Cognitive Processing Speed Predicts Disease Progression in Secondary Progressive Multiple Sclerosis: Post Hoc Analysis from the EXPAND Study

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Disclosures

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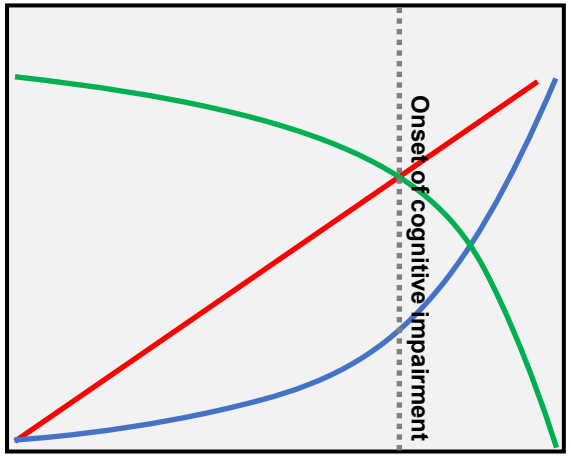
Background

- Cognitive impairment has a substantial impact on patient's QoL becoming more prevalent (up to 80%) and more severe in patients with SPMS vs those with RRMS[1,2]
- Studies suggest cognitive reserve can act as a buffer to disability progression and loss of cognitive reserve may explain the onset of progressive disease in MS[3]
- CPS may be indicative of functional brain reserve and network efficiency, reflecting the ability of the brain to compensate for neuro-axonal damage/loss that accumulates with disease progression[4]
- Several smaller studies have suggested that cognitive impairment/CPS in MS can predict long-term physical disability progression[5,6]
- In the Phase 3 EXPAND study, compared with placebo, siponimod significantly reduced the risk of disability progression and worsening of CPS in patients with SPMS[7,8] and the effect was sustained in the long-term[9]
- Here, we assessed the association between CPS, as measured by SDMT, and physical disability progression in the large EXPAND clinical trial dataset

Neuronal network dysfunction (network collapse)[10]



CPS, cognitive processing speed; MS, multiple sclerosis; QoL, quality of life; RRMS, relapsing-remitting MS; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive MS

1. Ruano L, et al. *Mult Scler*. 2017;23(9):1258-1267; 2. Wachowius U, et al. *J Clin Exp Neuropsychol*. 2005;27(1):65-77; 3. Schwartz CE, et al. *Arch Phys Med Rehabil*. 2013;94(10):1971-81; 4. Gaetani L, et al. *Neural Regen Res*. 2021;16(1):36–42; 5. Moccia M, et al. *Mult Scler*. 2016;22(5):659-67; 6. Pitteri M, et al. *Mult Scler*. 2017;23(6):848-854; 7. Benedict RHB, et al. *Neurology* 2021;96(3):e377-e386; 8. Kappos L, et al. *Lancet*. 2018;391:1263–73; 9. Cree BAC. *Mult Scler*. 2022;In press; 10. Schoonheim MM, et al. *Front Neurol*. 2015;6:82.

Objectives

- To assess the predictive value of cognitive processing speed (baseline and on-study changes) assessed by the SDMT score, in patients with SPMS for physical disability progression measured by:
  - Time to wheelchair (T2W) (sustained deterioration to EDSS score ≥7)
  - 6-month confirmed disability progression (6mCDP) on EDSS

EDSS, Expanded Disability Status Scale; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive multiple sclerosis

Methods

- This post hoc analysis used data from the core and extension parts of the phase 3 EXPAND study in SPMS
- Patients (1628/1651) were categorized into quartiles by baseline SDMT score and on-study (M0–24) SDMT change: worst [Q1], intermediate [Q2-Q3], and best [Q4]
- The predictive value for disability progression was assessed by comparing worst vs best quartile of baseline SDMT or on-study change in SDMT by Cox regression:
  - For *baseline SDMT*, model was adjusted for treatment, age, gender, baseline EDSS, baseline SDMT quartile, and treatment-by-baseline SDMT quartile interaction
  - For *on-study change in SDMT*, model was adjusted for treatment, age, gender, baseline EDSS, baseline SDMT, and on-study change in SDMT quartile
- Kaplan Meier curves which were not adjusted for baseline EDSS score were also generated. Since more patients in the worst versus best baseline SDMT category had baseline EDSS = 6.5 (35% versus 19%, respectively), it should be noted that the worst subset is at increased risk of T2W in unadjusted Kaplan Meier analysis

EDSS, Expanded Disability Status Scale; M, month; MS, multiple sclerosis; Q, quartile; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive MS; T2W, time to wheelchair

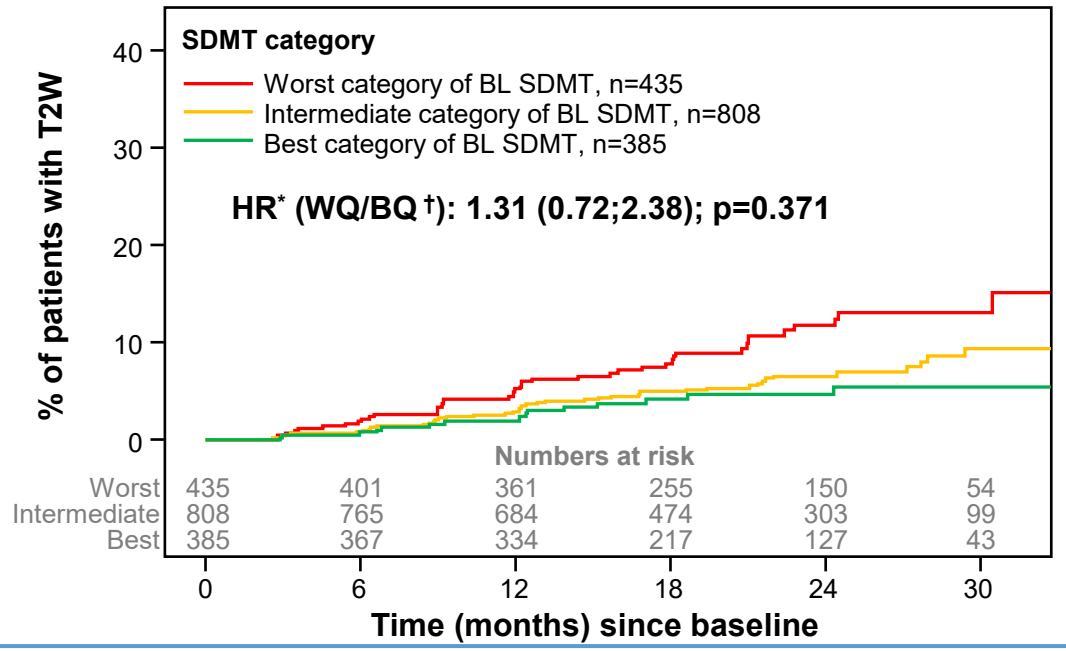
Methods (Contd.)

Analyses	
Core part (up to 37 months) (all patients, siponimod arm, placebo arm)	**Core+extension (up to 5 years)** (all patients)
• Baseline SDMT as a predictor for T2W (EDSS score ≥7) and 6mCDP	• Baseline SDMT as a predictor for T2W and 6mCDP • On-study change in SDMT (month 0–24) as a predictor for subsequent disability progression (T2W)

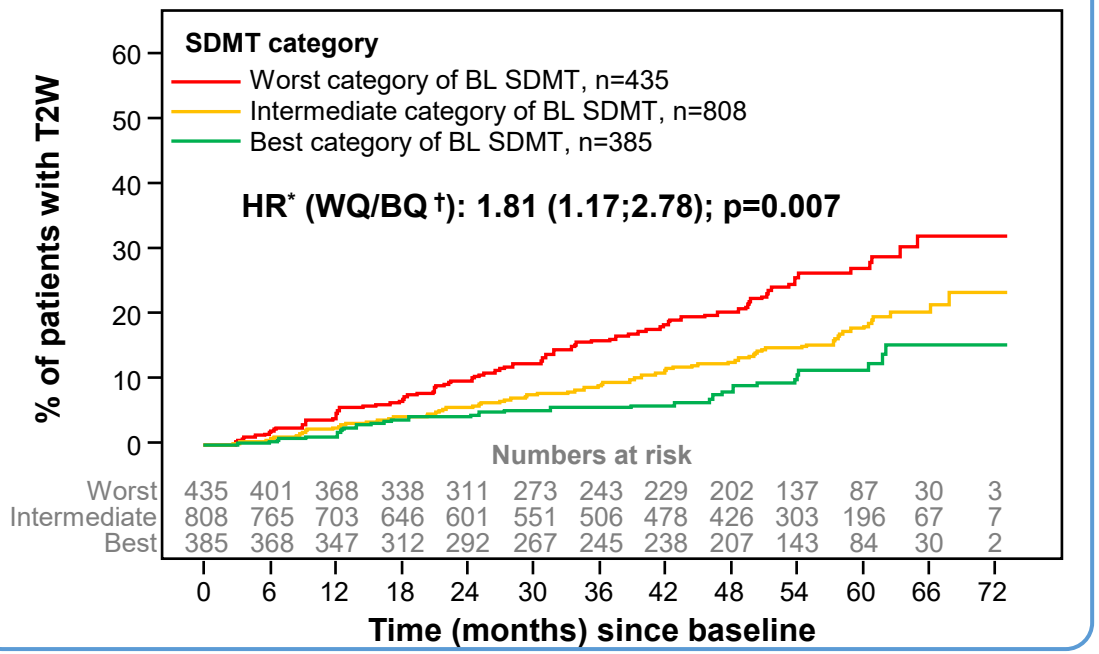
EDSS, Expanded Disability Status Scale; SDMT, Symbol Digit Modalities Test; T2W, time to wheelchair; 6mCDP, 6-month confirmed disability progression

Results: Predictive value of baseline SDMT for time to wheelchair (all patients)

Core study



Core+extension study



- In the Core study, patients in the worst quartile of SDMT at baseline were at a numerically higher risk of reaching T2W vs patients in the best quartile of SDMT
- The predictive value of baseline SDMT increased with long-term follow-up (an almost 2-fold increased risk of T2W [WQ/BQ]) in Core+extension study

*Adjusted for baseline EDSS and other confounders
†WQ of BL SDMT score ≤29 (minimum 0); BQ of BL SDMT score ≥49 (maximum 83)
BL, baseline; BQ, best quartile; CPS, cognitive processing speed; SDMT, Symbol Digit Modalities Test; T2W, time to wheelchair; WQ, worst quartile

Results: Predictive value of baseline and on-study change in SDMT for physical disability progression (T2W and 6mCDP): Core study and core+extension

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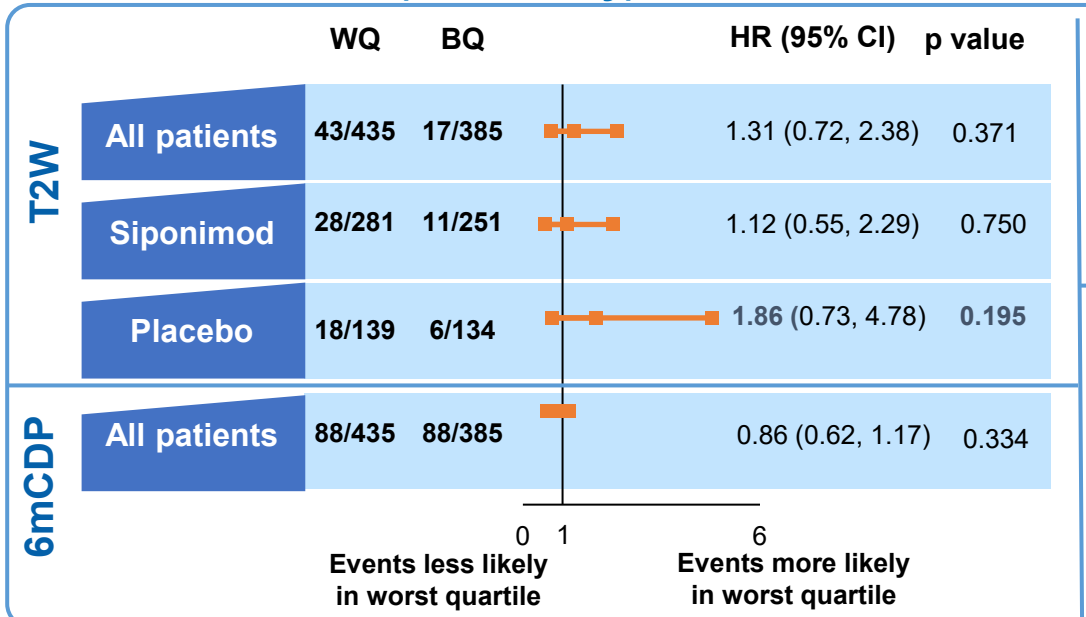
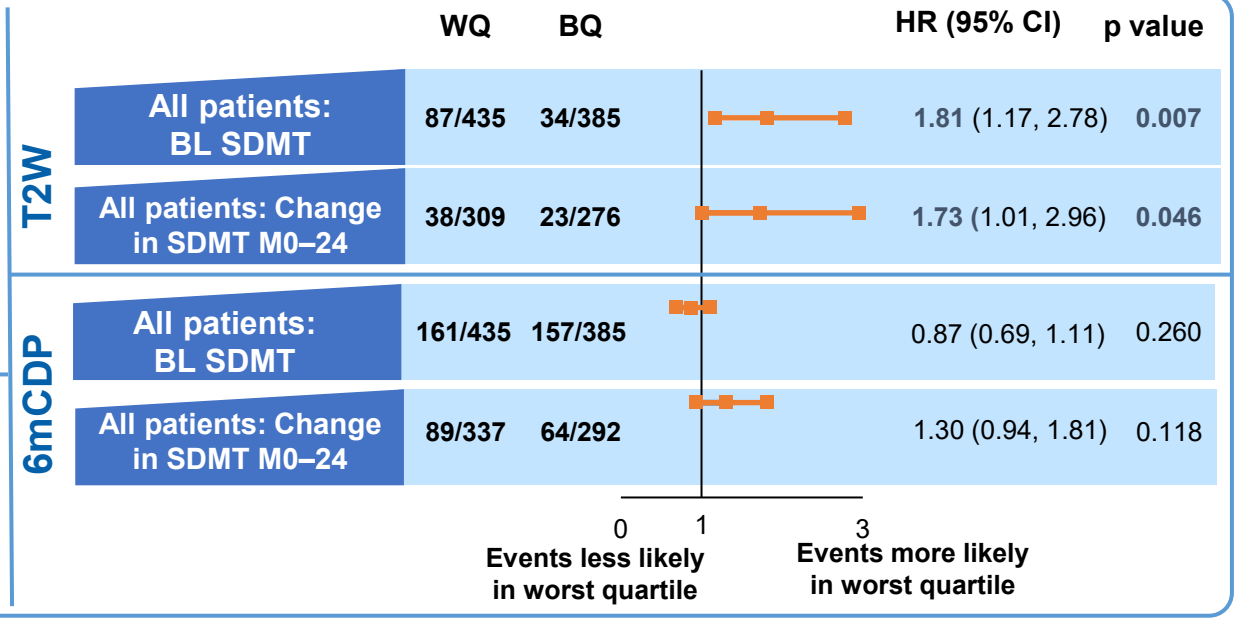
Short-term predictive value of baseline SDMT (core study)



Long-term predictive value of baseline SDMT and on-study SDMT change (core+extension study)



- Baseline SDMT and on-study change in SDMT were predictive of T2W in the long-term, but not predictive of 6mCDP
- The short-term predictive value of baseline SDMT for T2W was more obvious in the placebo arm ($HR_{WQ/BQ}$=1.86) vs siponimod arm ($HR_{WQ/BQ}$=1.12) likely due to the treatment effect of siponimod preventing relatively more T2W events in the WQ and hence reducing the risk of reaching T2W

BQ, best quartile; HR, hazard ratio; MS, multiple sclerosis; SDMT, Symbol Digit Modalities Test; SPMS, secondary progressive MS; T2W, time to wheelchair; WQ, worst quartile; 6mCDP, 6-month confirmed disease progression

Conclusions

- Both baseline and on-study change in CPS, as measured by SDMT, were predictive of physical disability progression over the longer term (up to 5 years) as indicated by the significant association with the stringent outcome of reaching the milestone of EDSS score ≥7
- The results support the predictive value of CPS for future disease progression as an indirect measure of network efficiency and functional brain reserve in line with previous smaller published studies
- Furthermore, CPS monitoring could be of relevance in daily practice to help identify patients at risk of progression and help uncover ‘silent’ signs of progression

CPS, cognitive processing speed; EDSS, Expanded Disability Status Scale; SDMT, Symbol Digit Modalities Test