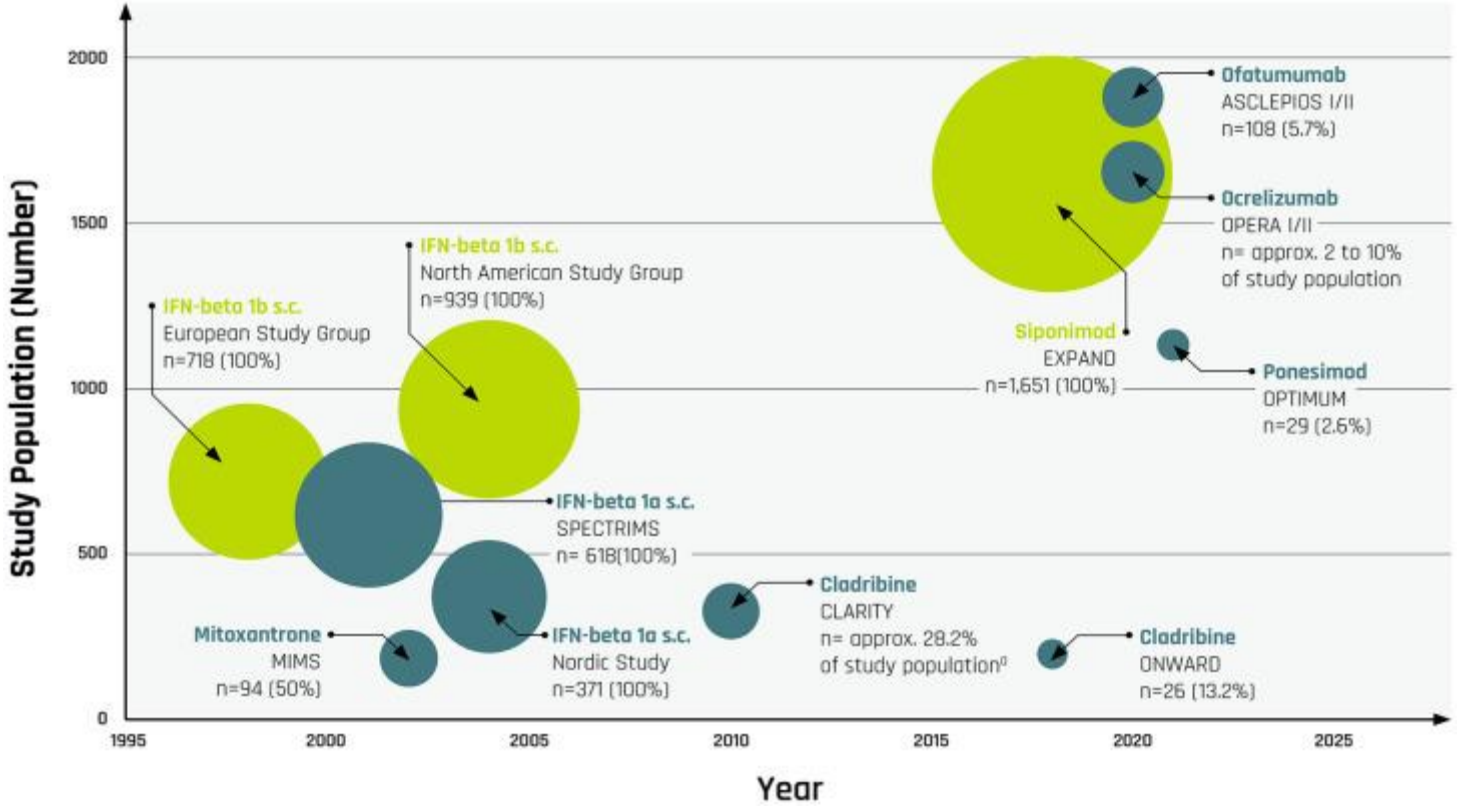
BMI < 30	907	688	542	412
BMI ≥ 30	159	118	104	77

Lutfullin et al. 2023 JNNP

Schlussfolgerung:

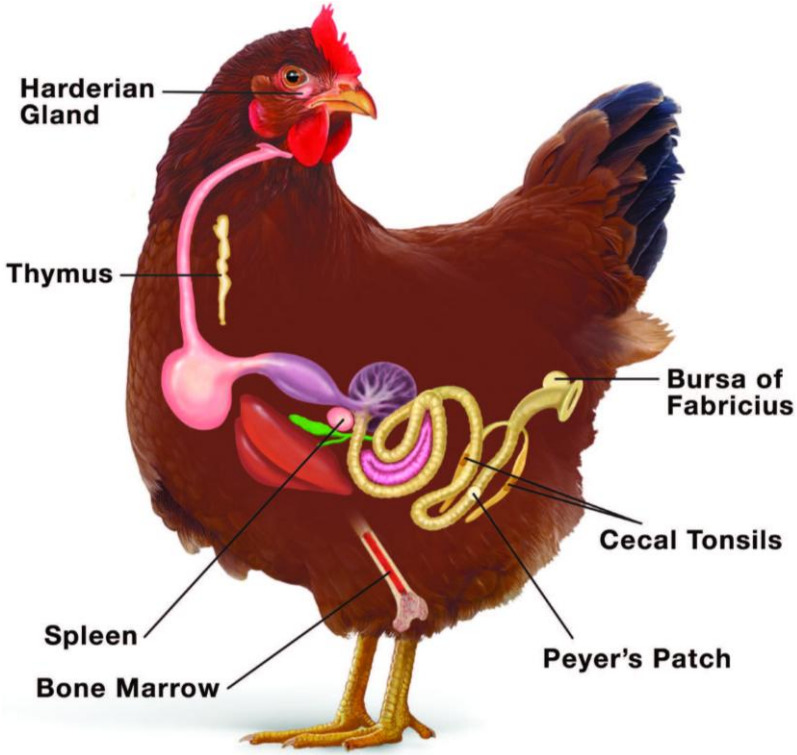
- Adipositas stellt einen Risikofaktor hinsichtlich der Behinderungsprogression dar

SPMS-Anteil



Bayas,..,Pul,...,Meuth 2023 *TAND*

Bruton-Tyrosinkinaseinhibitoren



1952 Bruton Syndrom

Ogden C. Bruton berichtete über einen 8 Jahre alten Jungen mit rezidivierender Pneumokokkensepsis und Agammaglobulinämie (XLA).

Tiermodelle zu Immundefizienz (Bursa/Thymus)

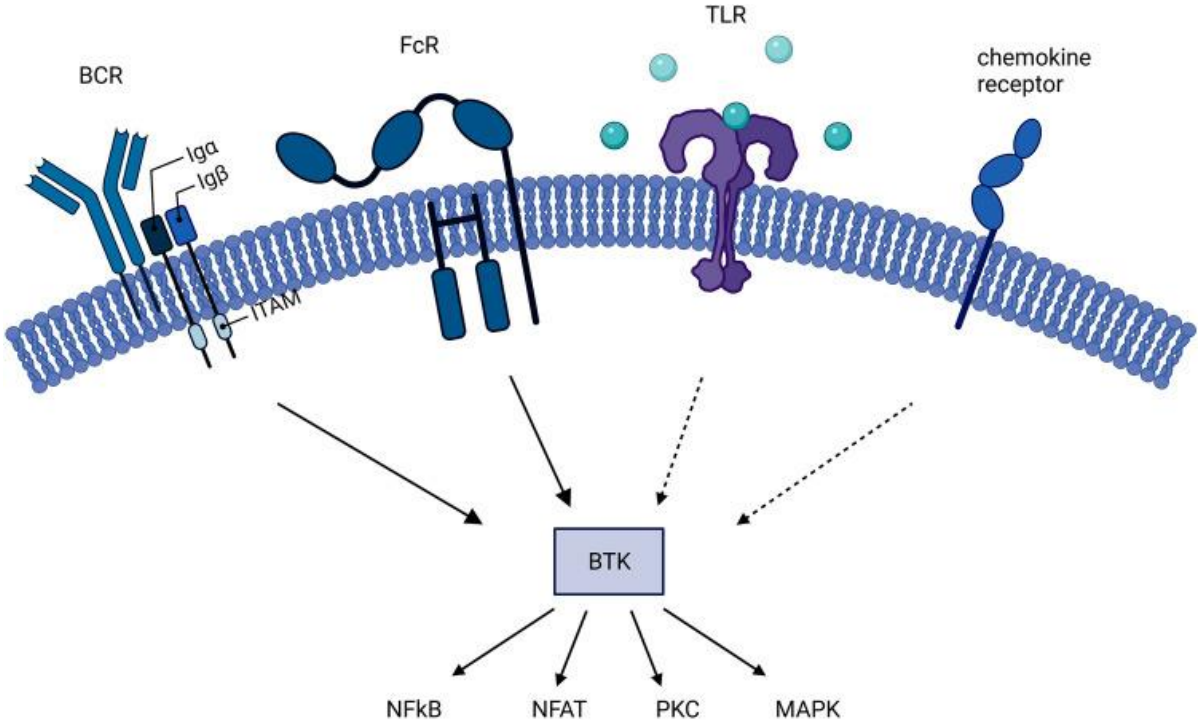
1962 Peterson et al., J. Nat. Cancer Inst.
1962 Szenberg and Warner, Nature

1965 Lymphozyten in B- und T-Zellen (Cooper)

1990s wurde die ursächliche Mutation im BTK-Gen und der Zusammenhang mit der gestörten Signaltransduktion über den B-Zellrezeptor nach AG-Kontakt entdeckt.

Quelle: https://www.scoopfromthecoop.com/wp-content/uploads/2021/12/Chicken-Immune-System_1221-v4.jpg

Bruton-Tyrosinkinaseinhibitoren



B-Zellen

Mikroglia
Makrophagen
Dendritischen Zellen

Thrombozyten
Erythrozyten
Neutrophile

Geladaris et al. 2022 *CNS Drugs*

Bruton-Tyrosinkinaseinhibitoren

2007 Ibrutinib
2013 Zulassung zur Behandlung des Mantelzellymphoms (MZL)
2014 Zulassung zur Behandlung der chronisch lymphatischen Leukämie (CLL)

2020 Acalabrutinib zur Behandlung der CLL
2020 Zanubrutinib zur Behandlung des Morbus Waldenströms, CLL, MZL, FL
2021 Pirtobrutinib zur Behandlung des MZL, CLL
2024 Rilzabrutinib zur Behandlung der Immunthrombozytopenie

Siveen et al. 2018 *Molecular Cancer*

Table 2 | Characteristics of oral Bruton tyrosine kinase inhibitors in development for multiple sclerosis

Characteristics	Evobrutinib	Tolebrutinib	Fenebrutinib	Remibrutinib	Orelabrutinib
Molecular weight[a]	429.5	455.5	664.8	507.5	427.5
Formula	$C_{25}H_{27}N_5O_2$	$C_{26}H_{25}N_5O_3$	$C_{37}H_{44}N_8O_4$	$C_{27}H_{27}F_2N_5O_3$	$C_{26}H_{25}N_3O_3$
Mechanism of action	Irreversible covalent binding	Irreversible covalent binding	Reversible non-covalent binding	Irreversible covalent binding	Irreversible covalent binding
Kinase selectivity	BMX (89–93%), BTK (90%), TEC (80–82%), BLK (36–42%), TXK (30–36%), ITK (−2 to 13%), ERBB2 (1%), EGFR (0–1%), JAK3 (0%)	>90% Inhibition for 7 of 250 kinases tested at 1 μM	BTK (99%), BMX (56%), TEC (23%), BLK (6%), JAK3 (5%), TXK (4%), ERBB4 (1%), ERBB2 (−1%), ITK (−1%), EGFR (−7%)	BTK (99%), TEC (76%), JAK3 (51%), BMX (47%), ERBB2 (20%), EGFR (18%), ITK (12%), TXK (10%), BLK (0%), ERBB4 (0%)	>90% Inhibition of BTK at 1 μM
BTK occupancy	Dose-dependent; ≥86% median occupancy for all dose groups at day 14	>75% Mean occupancy for all dose groups at day 10	ND	>95% Median occupancy for all dose groups at day 12	>99% For doses ≤50 mg (sustained 24 h after dosing)
BTK IC_{50}	8.9 nM (8.8 ng/ml) 37.9 nM (16.3 ng/ml) 58 nM (24.9 ng/ml)	0.7 nM (0.3 ng/ml)	2.3 nM (1.5 ng/ml)	1.3 nM (0.7 ng/ml)	1.6 nM (0.7 ng/ml)
	~~Phase III~~	Phase III	Phase III	Phase III	Phase II

Krämer et al. 2023, Nat Rev

Table 2 | Characteristics of oral Bruton tyrosine kinase inhibitors in development for multiple sclerosis

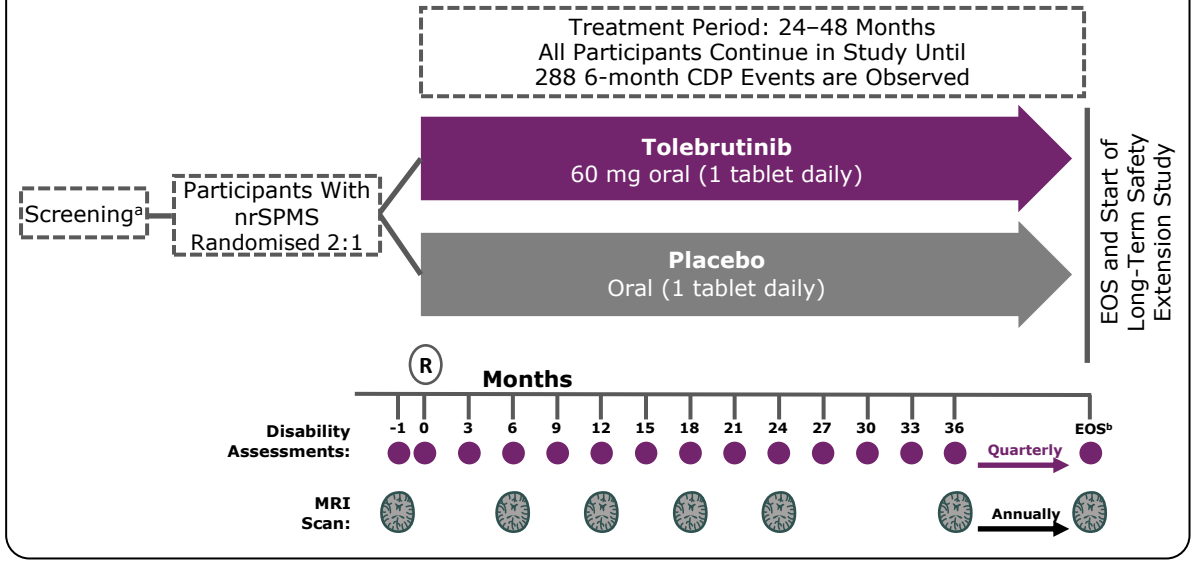
Characteristics	Evobrutinib	Tolebrutinib	Fenebrutinib	Remibrutinib	Orelabrutinib
Molecular weight[a]	429.5	455.5	664.8	507.5	427.5
Formula	$C_{25}H_{27}N_5O_2$	$C_{26}H_{25}N_5O_3$	$C_{37}H_{44}N_8O_4$	$C_{27}H_{27}F_2N_5O_3$	$C_{26}H_{25}N_3O_3$
Mechanism of action	Irreversible covalent binding	Irreversible covalent binding	Reversible non-covalent binding	Irreversible covalent binding	Irreversible covalent binding
Kinase selectivity	BM[illegible], BTK (90[illegible]0–82%), BLK [illegible]), TXK (30–3[illegible]TK (−2 to 13%), [illegible]2 (1%), EGFR (0–1%[illegible]3 (0%)	>90% Inhibition for 7 of 250 kinases tested at 1 μM	BTK (99%), BMX (56%), TEC (23%), BLK (6%), JAK3 (5%), TXK (4%), ERBB4 (1%), ERBB2 (−1%), ITK (−1%), EGFR (−7%)	BTK (99%), TEC (76%), JAK3 (51%), BMX (47%), ERBB2 (20%), EGFR (18%), ITK (12%), TXK (10%), BLK (0%), ERBB4 (0%)	>90% Inhibition of BTK at 1 μM
BTK occupancy	Dos[illegible]lent; ≥86[illegible]ed oc[illegible]anc[illegible]all dose groups at day 14	>75% Mean occupancy for all dose groups at day 10	ND	>95% Median occupancy for all dose groups at day 12	>99% For doses ≤50 mg (sustained 24 h after dosing)
BTK IC_{50}	8.9 nM (8.8 ng/ml) 37.9 nM (16.3 ng/ml) 58 nM (24.9 ng/ml)	0.7 nM (0.3 ng/ml)	2.3 nM (1.5 ng/ml)	1.3 nM (0.7 ng/ml)	1.6 nM (0.7 ng/ml)

06.12.2023

Krämer et al. 2023, Nat Rev

HERCULES: Study Design

Phase 3, Multicentre, Randomised, Double-Blind, Placebo-Controlled, Event-Driven, Trial in Participants With nrSPMS



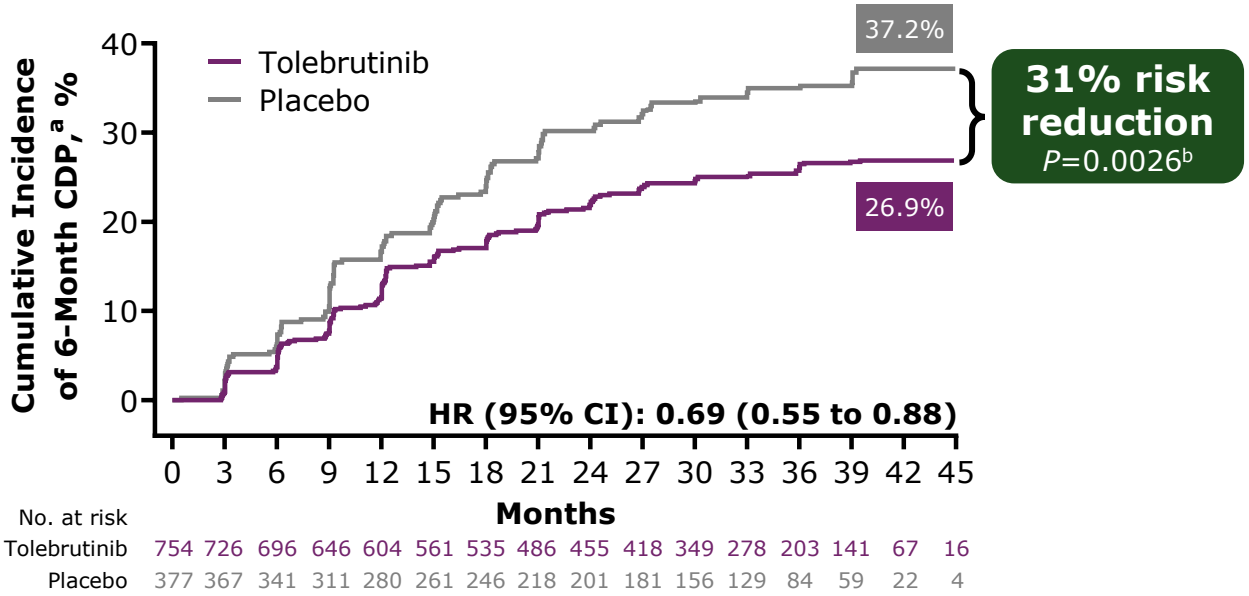
Key Eligibility Criteria

- Age 18–60 years
- Diagnosis of SPMS
- Absence of clinical relapses in the 24 months before screening
- Documented evidence of disability progression in the 12 months before screening
- EDSS score ≥3.0 and ≤6.5 at screening

MAT-GLB-2406069 - 1.0 - 09/2024

[a]The 28-day screening period was considered Month –1. [b]EOS safety follow-up visit occurred 4 weeks after the last dose of study treatment for participants not entering the long-term safety study.
CDP=confirmed disability progression; EDSS=Expanded Disability Status Scale; EOS=end of study; MRI=magnetic resonance imaging; nrSPMS=non-relapsing secondary progressive MS; R=randomisation; SPMS=secondary progressive MS.

Primary Endpoint: Time to 6-Month CDP

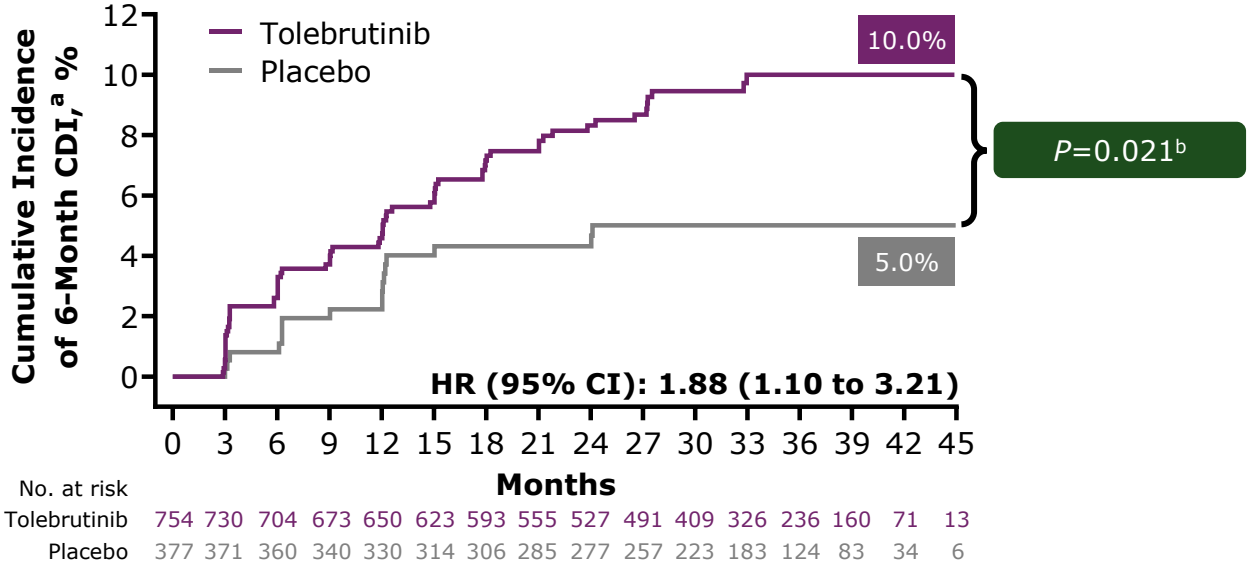


- Tolebrutinib demonstrated a significant effect on disability accumulation in a non-relapsing SPMS population

[a]6-month CDP is defined as an increase of ≥1.0 point from baseline EDSS score when baseline score is ≤5.0 or an increase of ≥0.5 points when baseline score is >5.0, confirmed over ≥6 months. [b]P-value is from Cox proportional hazards model.
CDP=confirmed disability progression; CI=confidence interval; EDSS=Expanded Disability Status Scale; HR=hazard ratio.

MAT-GLB-2406069 - 1.0 - 09/2024

Secondary Endpoint: Time to 6-Month CDI

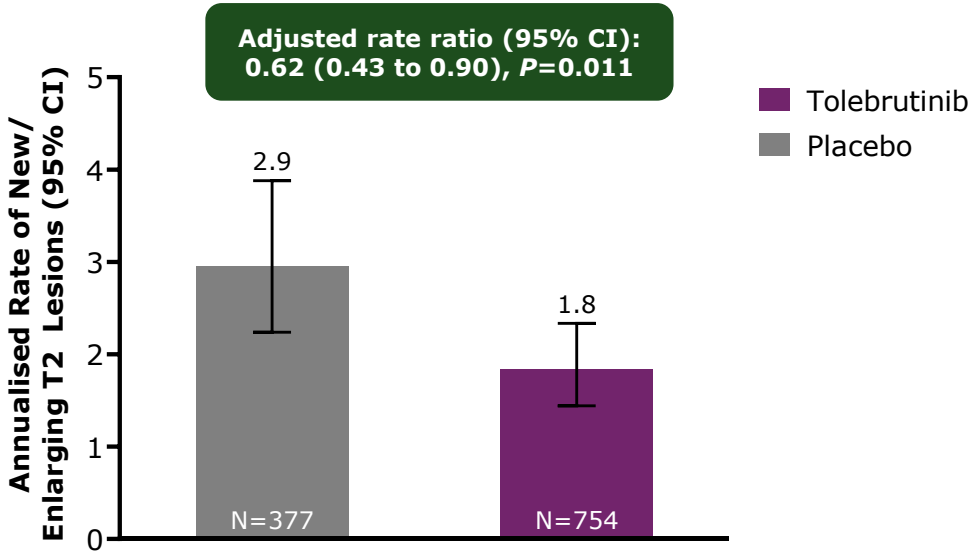


- Proportionally more participants experienced CDI on tolebrutinib vs. placebo

[a]6-month CDI is defined as a decrease of ≥1.0 point from baseline EDSS score confirmed over ≥6 months. [b]Nominal p-value from Cox proportional hazards model.
CDI=confirmed disability improvement; CI=confidence interval; EDSS=Expanded Disability Status Scale; HR=hazard ratio.

MAT-GLB-2406069 - 1.0 - 09/2024

Secondary Endpoint: New/Enlarging T2 Lesions

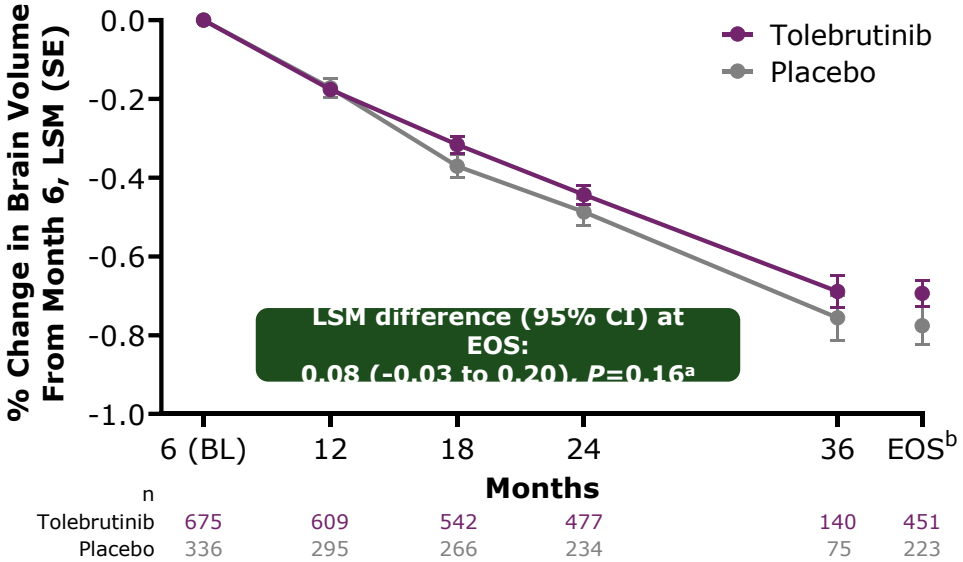


- Tolebrutinib significantly lowered the annualised rate of new/enlarging T2 lesions vs. placebo

CI=confidence interval.

MAT-GLB-2406069 - 1.0 - 09/2024

Secondary Endpoint: Brain Volume Loss (BVL)

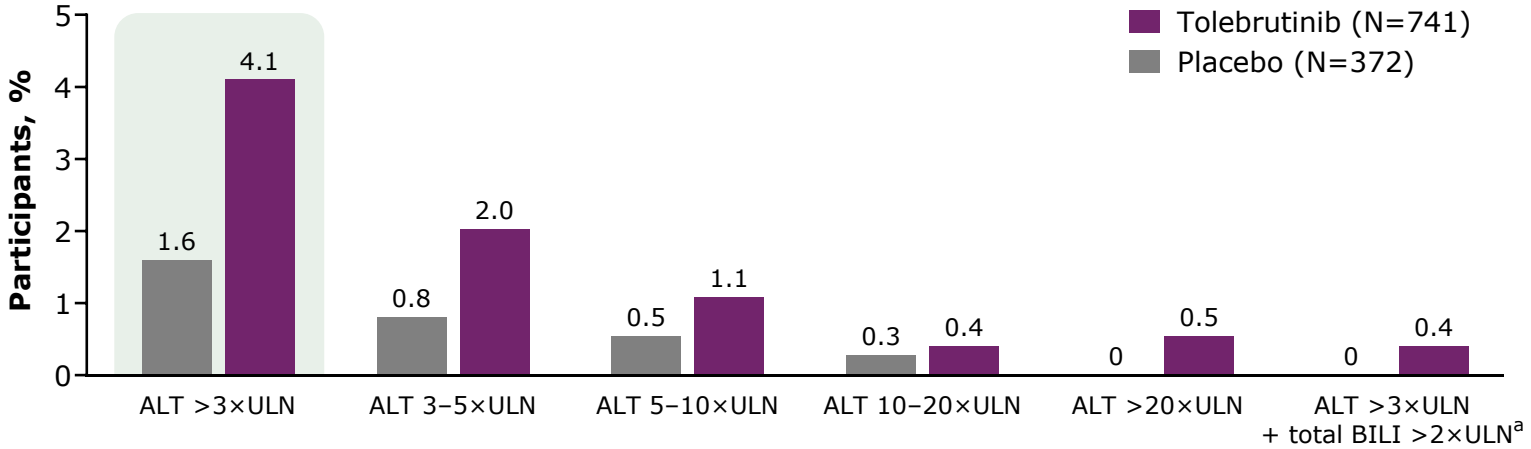


- BVL from Month 6 to EOS was low for both tolebrutinib and placebo groups

Note: BVL is measured as percentage change in brain volume from Month 6 to exclude the potential confounding effect of pseudoatrophy.
[a]Nominal p-value. [b]The mean trial duration was 27 months.
BL=baseline; EOS=end of study; LSM=least squares mean; SE=standard error.

MAT-GLB-2406069 - 1.0 - 09/2024

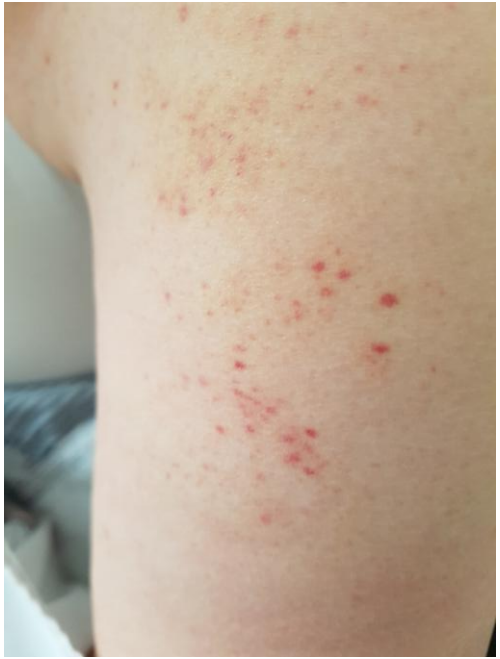
Liver Safety

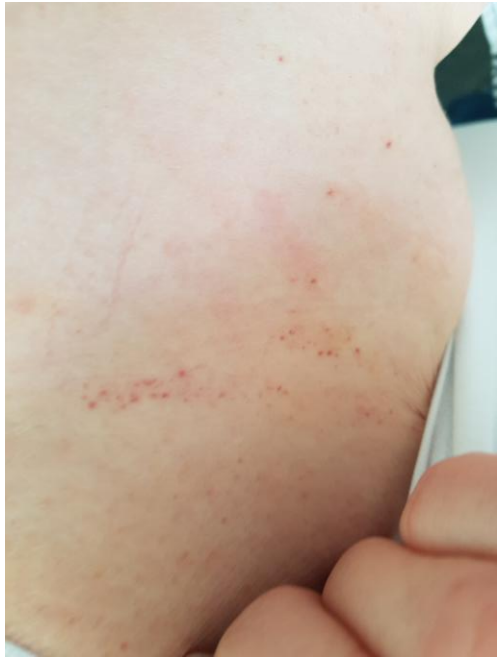


- A small (0.5%) proportion of participants in the tolebrutinib group experienced peak ALT increases of >20×ULN, all occurring within the first 90 days of treatment and most resolving without sequelae

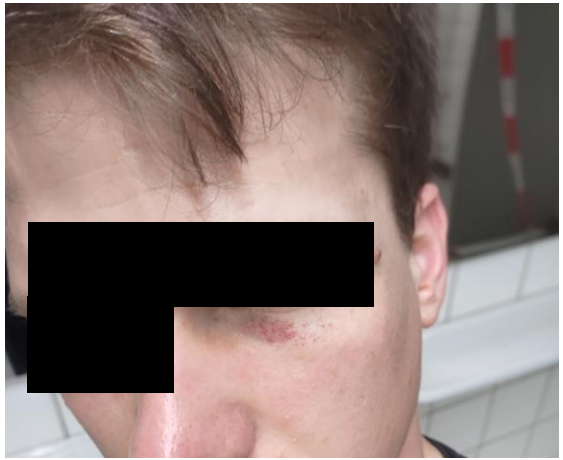
[a]One participant on tolebrutinib received a liver transplant and died due to post-operative complications. This case occurred prior to the implementation of a revised protocol with more stringent monitoring.
ALT=alanine aminotransferase; BILI=bilirubin; ULN=upper limit of normal.

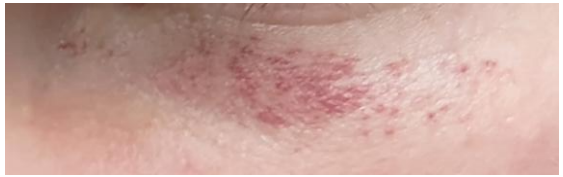
Nebenwirkungen

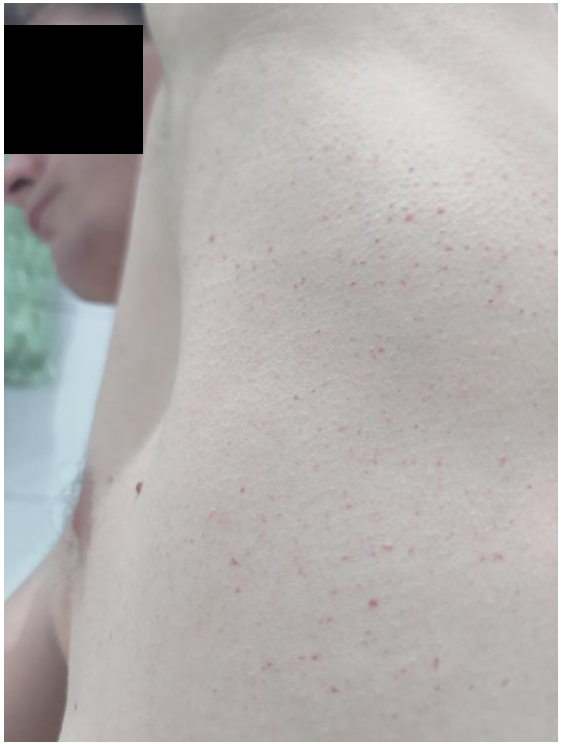


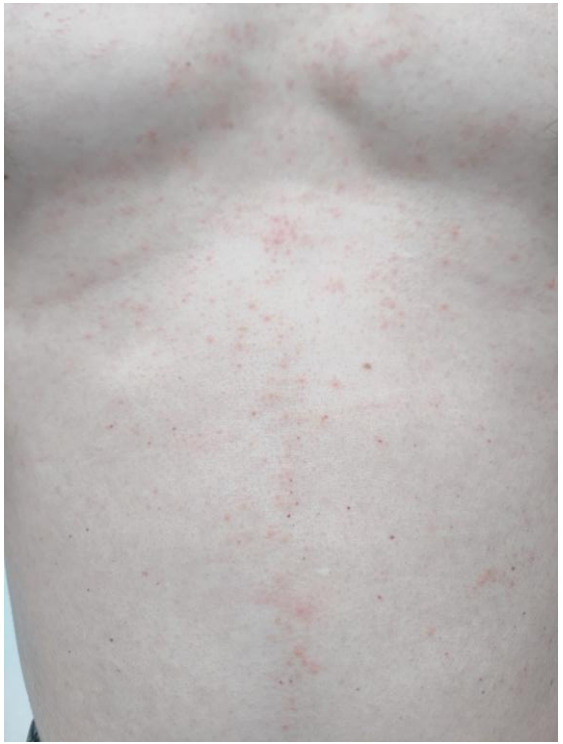


Nebenwirkungen









Vielen Dank für Ihre Aufmerksamkeit!

Klinik für Neurologie

https://www.facebook.com/Neurologie-Essen-443637079763753/

https://www.instagram.com/neurologie.essen/

https://neurologie.uk-essen.de/