Secondary endpoints

For secondary endpoints, a mixed effects model was calculated adjusting for baseline values and cumulative paclitaxel dose. Missing values were imputated (ITT cohort). Changes in NfL, a sensitive marker of neuroaxonal damage, after completion of chemotherapy was very similar between both the lithium carbonate and the placebo group (Figure 3A) with a calculated regression coefficient of 0.9 pg/ml, 95% CI 0.6-1.2 pg/ml. The difference to baseline in brain volumes calculated from MRIs was slightly higher (total intracanial volume) or very similar (hippocampal volume) in the lithium group compared to placebo (Figure 3B+C) with a calculated difference of -1020 mm^3, 95% CI -2670 – 630 mm^3 (total intracranial volume) and +7mm^3, 95% CI -26 – 40 mm^3 (hippocampal volume), respectively. Assessment of cognitive outcome parameters with the CANTAB battery showed a strong trend towards better performance in the hippocampus dependent tasks such as delayed matching to sample (DMSPC12) and spatial working memory (SWMBE12) (Figure 3D) in favor of the lithium carbonate group.

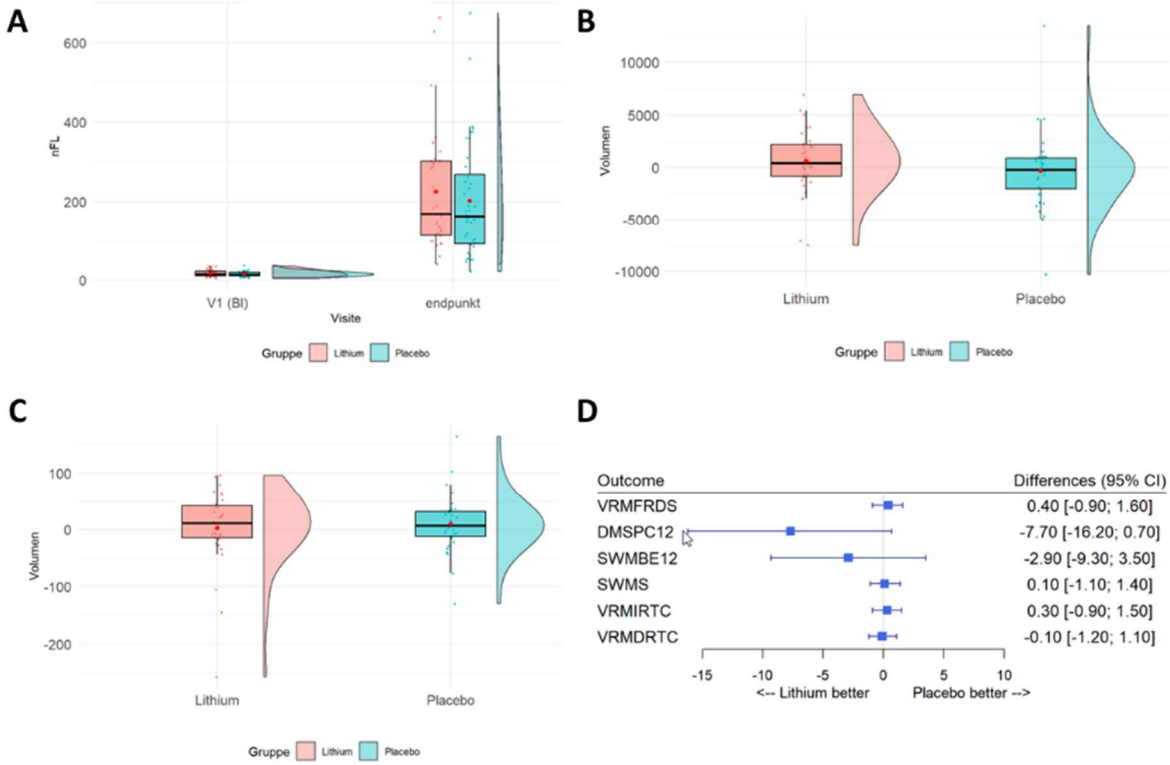

Figure 3: Summary of key secondary endpoints. (A) Serum levels of neurofilament light chain protein after taxane chemotherapy. (B-C) MRI datasets were evaluated and the difference in total brain volume (B) as well as hippocampal volume (C) was calculated. (D) Forest plot of key cognitive outcome parameters measured with the CANTAB test battery: VRMFRDS – Verbal Recognition Memory Free Recall (Delayed), DMSPC12 – Delayed Matching to Sample, Percent Correct (12-second delay), SWMBE12 – Spatial Working Memory Between Errors (12 boxes), SWMS – Spatial Working Memory Strategy, VRMIRTC – Verbal Recognition Memory Immediate Recognition Total Correct, VRMDRTC – Verbal Recognition Memory Delayed Recognition Total Correct.

The rate of patient reported outcome measures (PROM) completion was 77 of 78 (99%) at baseline and 74 of 78 (95%) at the endpoint visit. Patients in the lithium group had a consistently higher global health status (GHS)/Quality of Life (QoL) score assessed by the EORTC QLQ-C30 questionnaire (Figure 4A). Comprehensive analysis of all PROMs and QoL subscales with a mixed effects model was performed for measurements closest to the termination of taxane chemotherapy and is summarized in a forest blot (Figure 4B). The between-group difference in QLQ-C30 global health status was 11 AU (95% CI: -18 – -4) and 14 AU (95% CI: -27 – 0) in the pain subscale, both in favor of the lithium group, which exceeds the established EORTC standards of a minimal clinically important difference. The

latter finding was supported by a lower reported intake of pain medication in the lithium group of 54% vs 70% in the placebo group (10 vs. 9 patients did not provide feedback on the use of pain medication). Indeed, patients in the lithium carbonate group reported better outcomes in all EORTC QLQ-C30 subscales, but effects on the pain subscale and GHS were most pronounced (Figure 4B). We observed a similar trend favoring the lithium group in self-reported symptoms of CIPN as outlined by the total score and sum scorer of the sensory items (Figure 4B). Last, patients in the lithium carbonate group also reported less symptoms of anxiety and depression (PHQ-4 questionnaire), but to a lesser extent.

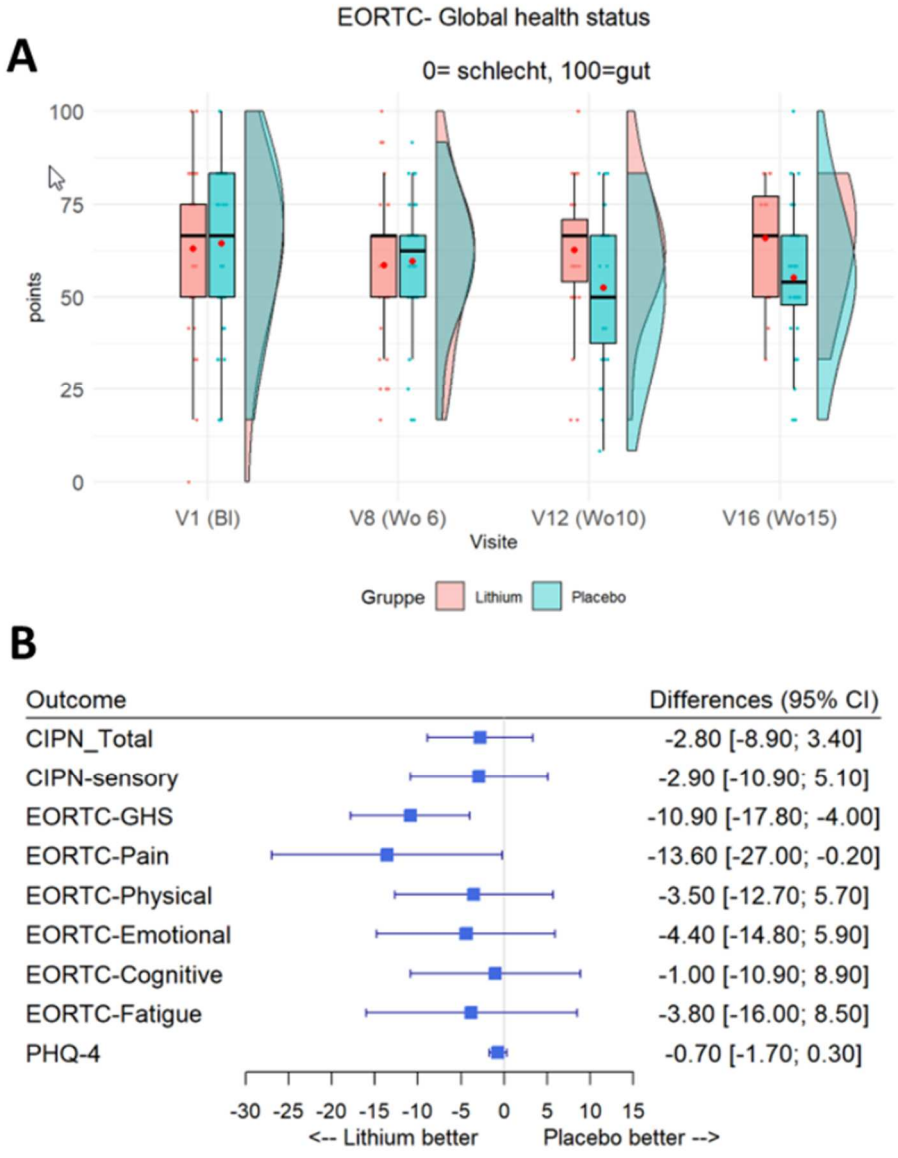

Figure 4: Overview of patient reported outcome measures. (A) Patient-reported quality of life was assessed longitudinally with the EORTC-QLQ-C30. (B) Treatment effects were measured with the EORTC QLQ – CIPN20, EORTC-QLQ-C30 and PHQ-4 questionnaires, and a mixed effects model was calculated for measurements closest to the termination of taxane chemotherapy. Effects were most pronounced in the sub-scales global health status und pain. PHQ-4 values were not transformed to a 0-to-100-point scale as this is not an established procedure.

Safety Results:

Safety analysis was done on all patients who received the trial medication and for whom follow-up data was available. A total of 11 serious adverse events (SAE) were reported in the trial, six in the placebo group and five in the lithium carbonate group, one of which, a