How disability progression is associated with serum neurofilament light chain dynamics in relapsing remitting multiple sclerosis patients treated with Alemtuzumab: results from a mechanistic drug disease joint model

PAGE 2025: Modelling neurodegenerative progression

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[2]*Translational Medicine Unit, Quantitative Pharmacology, Disease modeling, Sanofi, Gentilly, France*
[3]*Clinical modeling & Evidence Integration, Sanofi, Gentilly, France*
[4]*Sanofi, Translational Medicine Unit, Quantitative Pharmacology, Disease modeling, Sanofi, Gentilly, France on behalf of IT&M Stats, 94250 Gentilly, France*

06/06/2025

Relapsing Remitting Multiple Sclerosis (RRMS)

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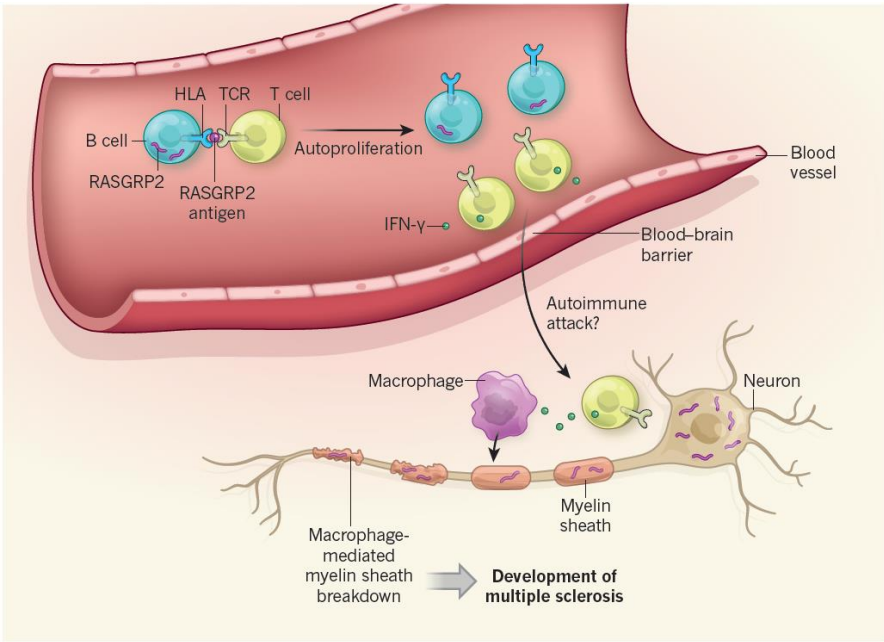
Disruption of neuronal signaling[1,2]



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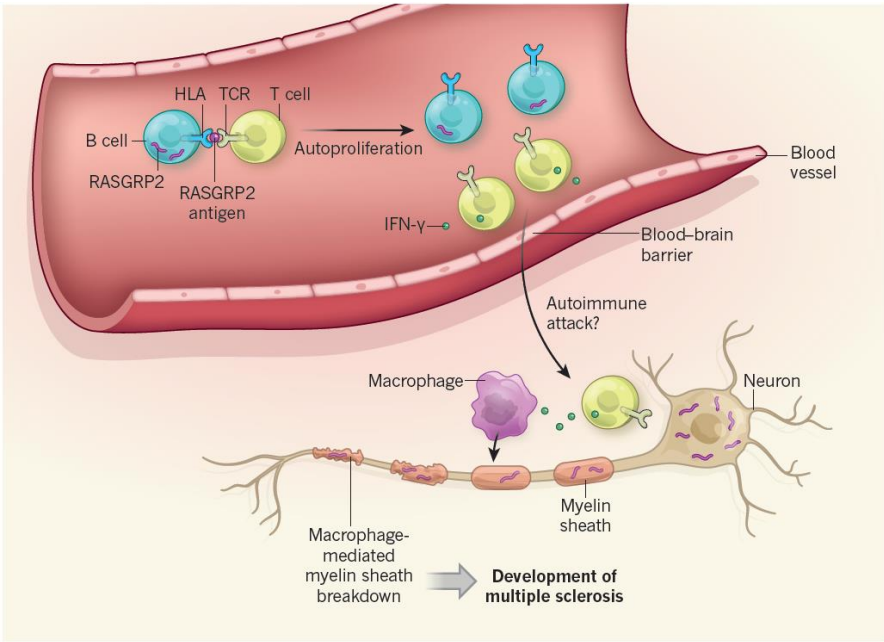
→ Disability



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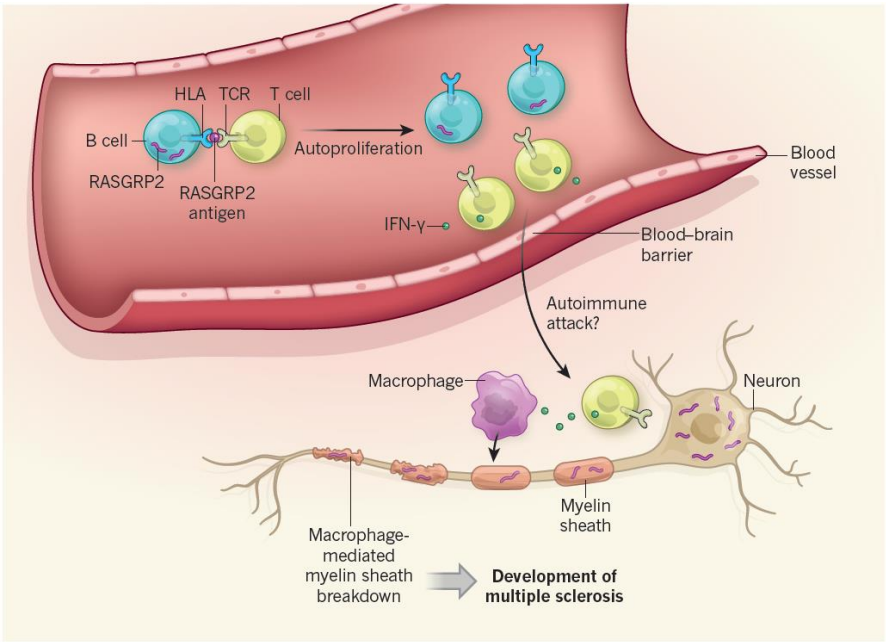

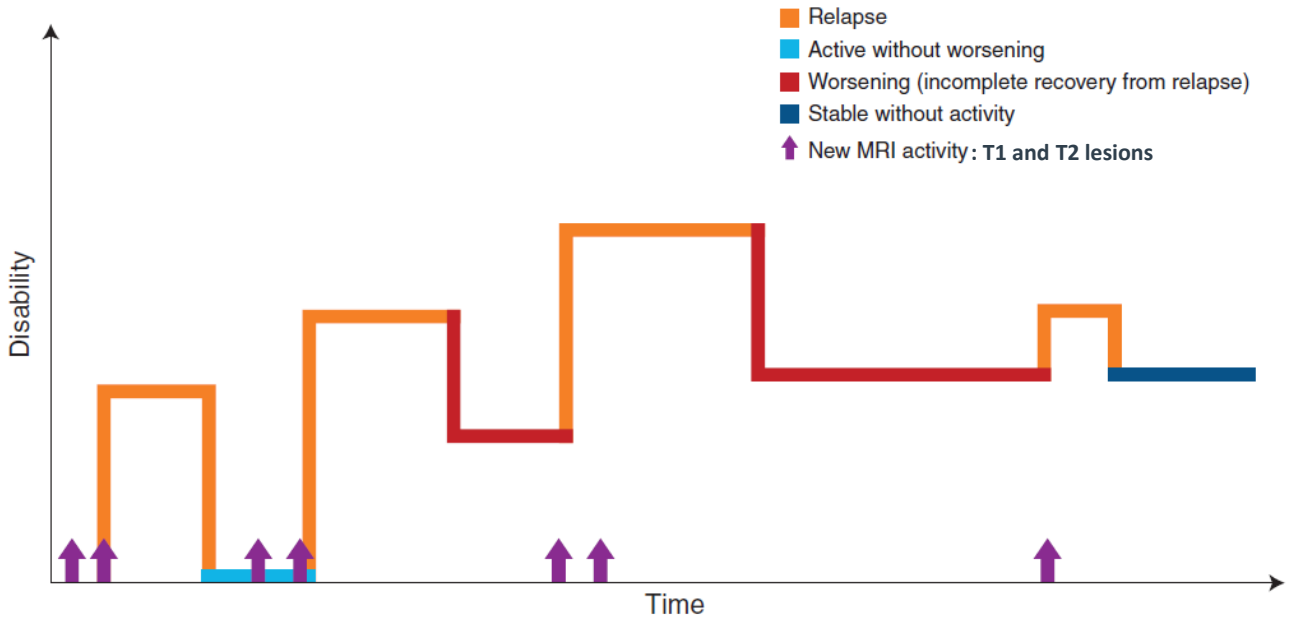

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Disability assessment in clinical trials

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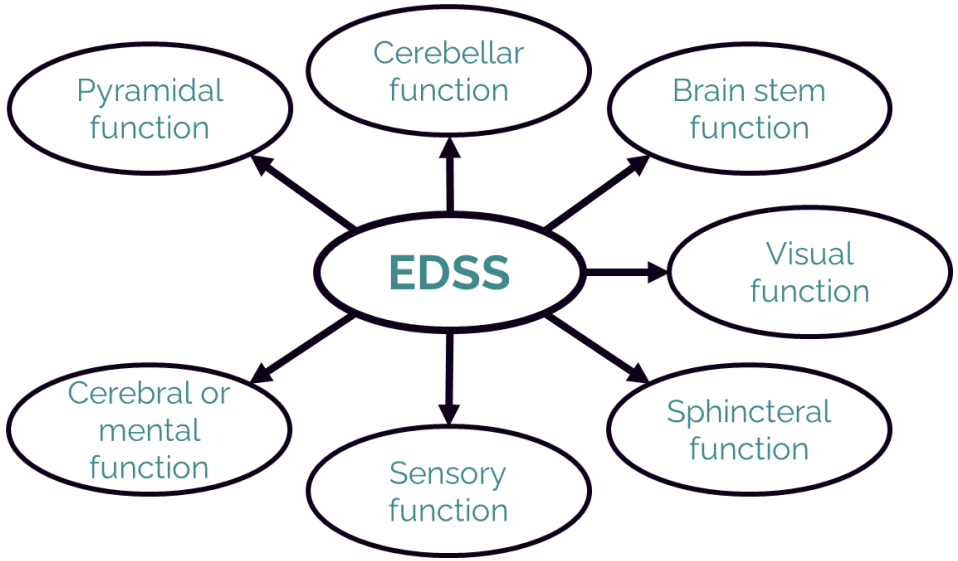

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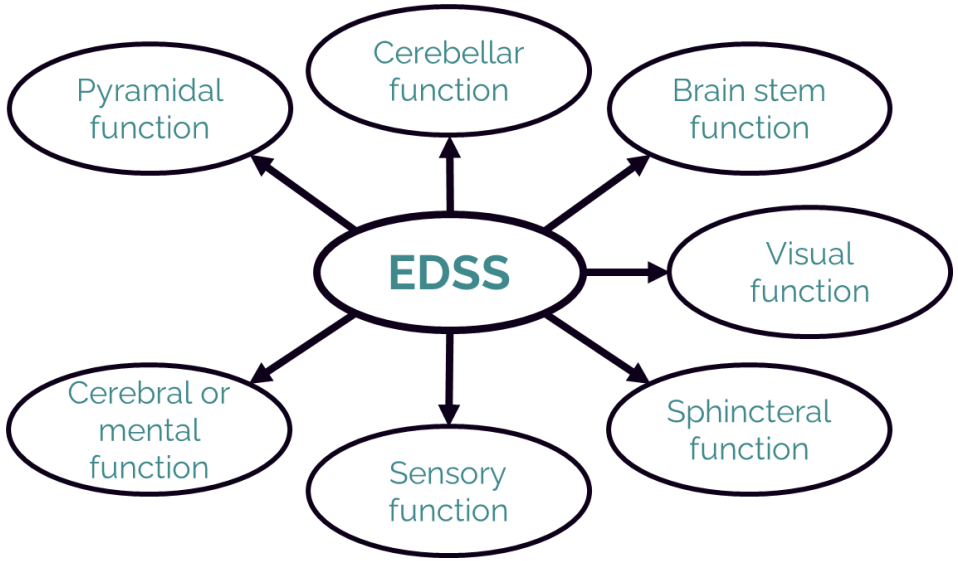

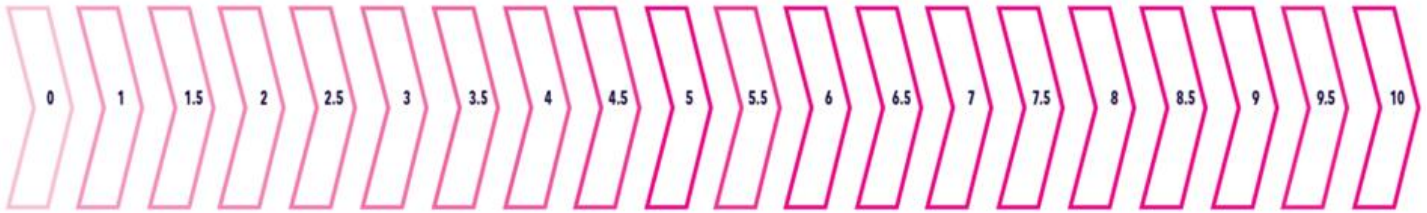

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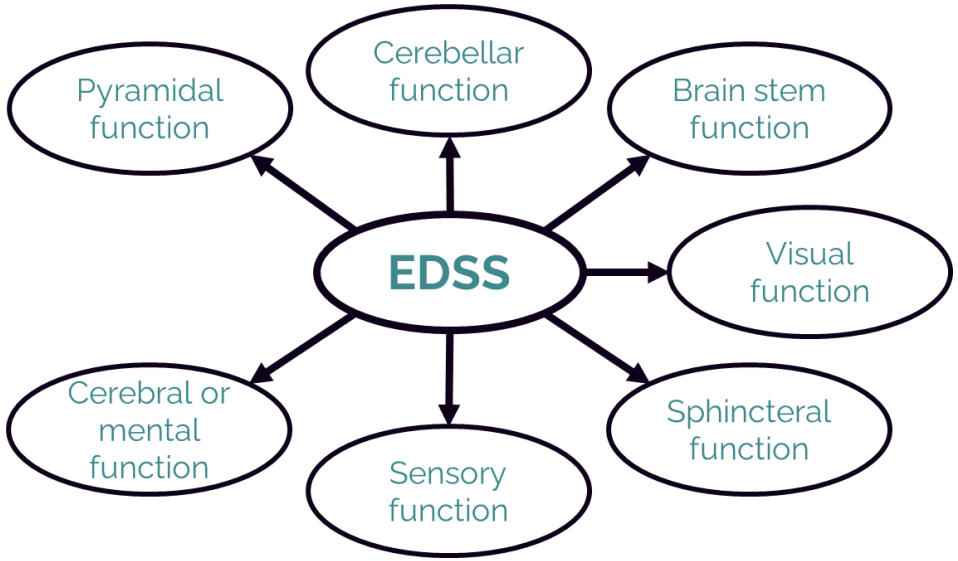

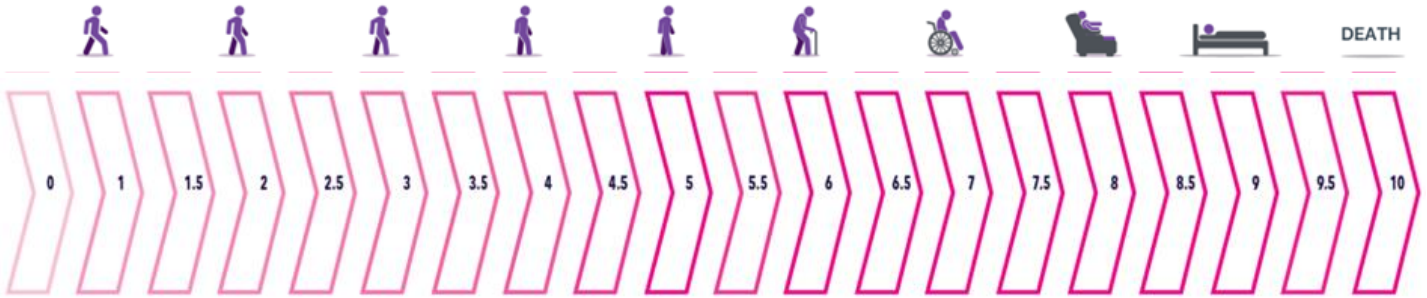

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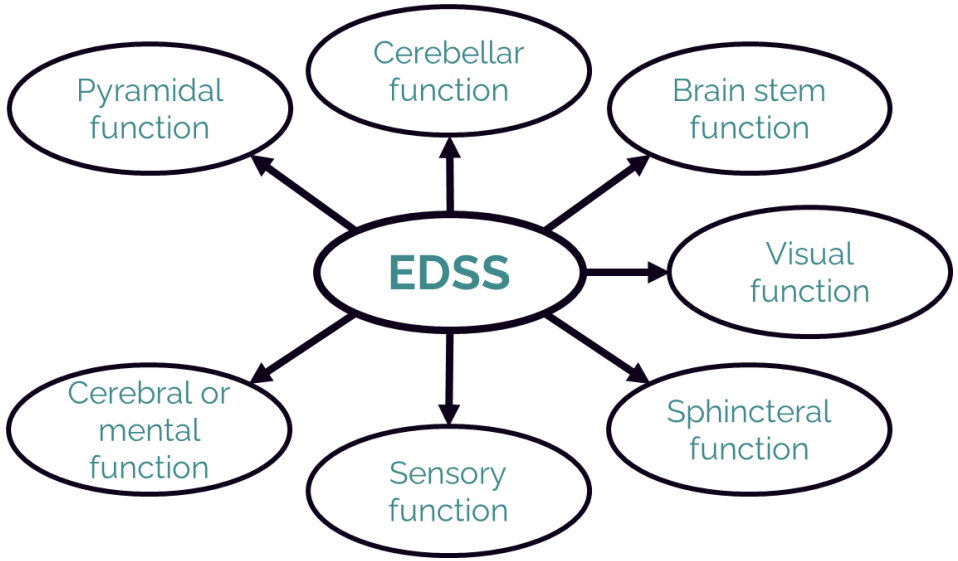

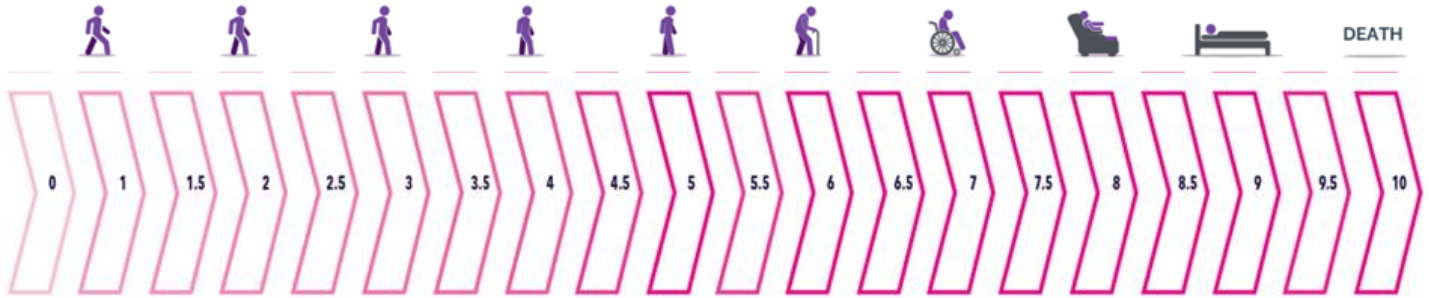

- Primary outcome
  - **Time to event**
  - Event: **first confirmed disability progression** sustained over 24 weeks[1,2,3]

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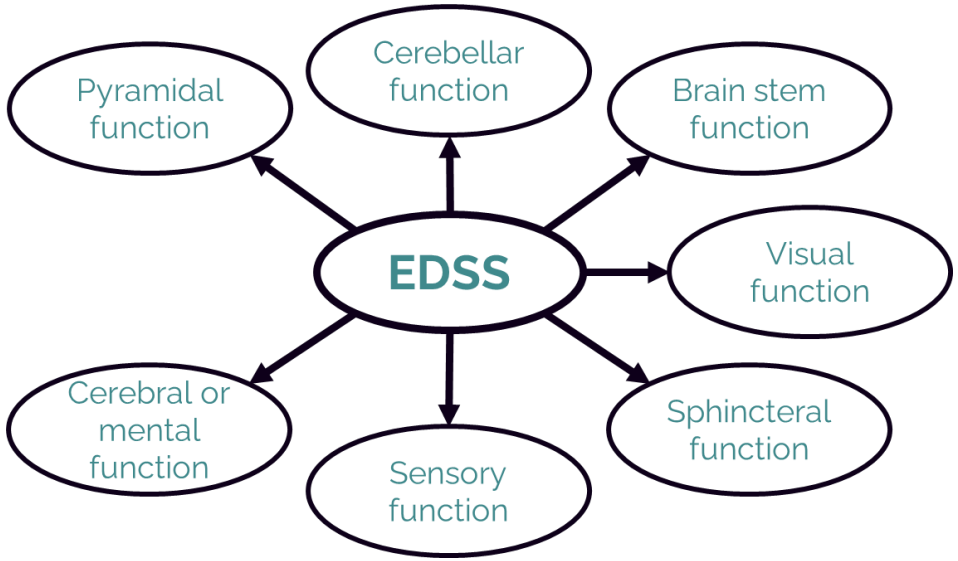

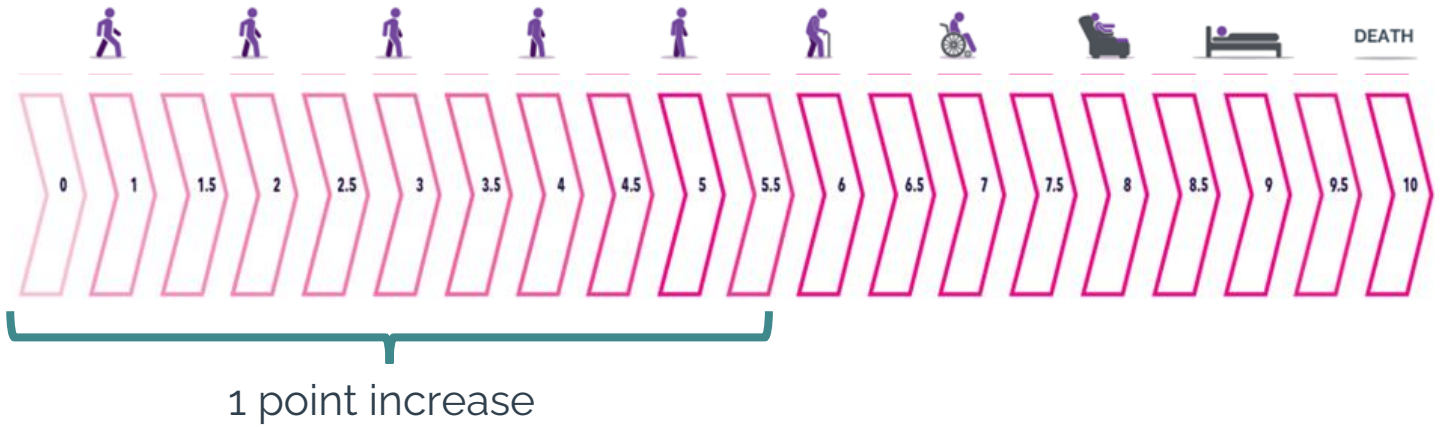

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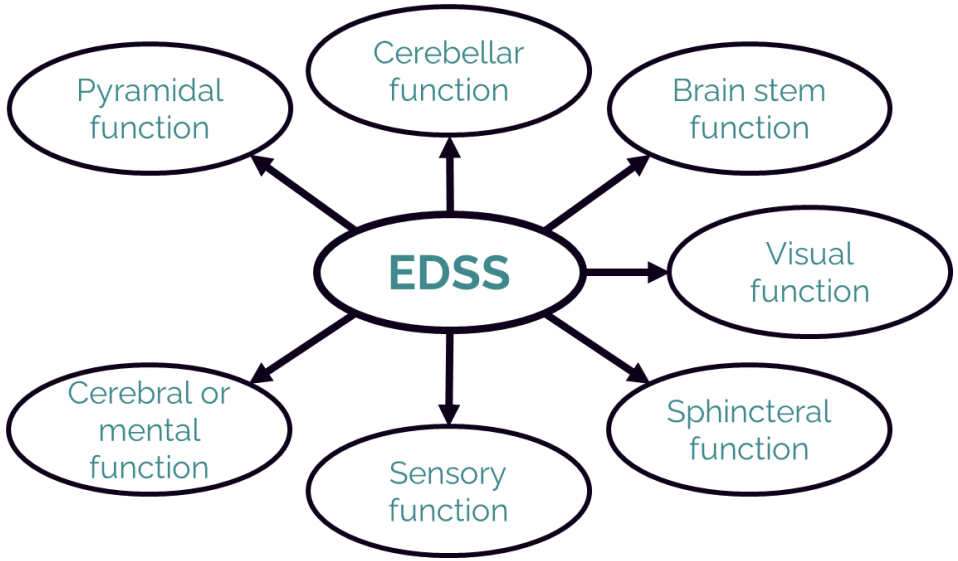

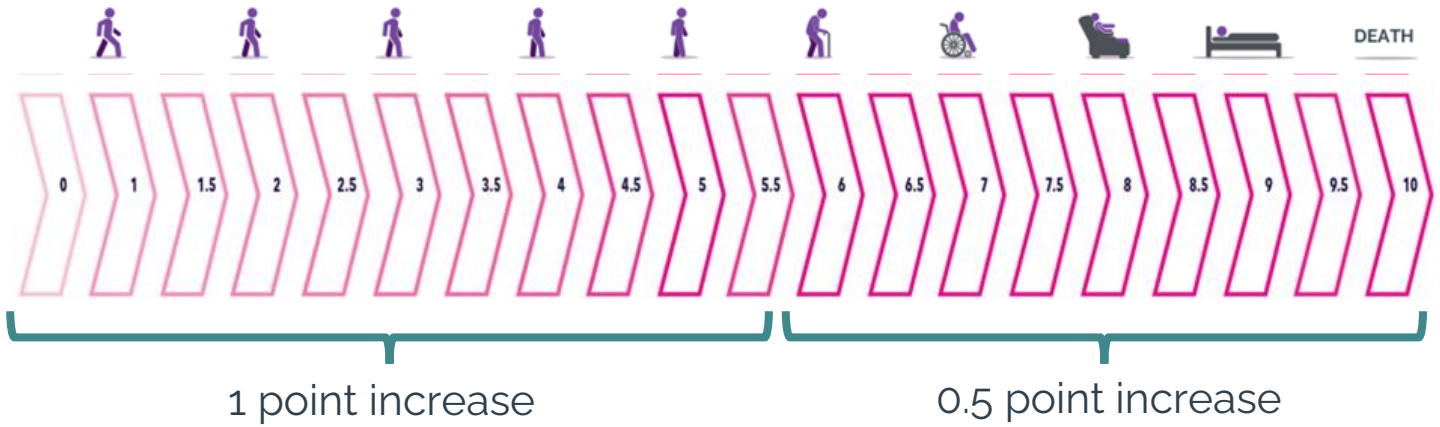

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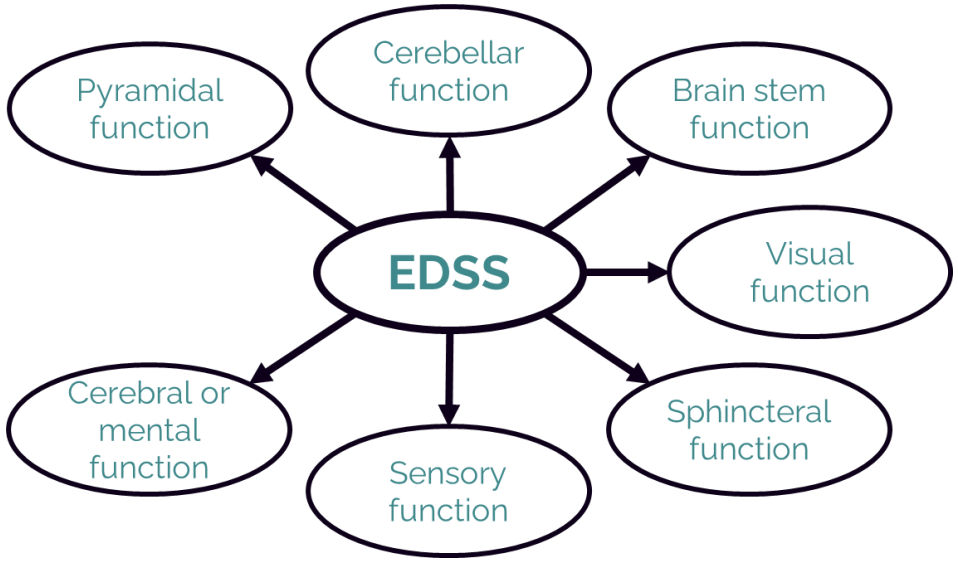

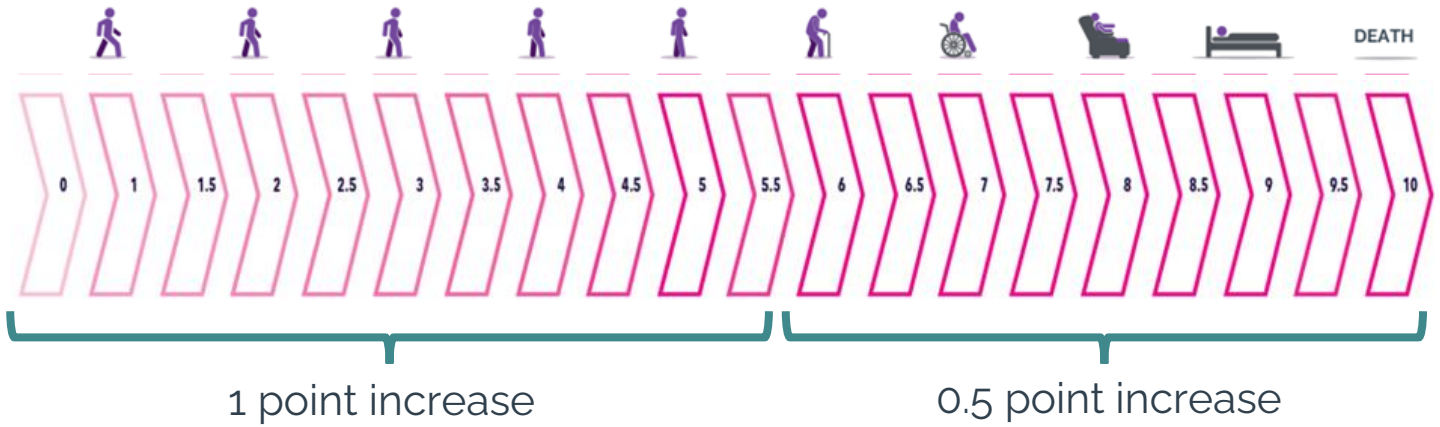

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→ EDSS long and difficult to assess
→ Need for a new blood biomarker

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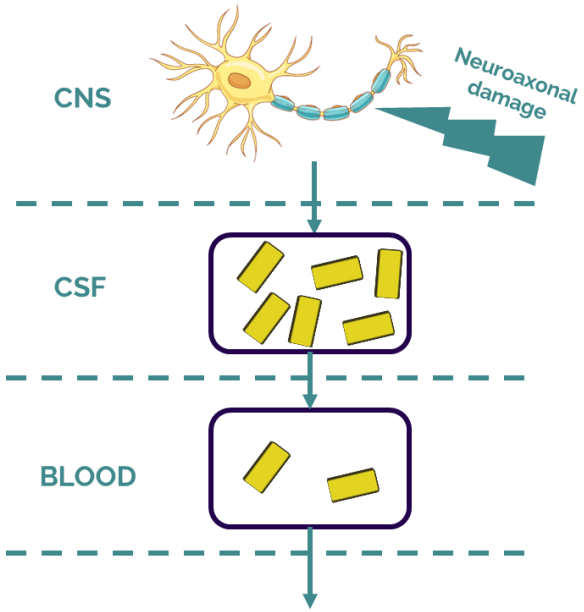
Candidate biomarker: Neurofilament Light chain

- Neuron-specific cytoskeletal protein released and measured in blood



- Serum Neurofilament Light chain (sNfL) levels decrease following administrations of disease modifying therapies
  - Natalizumab (anti-α4-integrin)
  - Ocrelizumab (anti-CD20)
  - **Alemtuzumab (anti-CD52)**

Khalil and al., Nat. Rev. Neurol., 2024

Alemtuzumab

1: Evan and al., Expert Opin Biol Ther., 2018
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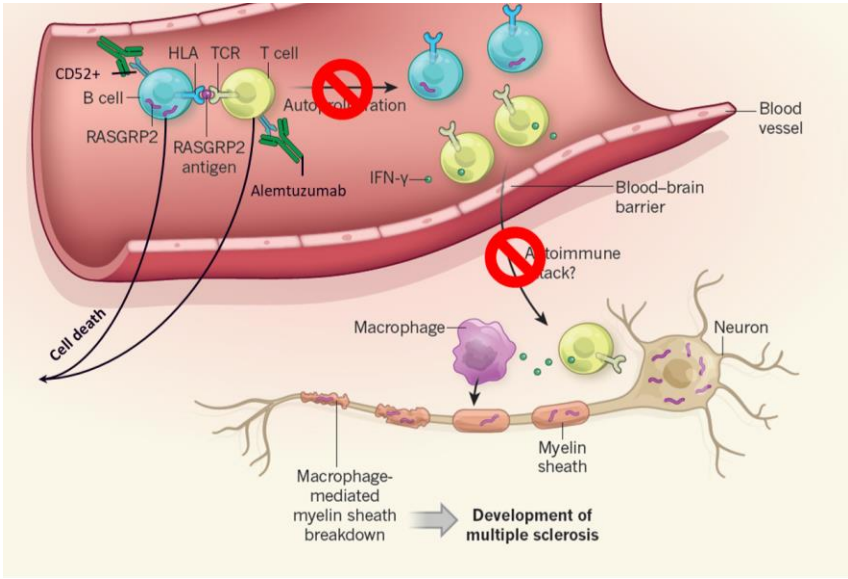
Alemtuzumab

- Lemtrada® commercialized by Sanofi
- Immunotherapy[1]
  - Monoclonal antibody
  - Selective depletion of CD52+ lymphocytes
  - Immune reconstitution therapy

Alemtuzumab

CD52+ receptor



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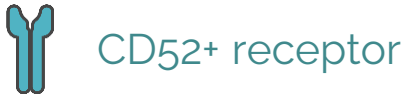

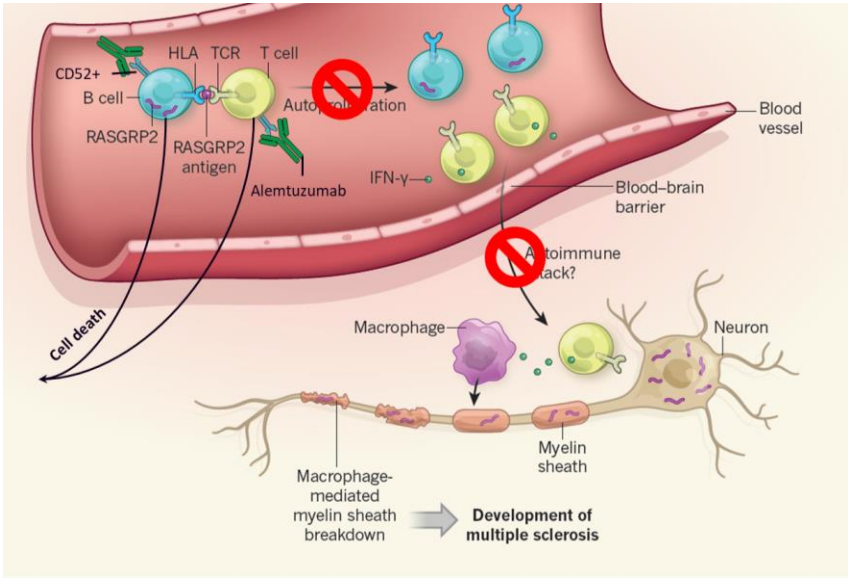

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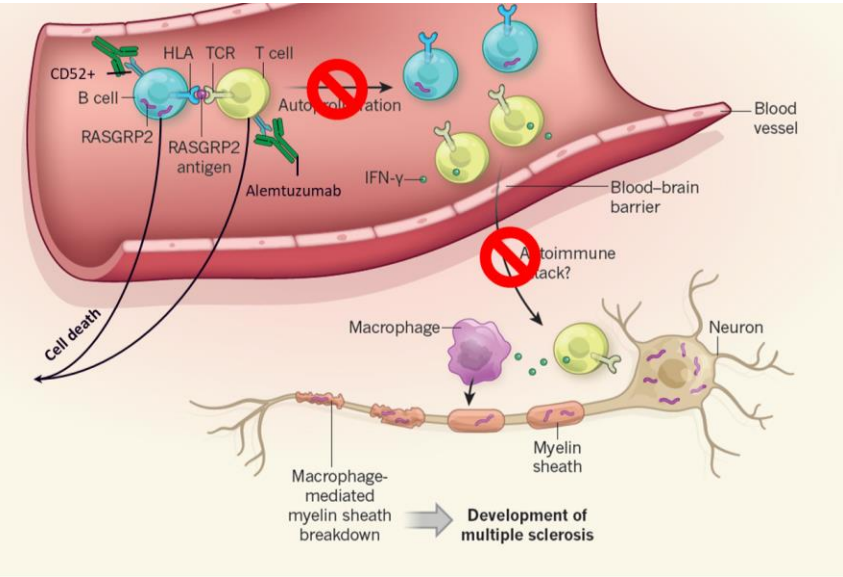

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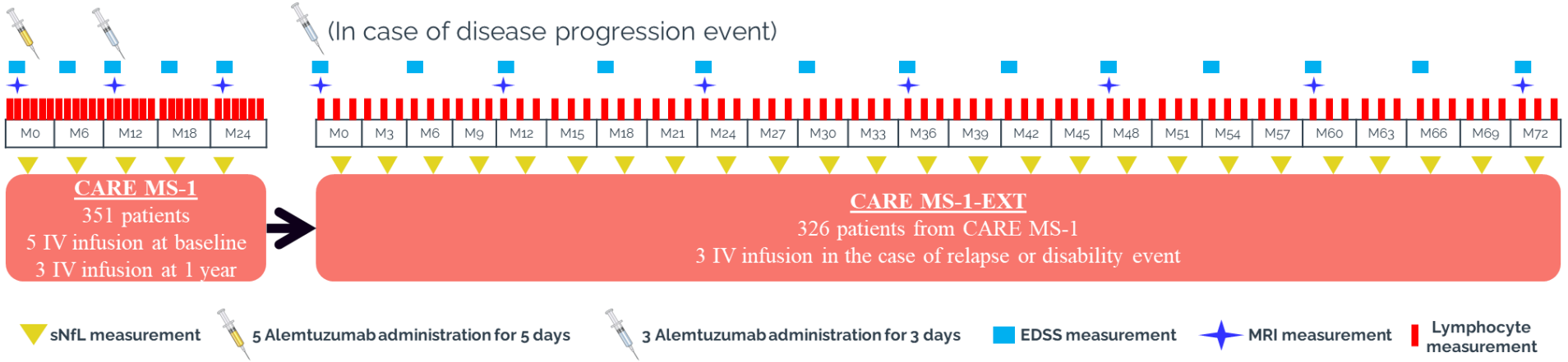

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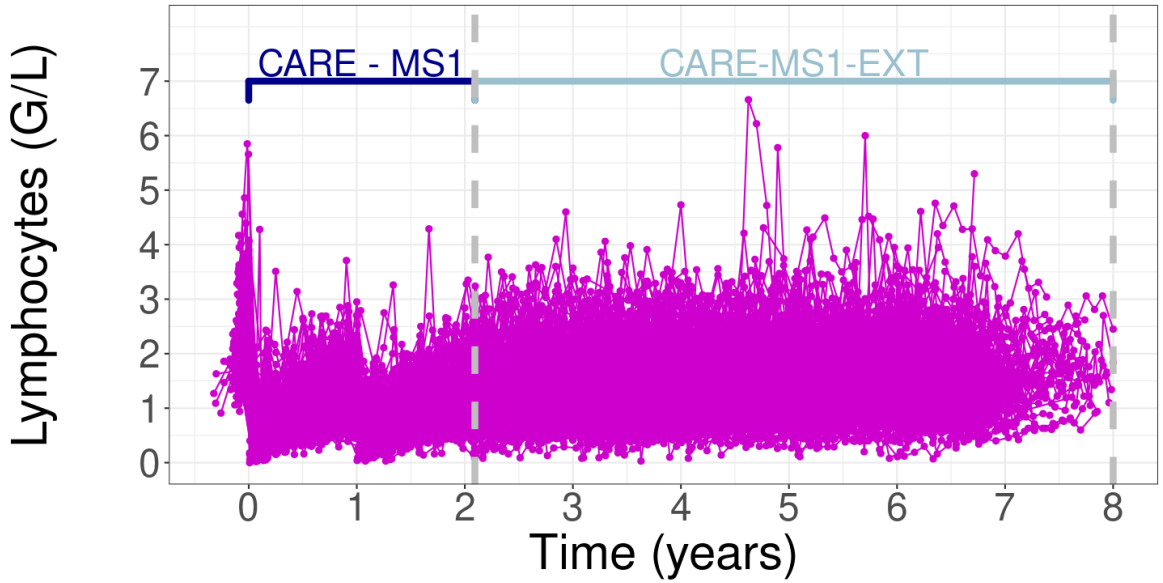
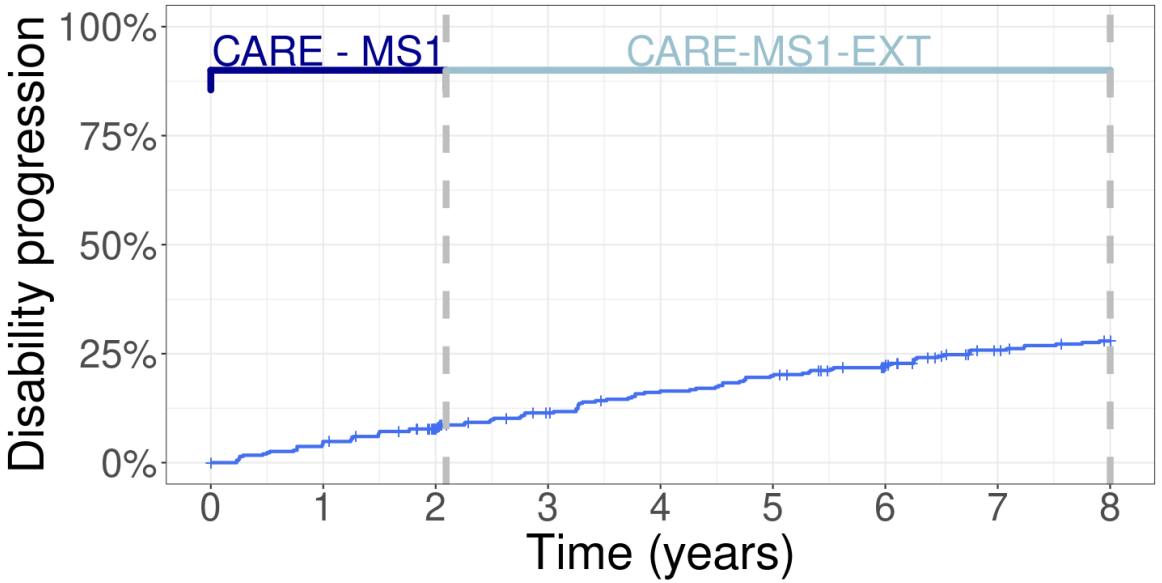
Aim

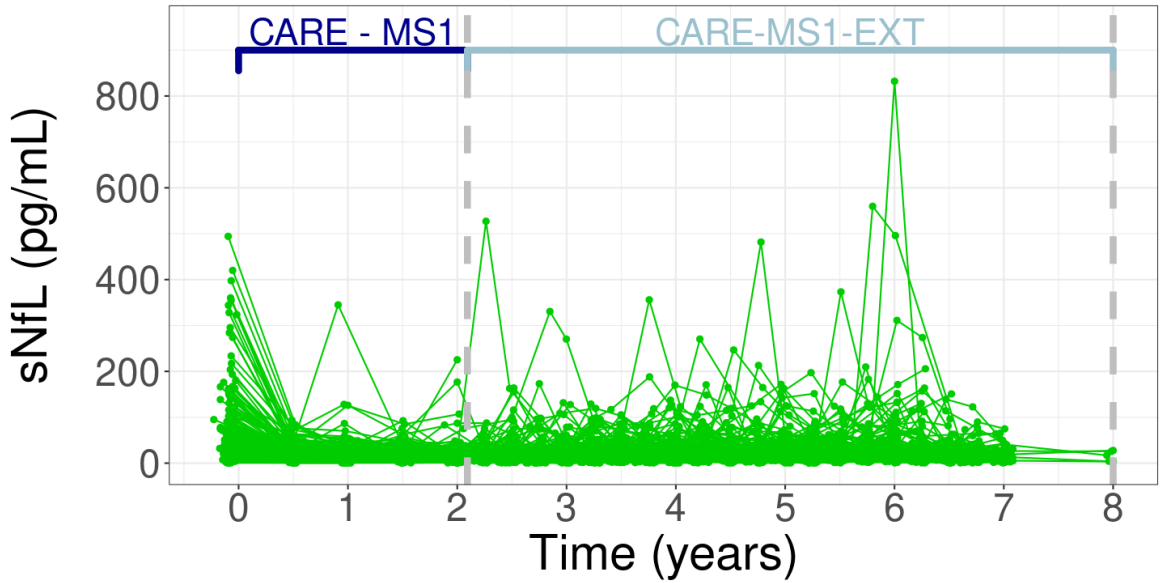
In RRMS patients treated with alemtuzumab in CARE MS1 and CARE-M1-EXT

→ assess the link between disability progression and sNfL dynamics

Lymphocytes, sNfL and disability progression after alemtuzumab administrations







Lymphocytes and sNfL trajectories pre and post disability progression event

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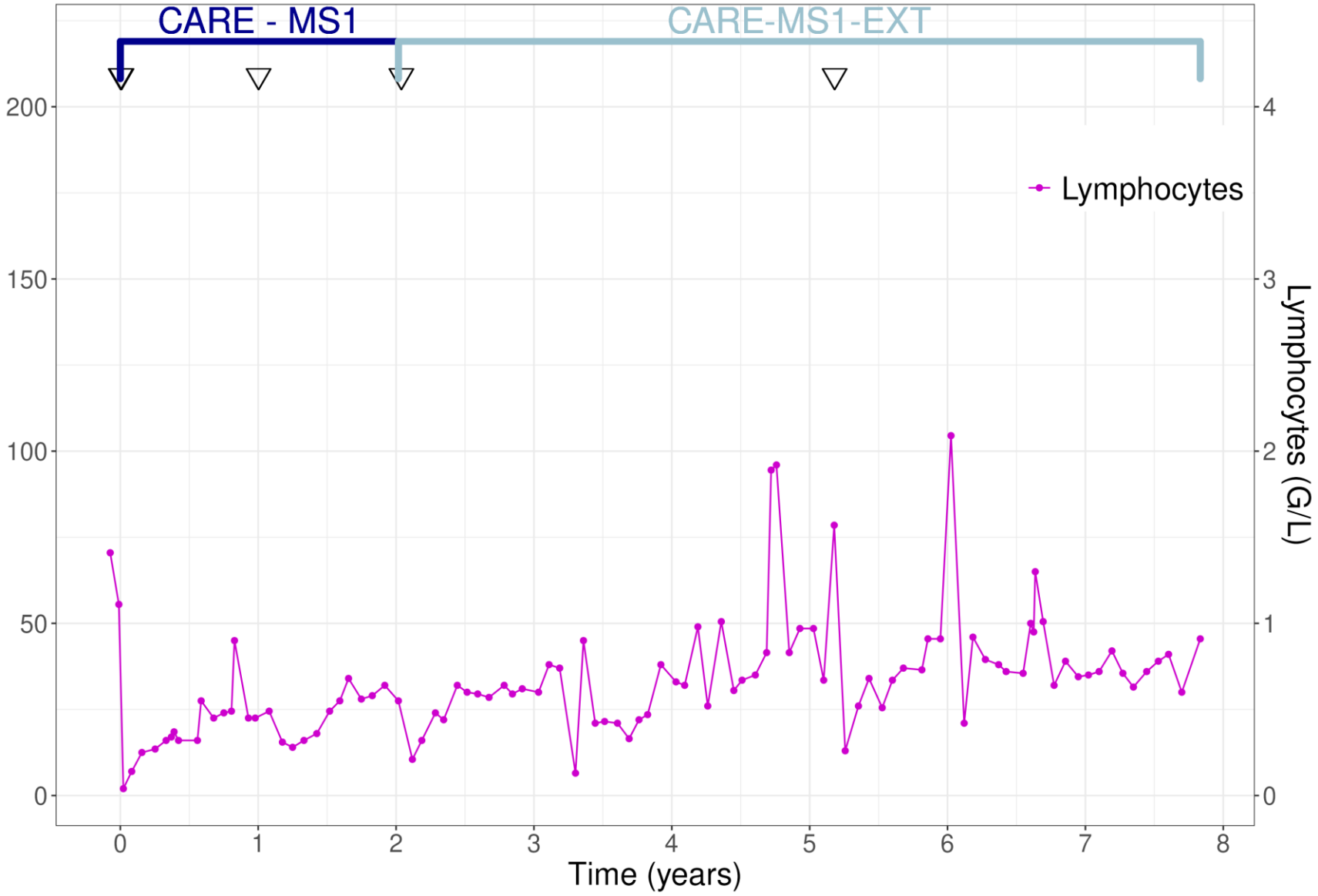

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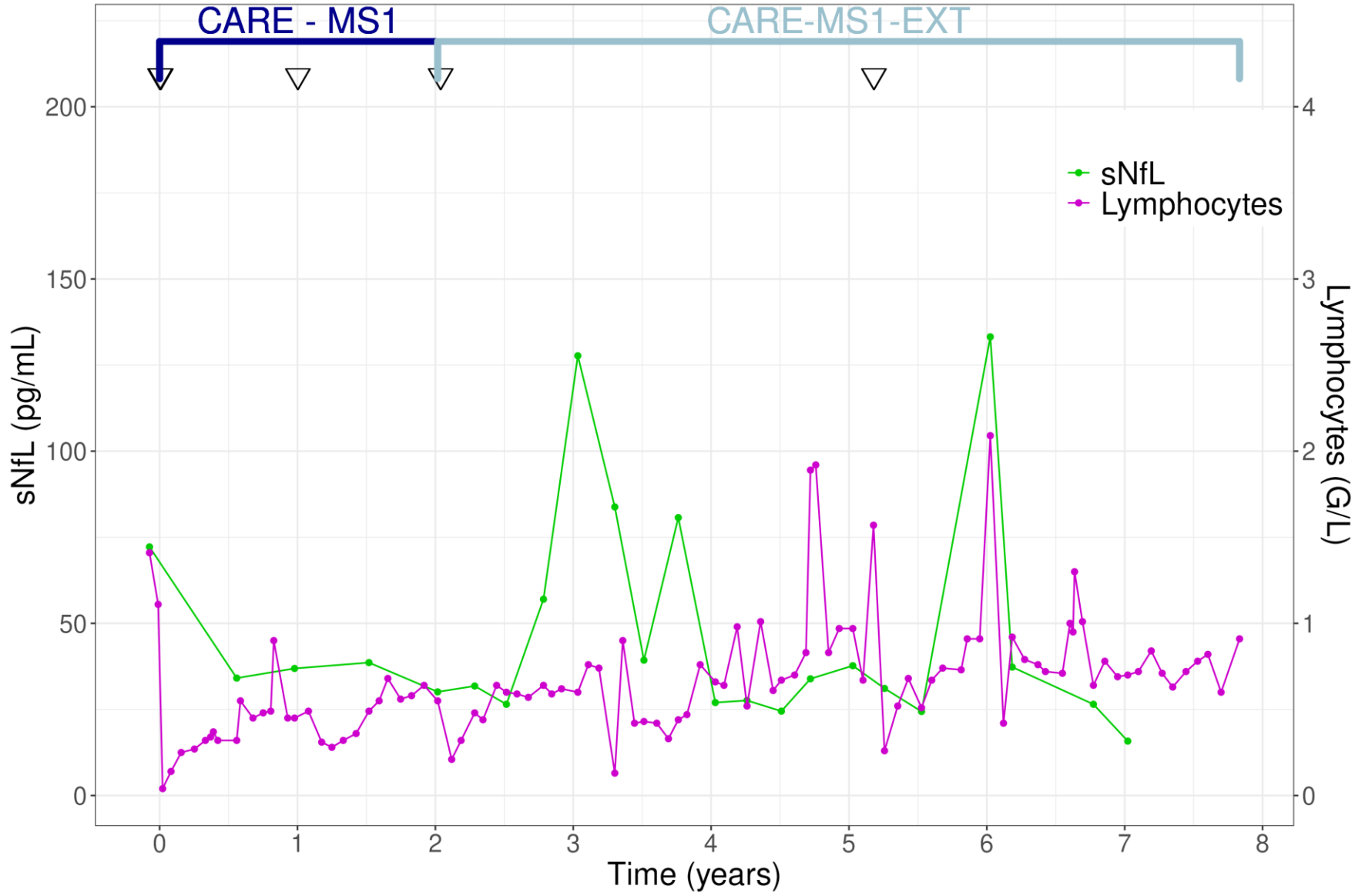

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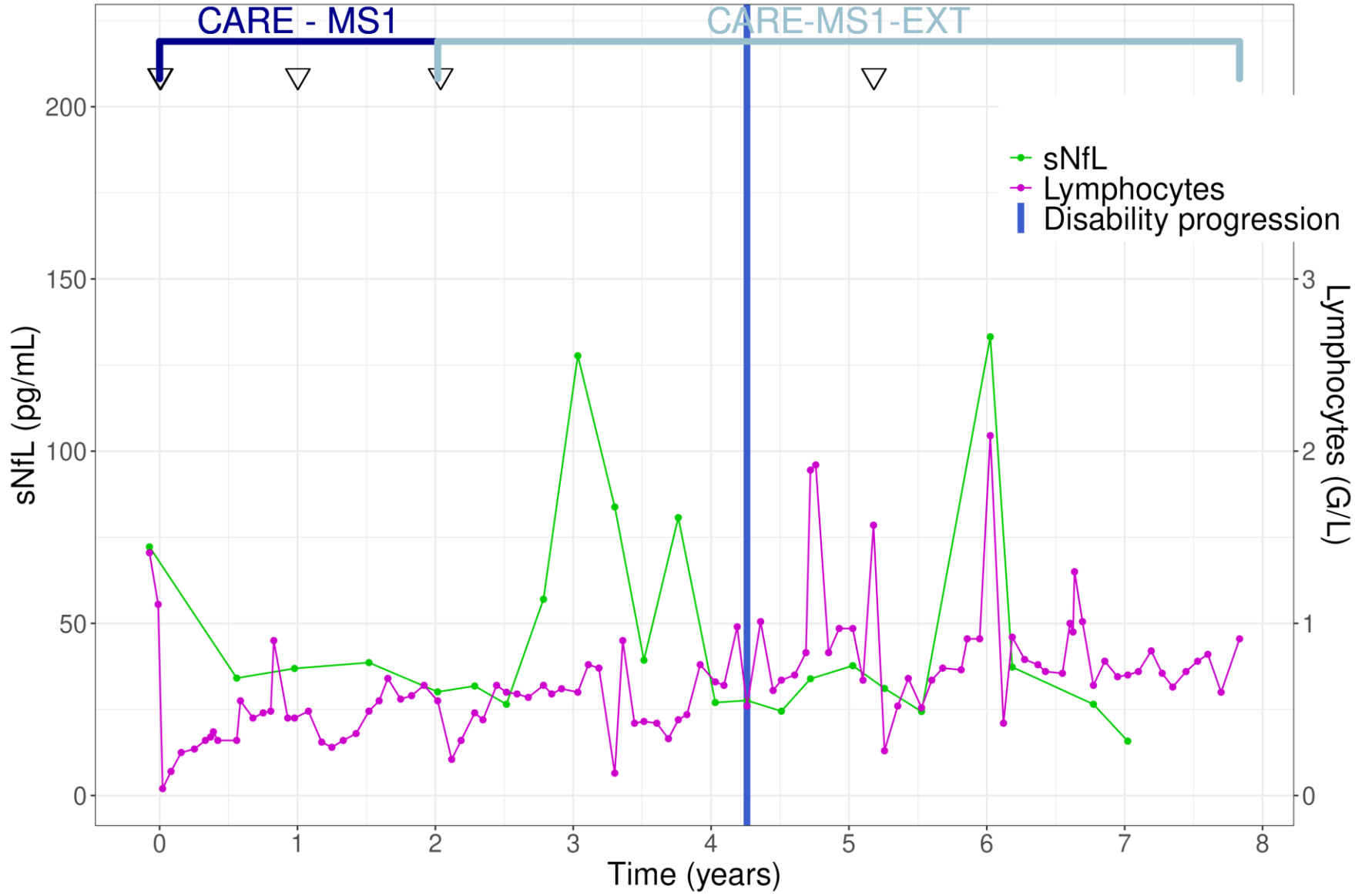

Patient characteristics at baseline

- Young population mainly composed of women (65%)
- Most of the patients in an inflammatory state
- Almost half of the patients with T1 and T2 lesions on magnetic resonance imaging

→ Population considered representative of RRMS typical patients

Two-stage approach

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1. Lymphocyte-sNfL model[1,2]
   - Non linear mixed effect modeling approach
   - Structural and statistical model selection on BICc[8]
     - Inter-individual random effects $\boldsymbol{\eta_i}$ to capture **patient i departure from population estimate**
     - Inter-occasion random effect $\boldsymbol{\kappa_{i,k}}$ to capture **sNfL peak of patient i at occasion k**
   - Covariate model building through
     - Screening step on empirical Bayes estimates
     - Backward selection on Wald test

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2. Disability progression model

Selection on BIC

- Parametric survival model
- Baseline hazard function
- Stepwise covariate model building approach
- Link function
  - Current sNfL value, sNfL(t)
  - Current slope of sNfL, $\frac{\mathbf{dsNfL(t)}}{\mathbf{dt}}$
  - Current change from baseline

Using predictions with $\hat{\kappa}_{i,k}$ **and** $\hat{\eta}_i$ → **capturing the peaks**
Predictions with only $\hat{\eta}_i$ → **ignoring the peaks**

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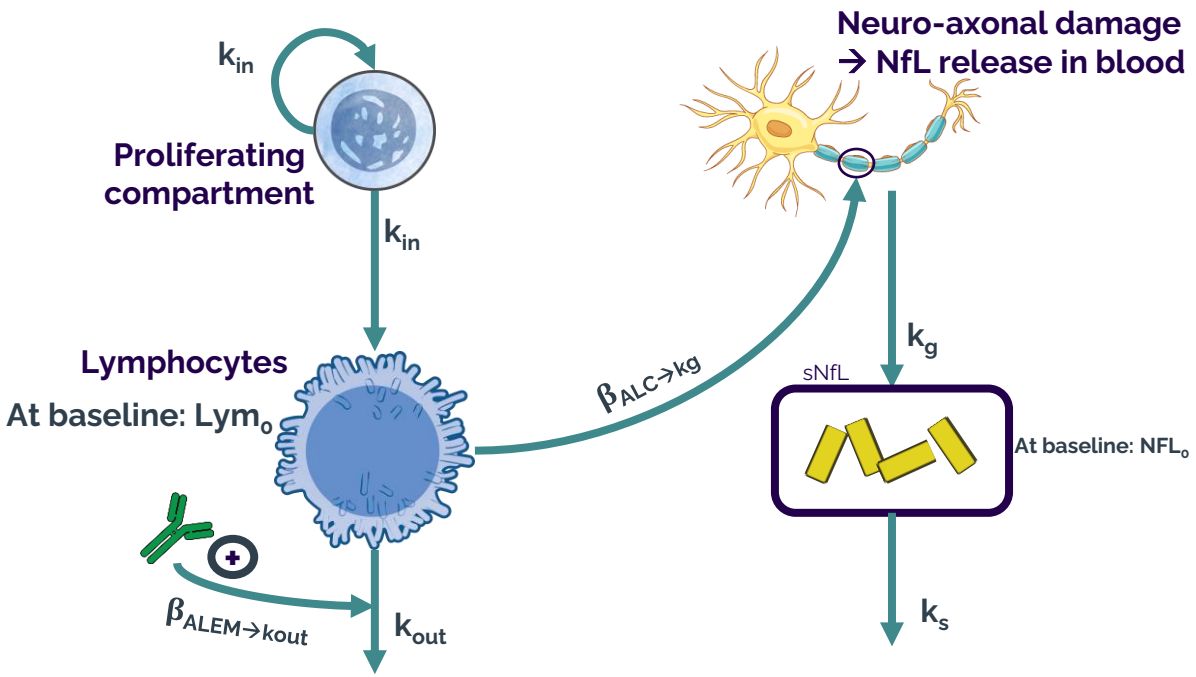
Lymphocytes-sNfL model

ODEs:

$$Lym(t=0) = Lym_0$$
$$sNfL(t=0) = NfL_0$$
$$\frac{dProl}{dt} = k_{in}.Prol - k_{in}.Prol$$
$$\frac{dLym}{dt} = k_{in}.Prol - k_{out}.(1 + \beta_{Alem \rightarrow kout}.C_{ALEM}).Lym$$

$$\frac{dsNfL}{dt} = k_g.(1 + \boldsymbol{\beta_{ALC \rightarrow kg}}.Lym) - k_s.sNfL$$



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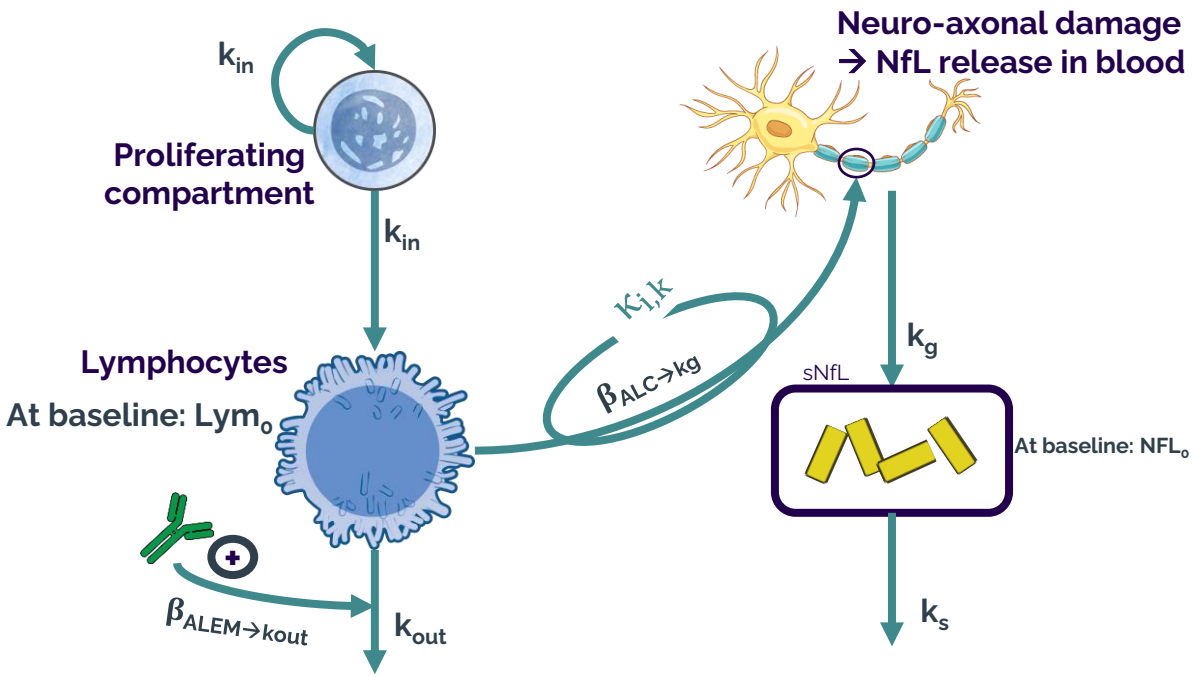

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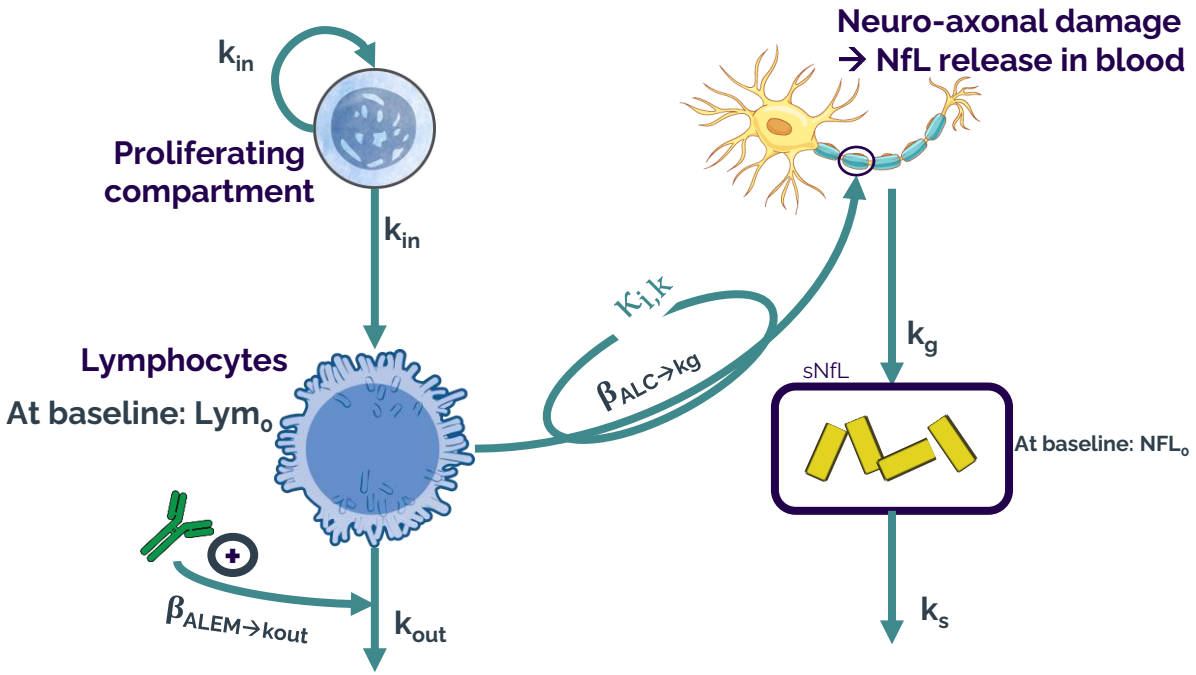

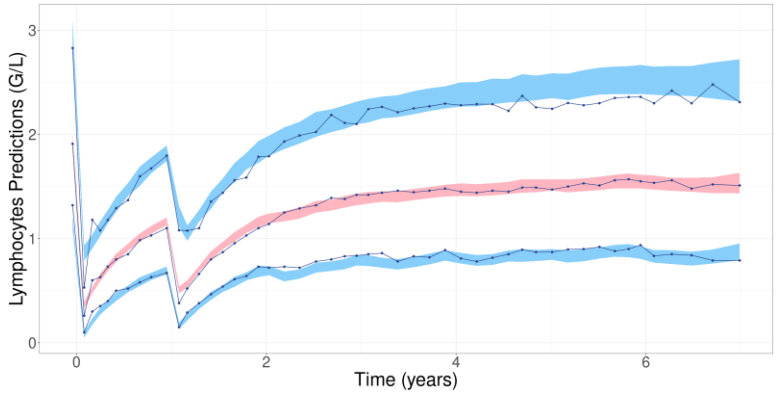

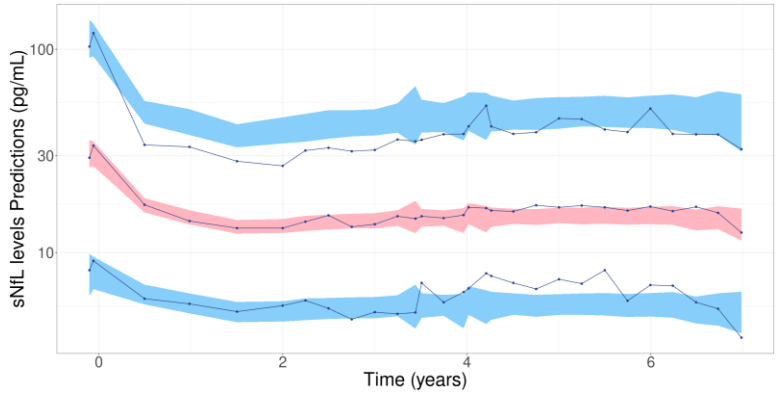

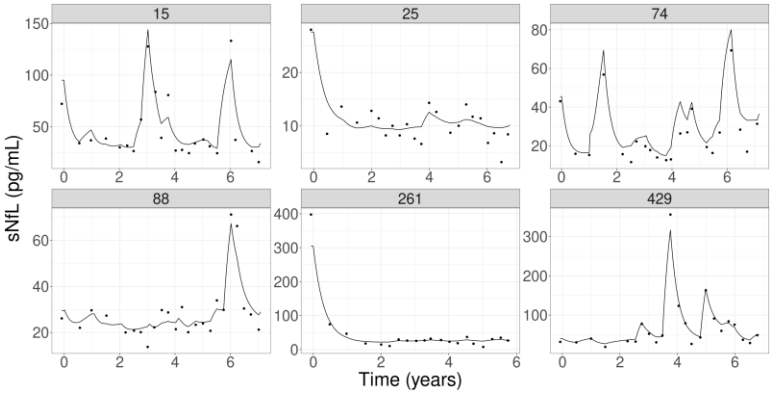

Baseline covariates impact on sNfL dynamics

High covariate value

Typical patient

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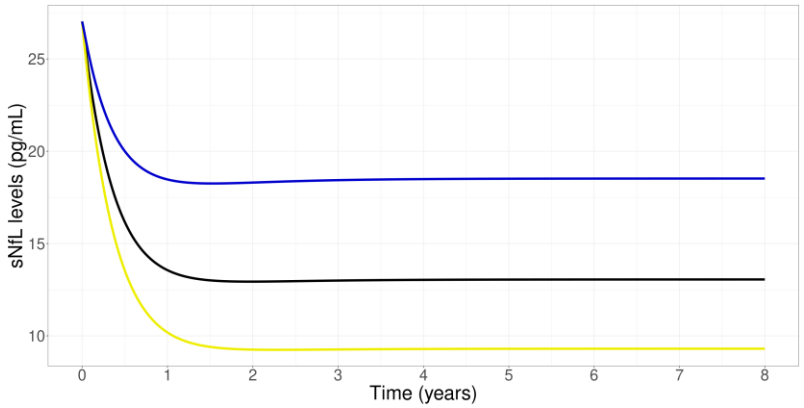
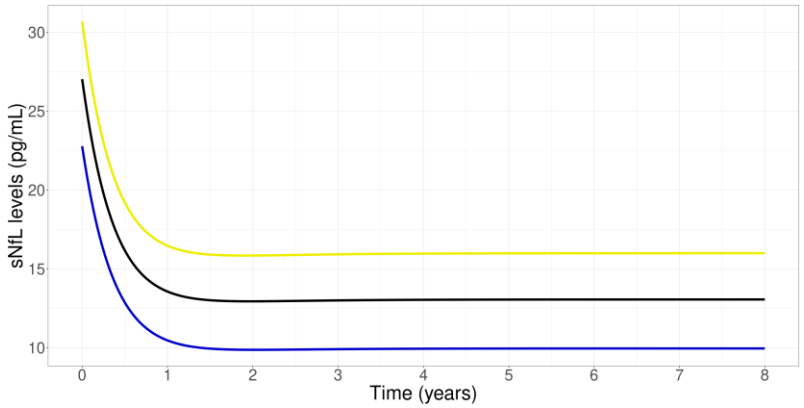
Age ⬆ k_g
(p-value < 2.10^{-12})



Body Mass Index ⬇ NFL_0 and k_g
(p-value < 1.10^{-2} and <3.10^{-12})



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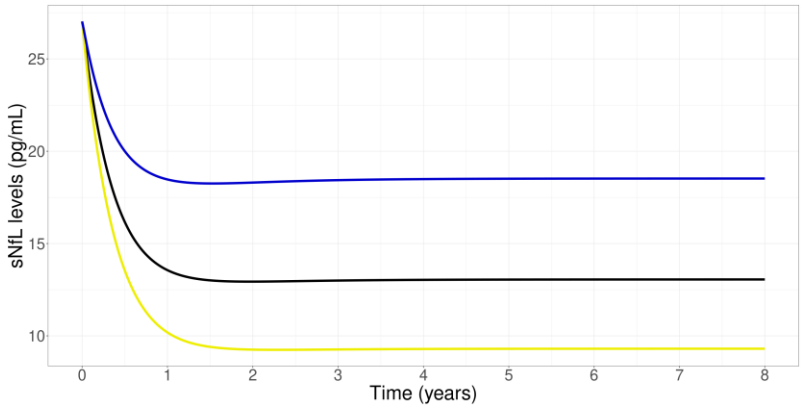

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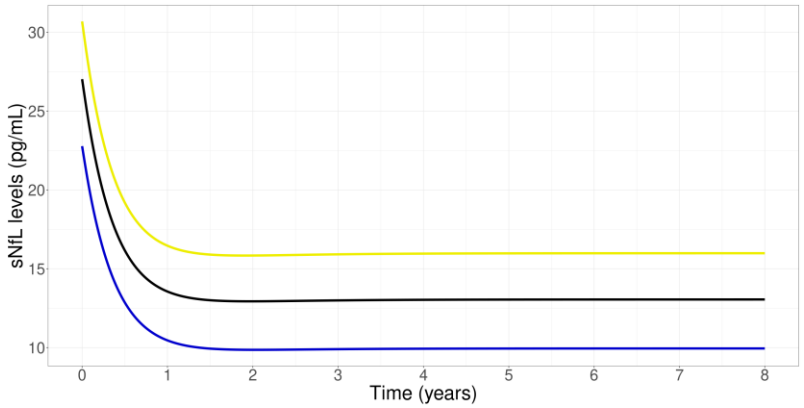
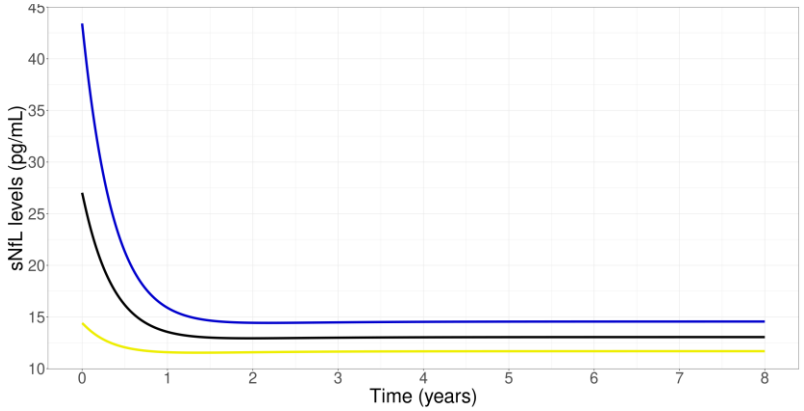
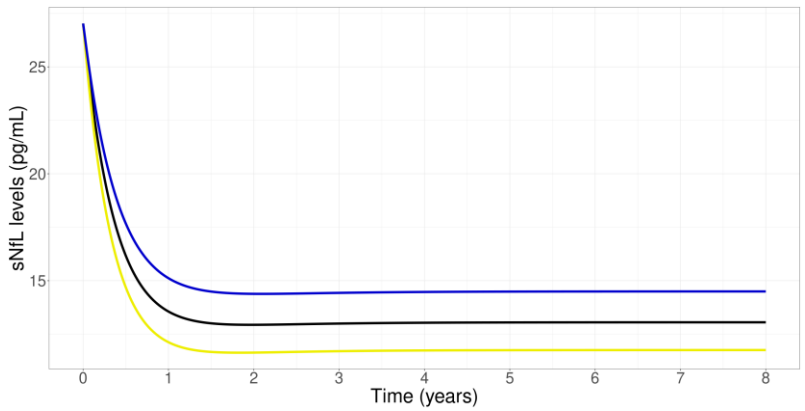


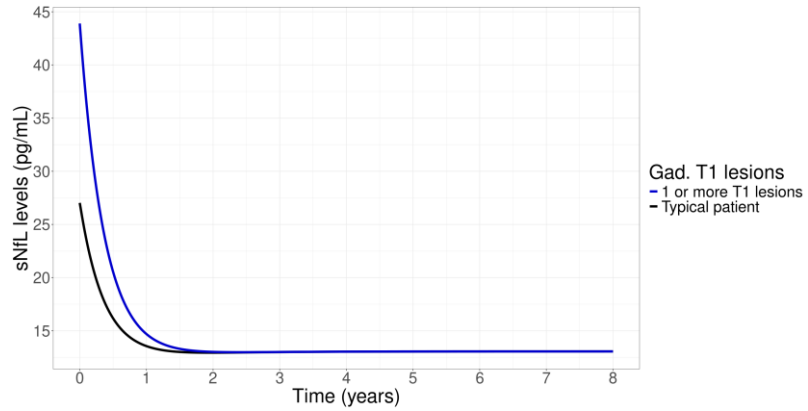
T2 lesion volume ⬆ NFL_0 and $\beta_{ALC \rightarrow kg}$
(p-value < 2.10^{-12} and <1.10^{-3})



$EDSS_0$ ⬆ NFLhalf-life
(p-value < 3.10^{-4})



Presence of T1 lesions ⬆ NFL_0
(p-value < 3.10^{-9})



Lymphocytes-sNFL-Disability progression model

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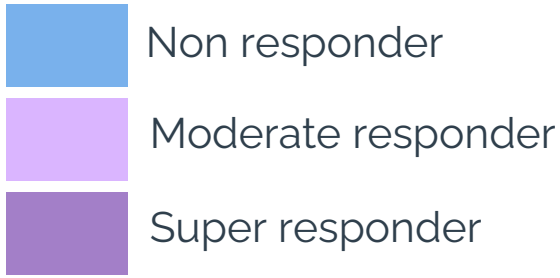

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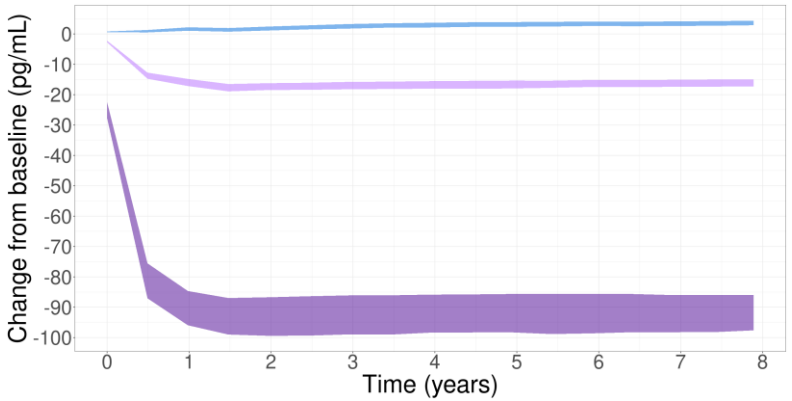
Non responder

Moderate responder

Super responder



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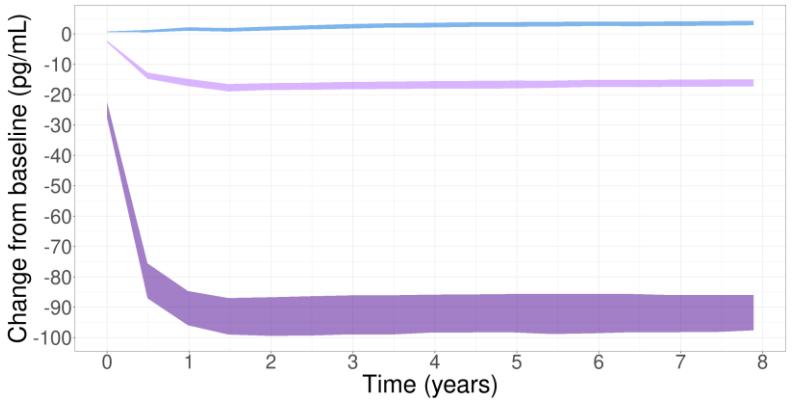

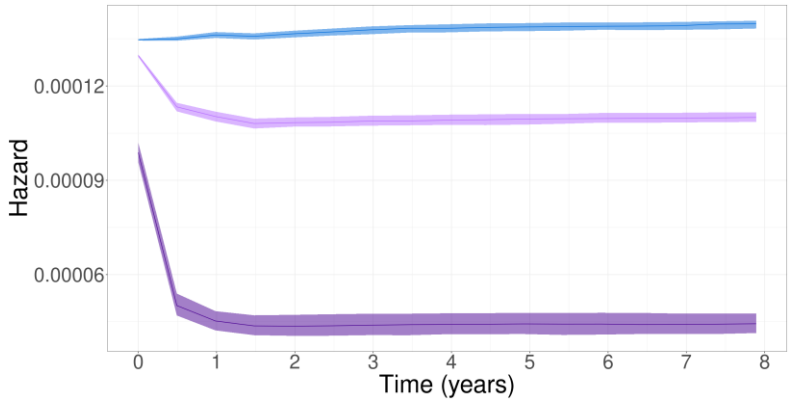

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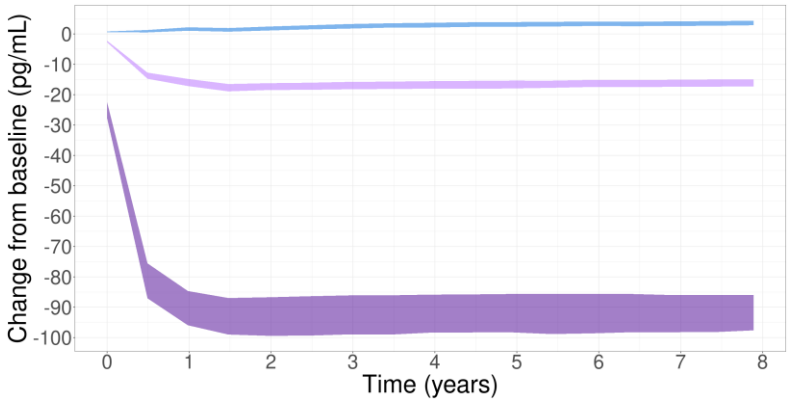

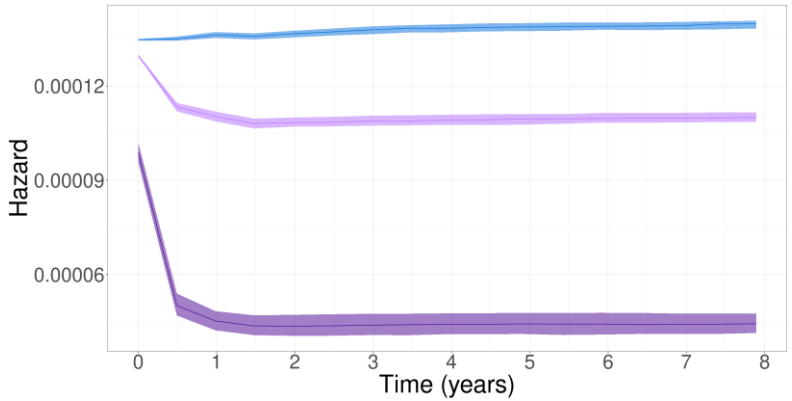

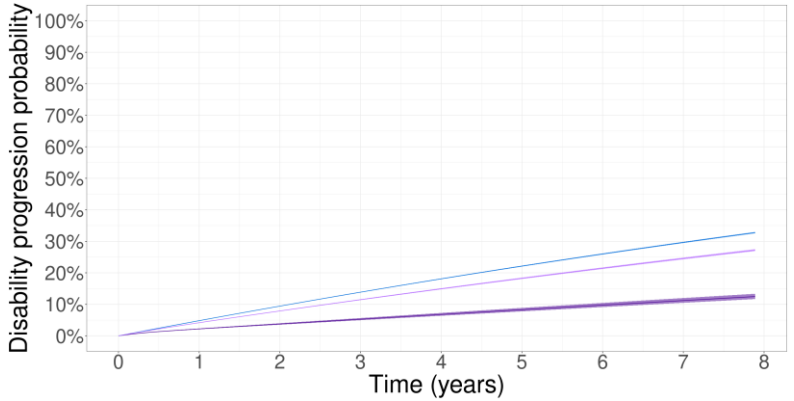

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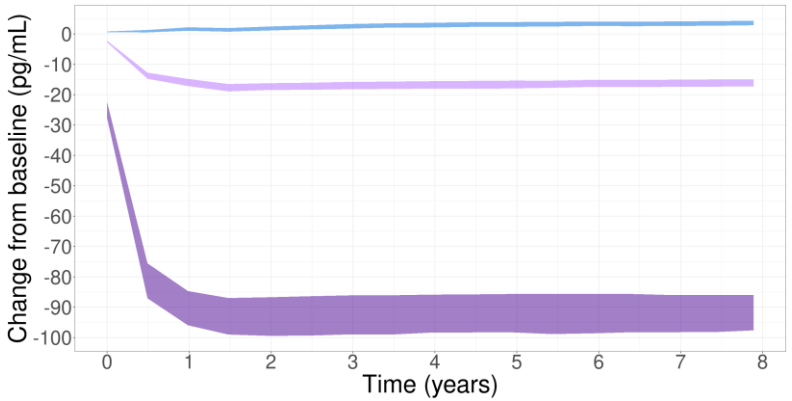
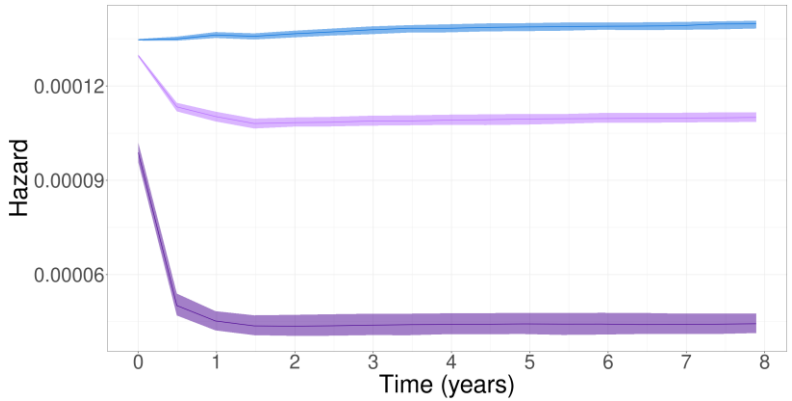
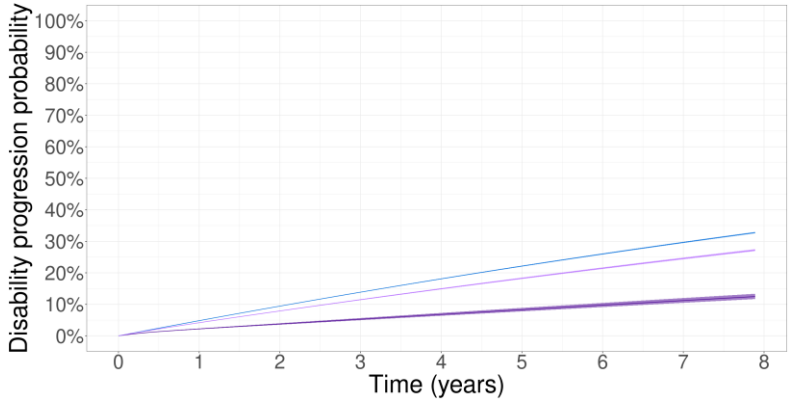
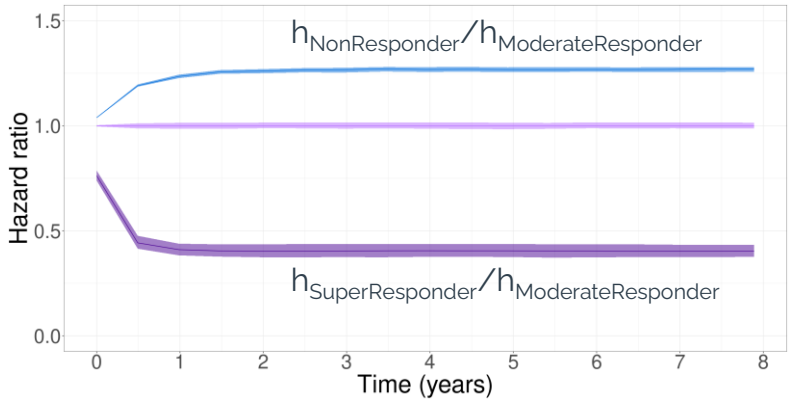






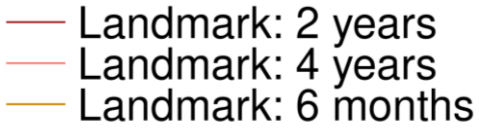


Discrimination and calibration

Desmée Sand al., BMC Med Res Methodol. 2017

Discrimination and calibration

- Individual dynamic predictions for Landmark times s



- Calibration[10] on Brier score scaled (sBS) on a Kaplan-Meier (KM)
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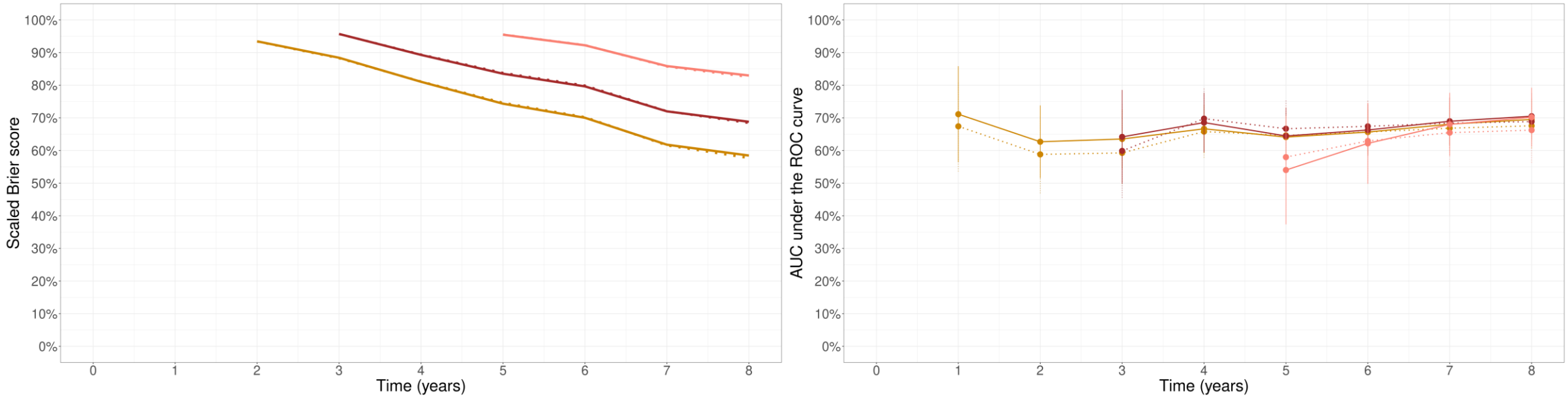

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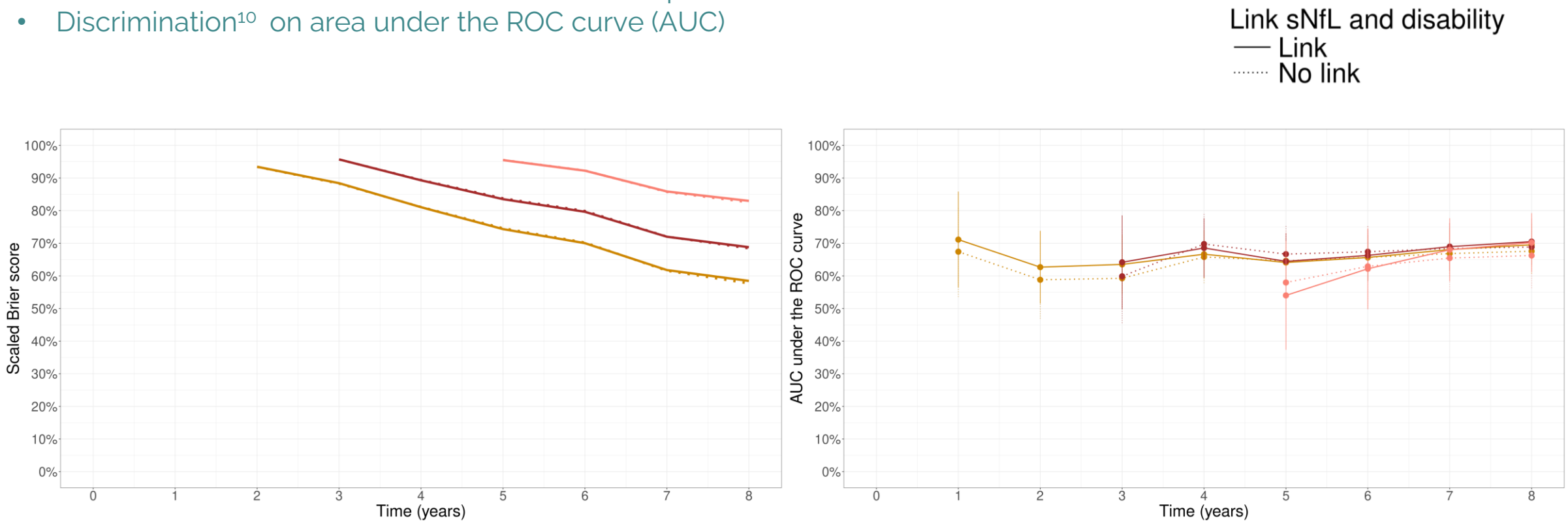

→ sNfl presents limited discrimination and prediction performance

Desmée Sand al., BMC Med Res Methodol. 2017

Conclusion

1: Benkert and al., Lancet Neurol. 2022
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- Next steps:
  - Modeling EDSS and sNfL trajectories via a latent variable model
  - Link with T1 and T2 lesion longitudinal data

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Thanks you for your attention!
Questions?

Acknowledgments

INSERM: Julie Bertrand

Sanofi: Hoai-Thu Thai, Vincent Thuillier, Sophie Fliscounakis-Huynh, Marc Cerou, Thomas Klabunde, and Christine Geffriaud-Ricouard

This PhD is funded by Sanofi and the French National Agency of Research and Technology (ANRT) through a CIFRE agreement

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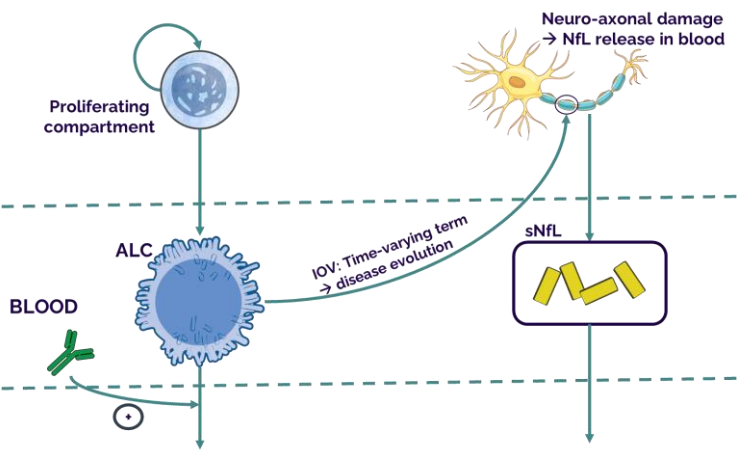
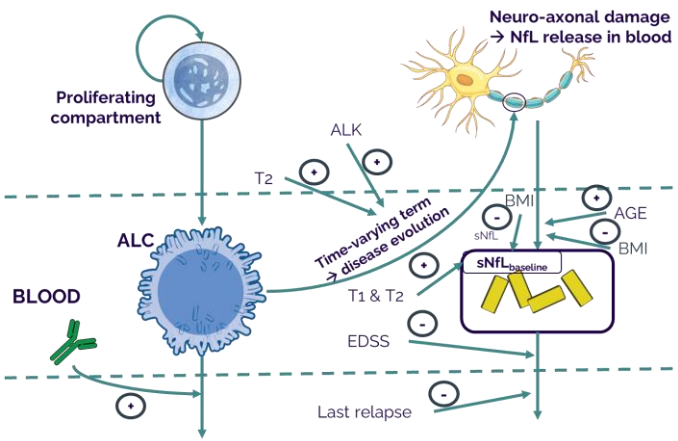
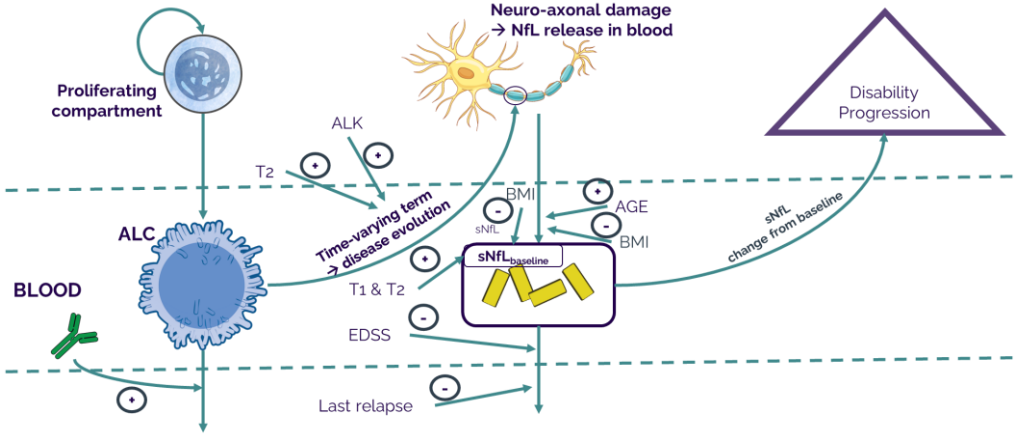


ALC-sNfL model



Covariate analysis for sNfL



sNfL & disability progression

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sanofi

Inserm

Université Paris Cité

Annexes

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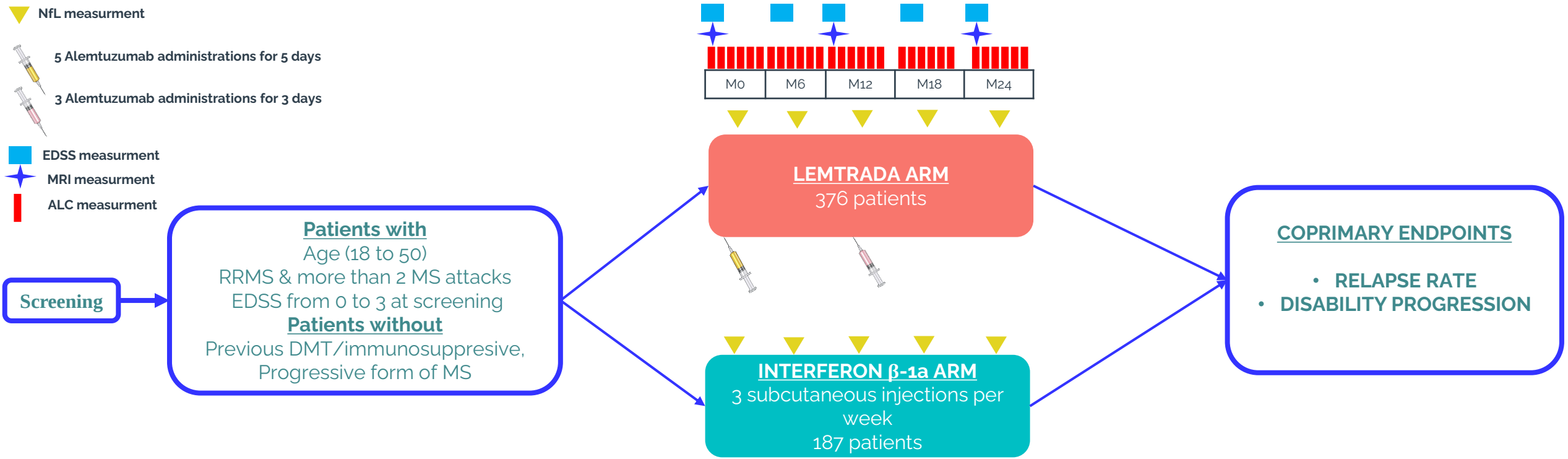
Alemtuzumab clinical trial: CARE MS-1



- **What is the study measuring?**[2]
  - Expanded Disability Status Scale (EDSS), every 6 months
  - T1-Gadolinium lesion number every year
  - T2-lesion volume every year
  - Absolute lymphocyte count (ALC) every month
  - Serum Neurofilament Light Chain levels (sNfL) every 6 months

→ **Interferon β-1-a arm is not considered for modeling**

(2) Cohen and al., Lancet, 2012

Final lymphocyte-sNfL model

	Base model	Final covariate model
BICc	59253 (0)	59102 (-151)
KDE	0.173 (Fixed)	0.173 (Fixed)
ALC_0	2.02 (2)	1.91 (3)
$\beta(ALC_0 \leftarrow REGION)$	-	0.0838 (35)
$\beta(ALC_0 \leftarrow BMIBL)$	-	0.278 (25)
K_{in}	0.00248 (3)	0.00248 (3)
k_{out}	0.00292 (4)	0.00291 (4)
$\beta_{ALEM \rightarrow kout}$	28.8 (3)	25.9 (5)
$\beta(\beta_{ALEM \rightarrow kout} \leftarrow SEX)$	-	0.164 (31)
(NFL_0)	32.4 (5)	25.1 (6)
$\beta(NFL_0 \leftarrow CATCGAD0)$	-	0.519 (17)
$\beta(NFL_0 \leftarrow BMIBL)$	-	-0.587 (38)
$\beta(NFL_0 \leftarrow T2VOL0)$	-	0.303 (10)
K_g	0.0585 (7)	0.0639 (7)
$\beta(k_g \leftarrow AGE)$	-	1.02 (11)
$\beta(k_g \leftarrow BMIBL)$	-	-1.03 (14)
k_s	0.00648 (6)	0.00976 (9)
$\beta(k_s \leftarrow EDSSBL)$	-	-0.108 (28)
$\beta(k_s \leftarrow MXTTRLS)$	-	-0.0277 (33)
$\beta_{ALC \rightarrow kg}$	0.252 (9)	0.238 (9)
$\beta(\beta_{ALC \rightarrow kg} \leftarrow ALKN)$	-	0.685 (37)
$\beta(\beta_{ALC \rightarrow kg} \leftarrow T2VOL0)$	-	0.196 (30)
$\omega(ALC_0)$	0.272 (5)	0.265 (5)
$\omega(k_{in})$	0.582 (4)	0.587 (4)
$\omega(k_{out})$	0.731 (4)	0.738 (4)
$\omega(\beta_{ALEM \rightarrow kout})$	0.543 (5)	0.542 (5)
$\omega(NFL_0)$	0.966 (4)	0.782 (4)
$\omega(k_g)$	0.787 (8)	0.789 (8)
$\omega(k_s)$	0.734 (7)	0.689 (8)
$\omega(\beta_{ALC \rightarrow kg})$	1.08 (8)	0.987 (8)
$\gamma(\beta_{ALC \rightarrow kg})$	1.18 (2)	1.2 (2)
$Corr(k_{in} vs. ALC_0)$	-0.0753 (86)	-0.0884 (73)
$Corr(k_{out} vs. ALC_0)$	0.233 (26)	0.222 (28)
$Corr(\beta_{ALEM \rightarrow kout} vs. ALC_0)$	-0.23 (28)	-0.196 (33)
$Corr(k_{out} vs. k_{in})$	0.844 (2)	0.844 (2)
$Corr(\beta_{ALEM \rightarrow kout} vs. kin)$	-0.484 (10)	-0.497 (10)
$Corr(\beta_{ALEM \rightarrow kout} vs. kout)$	-0.644 (6)	-0.651 (6)
$Corr(k_g vs. NFL_0)$	0.51 (14)	0.542 (12)
$Corr(k_s vs. NFL_0)$	0.324 (24)	0.327 (24)
$Corr(k_s vs. k_g)$	0.744 (5)	0.815 (4)
Additive errr (ALC)	0.134 (2)	0.134 (2)
Proportional error (ALC)	0.192 (1)	0.192 (1)
Proportional error(NFL)	0.309 (0)	0.308 (0)

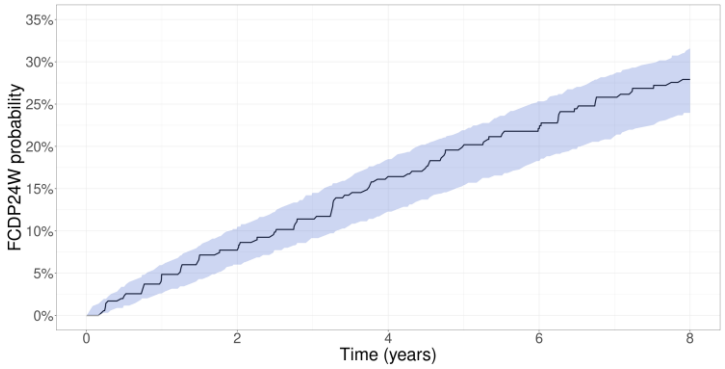
Lymphocyte-sNFL-Disability progression model

	No Link	CFB (Occ. Peaks)	**CFB (global trend)**
BICc	1806 (0)	1803 (-3)	**1798 (-8)**
Te	9710 (12)	8930 (12)	**7430 (14)**
β(Te←AGE)	-2.12 (22)	-2.1 (22)	**-1.89 (25)**
$\beta_{sNfl \rightarrow CDP}$		0.00369 (22)	**0.0118 (35)**

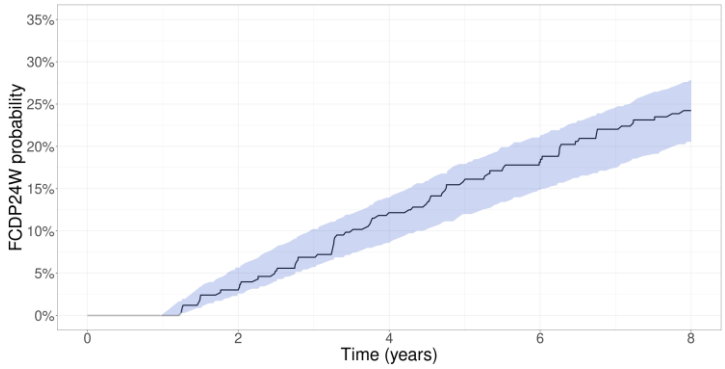
	No Link	CFB (global trend)
BICc	1470 (0)	1465 (-5)
Te	10200 (13)	7770 (15)
β(Te←AGE)	-2.28 (23)	-2.07 (26)
$\beta_{sNfl \rightarrow CDP}$		0.0115 (39)

	No link	CFB (global trend)
BICc	1259 (0)	1257 (-2)
Te	10100 (15)	7790 (17)
β(Te←AGE)	-2.62 (22)	-2.43 (24)
$\beta_{sNfl \rightarrow CDP}$		0.0103 (43)

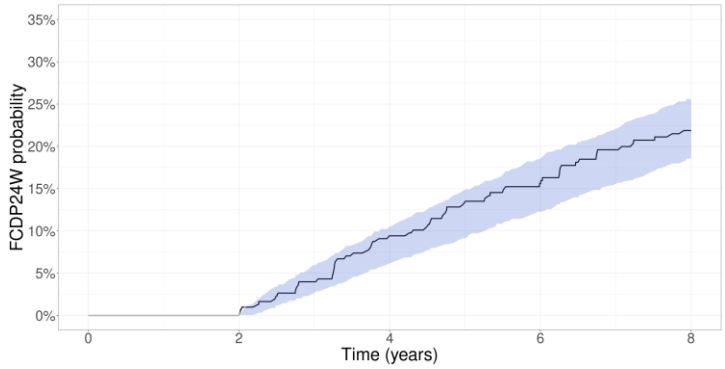
Current CFB global trend



CFB at 1 year (global trend)

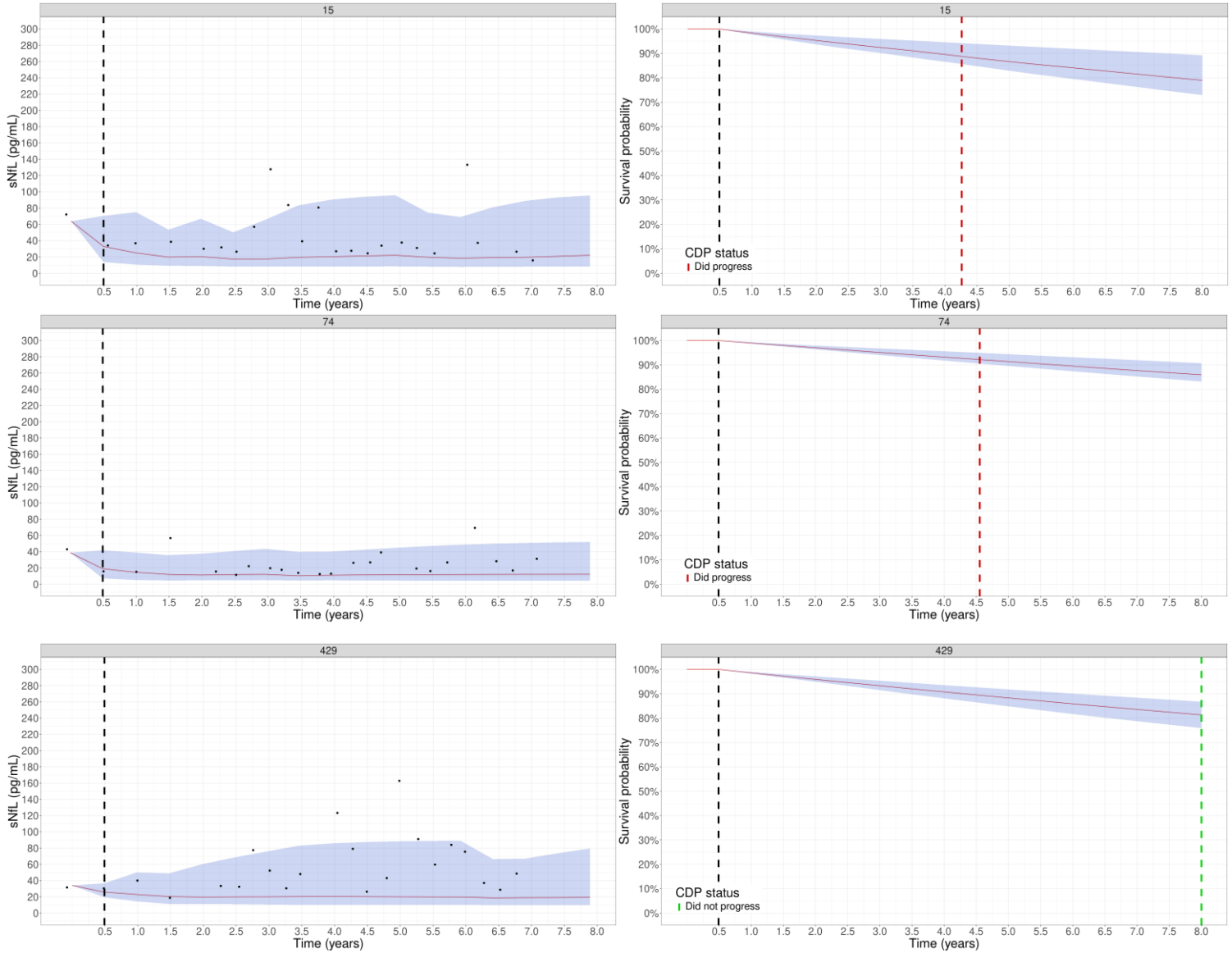


CFB at 2 years (global trend)

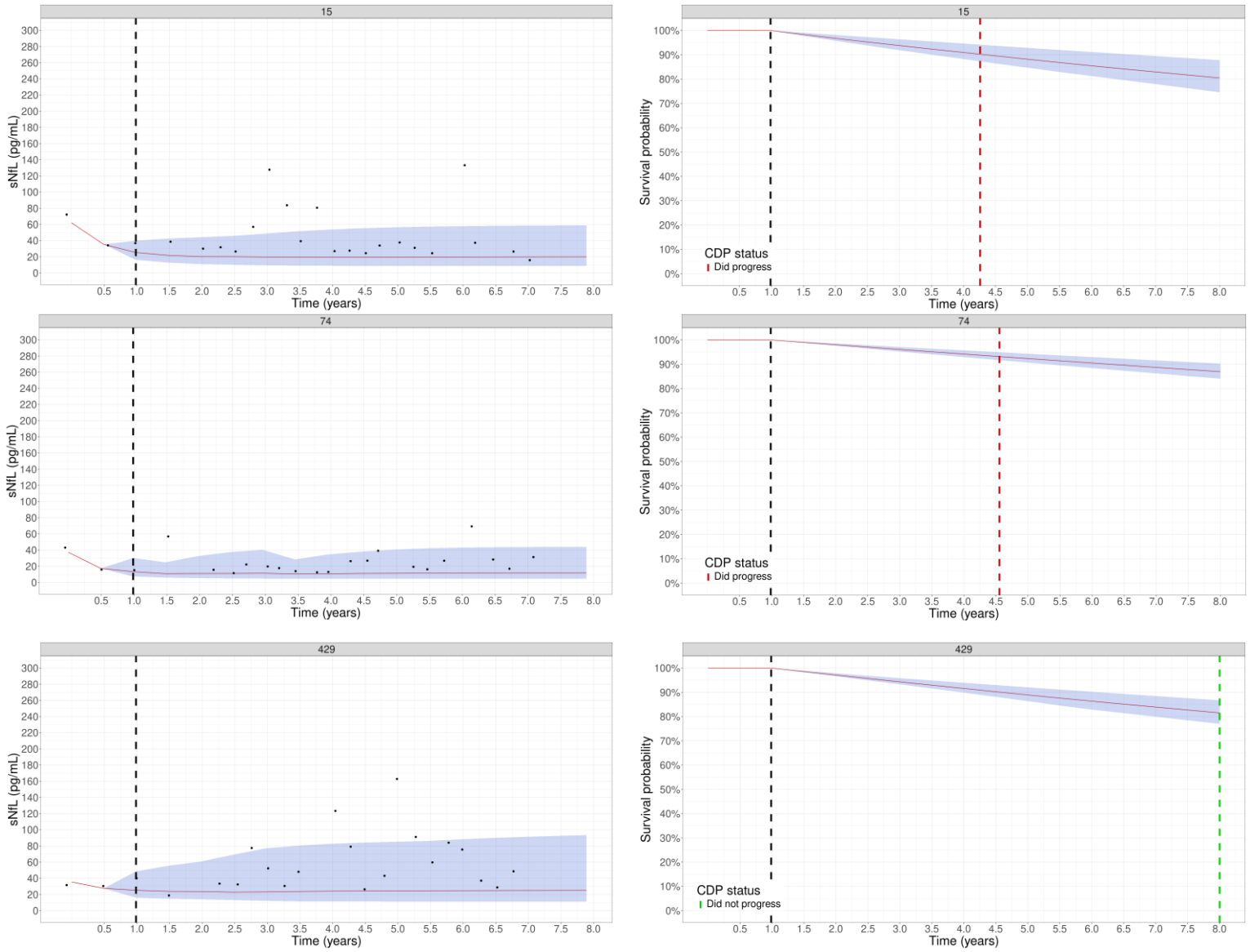


→ **Underlying sNfL dynamics better captures the link with disability progression through CFB**

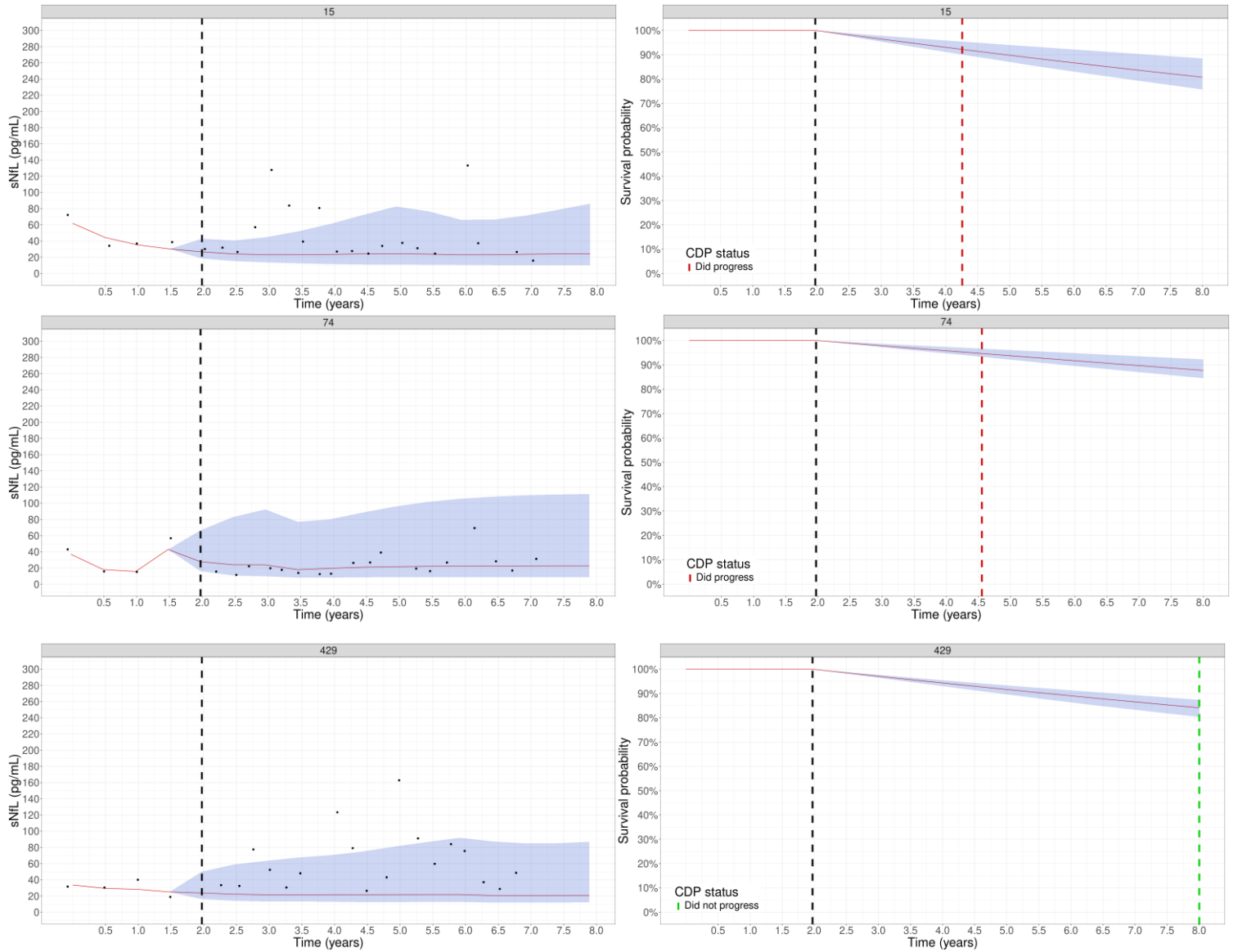
Individual dynamic predictions (6 months)



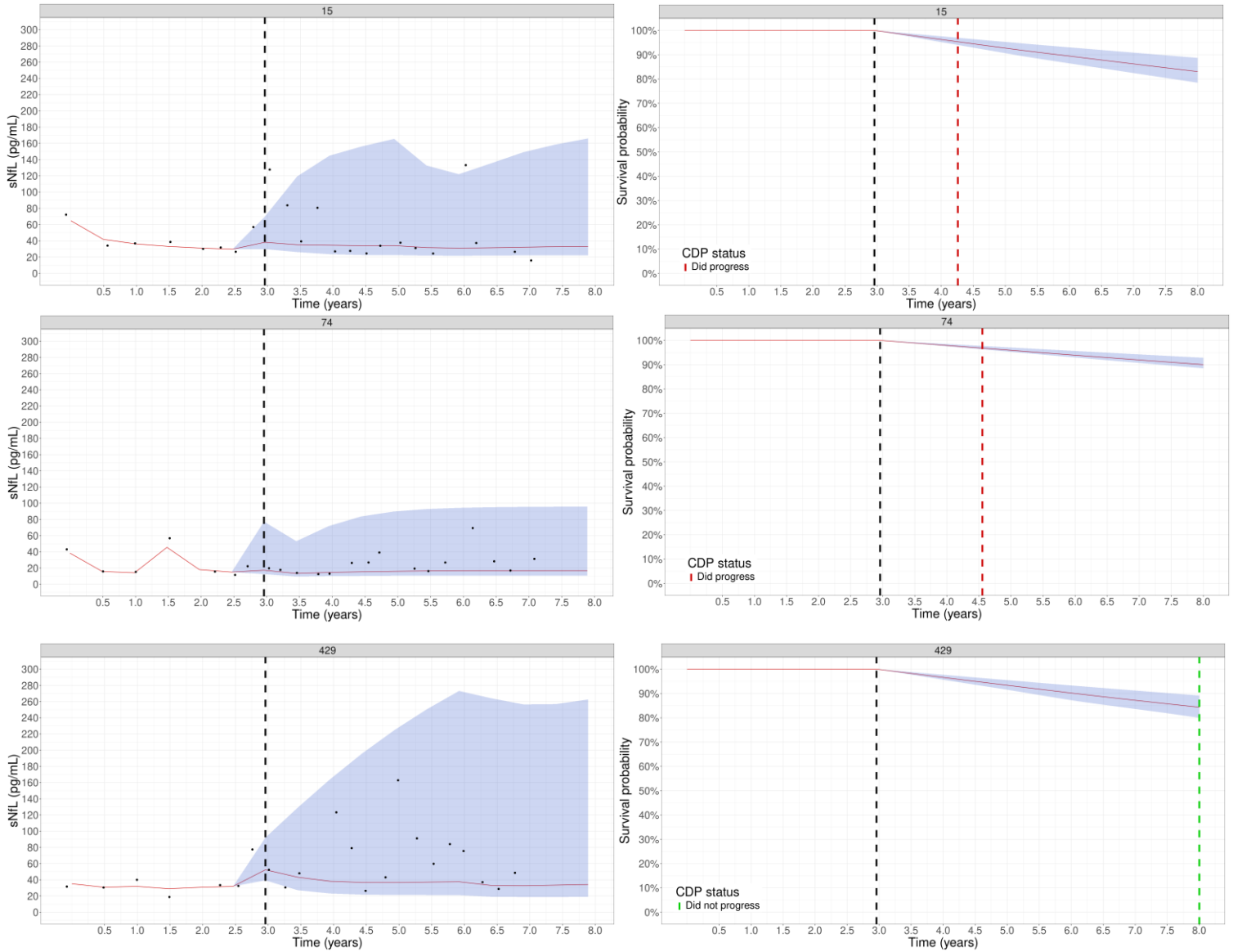
Individual dynamic predictions (1 year)



Individual dynamic predictions (2 years)



Individual dynamic predictions (3 years)



Individual dynamic predictions (4 years)