Health-related quality of life and neurocognitive functioning with lomustine–temozolomide versus temozolomide in patients with newly diagnosed, *MGMT*-methylated glioblastoma (CeTeG/NOA-09): a randomised, multicentre, open-label, phase 3 trial

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Summary

Background The CeTeG/NOA-09 trial showed significantly longer overall survival with combined lomustine–temozolomide therapy compared with standard temozolomide for patients with glioblastoma with methylated *MGMT* promoter. The trial also aimed to investigate the effect of lomustine–temozolomide therapy on health-related quality of life (HRQOL) and neurocognitive function, which we report here.

Methods In this randomised, multicentre, open-label, phase 3 trial, newly diagnosed, chemoradiotherapy-naive patients with *MGMT*-methylated glioblastoma, aged 18–70 years, with a Karnofsky performance score of 70% or higher, were recruited and enrolled at 17 university hospitals in Germany. Patients received standard radiotherapy (60 Gy) and were randomly assigned (1:1, stratified by centre by allocating complete blocks of six to a centre, without masking) to either six 6-week courses of oral combined lomustine (100 mg/m² on day 1) plus temozolomide (100–200 mg/m² on days 2–6) or standard oral temozolomide (75 mg/m² daily during radiotherapy plus six 4-week courses of temozolomide [150–200 mg/m²] on days 1–5, every 4 weeks). The primary endpoint was overall survival. HRQOL, assessed using the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire core-30 and the EORTC brain cancer module (BN20); and neurocognitive function, assessed using the Mini Mental State Examination (MMSE), plus a neurocognitive test battery (NOA-07), including Trail Making Test A and B (TMT-A and B), working memory tests, and tests for lexical (Controlled Oral Word Association [COWA]) and semantic verbal fluency, were secondary endpoints analysed in the modified intention-to-treat population (mITT; all randomly assigned patients who received at least one dose of study chemotherapy). We used linear mixed-model analyses to investigate differences between treatment groups regarding HRQOL (clinically relevant ≥10 points) and MMSE scores (clinically relevant ≥3 points). The trial is registered with ClinicalTrials.gov, NCT01149109.

Findings Between June 17, 2011 and April 8, 2014, 141 patients were randomly assigned and 129 patients began treatment and were included in the mITT population (63 in the temozolomide and 66 in the lomustine–temozolomide group). Median follow-up for HRQOL (the item global health) was 19·4 months (IQR 7·8–38·6), for MMSE was 15·3 months (4·1–29·6), and for COWA was 11·0 months (0–27·5). We found no significant impairment regarding any item of HRQOL in the lomustine–temozolomide group (difference between the groups for global health 0·30 [95% CI −0·23 to 0·83]; p=0·26). Differences in MMSE were in favour of the temozolomide group (difference −0·11 [95% CI −0·19 to −0·03]; p=0·0058) but were not clinically relevant (1·76/30 points over 4 years). We found no significant difference between the groups in any subtest of the neurocognitive test battery (difference for COWA 0·04 [95% CI −0·01 to 0·09]; p=0·14).

Interpretation The absence of systematic and clinically relevant changes in HRQOL and neurocognitive function combined with the survival benefit of lomustine–temozolomide versus temozolomide alone suggests that a long-term net clinical benefit exists for patients with newly diagnosed glioblastoma with methylation of the *MGMT* promoter and supports the use of lomustine–temozolomide as a treatment option for these patients.

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Research in context

Evidence before this study

We searched PubMed with no restrictions, using the terms "glioblastoma" and "randomised trial". Based on the results from a randomised, phase 3 trial, treatment with radiotherapy (60 Gy) and temozolomide chemotherapy became the standard treatment for first-line glioblastoma therapy. Following an encouraging phase 2 trial, the randomised, phase 3 CeTeG/NOA-09 trial reported a survival benefit for patients with newly diagnosed glioblastoma with methylated *MGMT* promoter who were treated with radiotherapy and combined lomustine-temozolomide chemotherapy compared with standard temozolomide therapy. The intensified lomustine-temozolomide chemotherapy regimen was associated with a moderate increase in adverse events such as haematotoxicity, nausea, and CNS adverse events. However, no detailed data are yet available on the effect of lomustine-temozolomide on patient-reported health-related quality of life (HRQOL) and on neurocognitive function, either during therapy or in long-term follow-up.

Added value of this study

This study provides prospective data on HRQOL and neurocognitive function in patients with glioblastoma with methylated *MGMT* promoter treated with lomustine-temozolomide combination therapy. Long-term HRQOL was not impaired by lomustine-temozolomide combination therapy. Extensive neurocognitive testing showed no systematic or clinically relevant differences between treatment groups.

Implications of all the available evidence

Radiotherapy plus lomustine-temozolomide combination therapy has a survival benefit when compared with treatment with radiotherapy plus temozolomide alone in patients with glioblastoma with methylated *MGMT* promoter. Although this combination therapy is associated with an increase in some adverse events that might be mirrored in the transient impairment of HRQOL, the absence of a long-term detrimental effect that is clinically relevant on HRQOL and neurocognitive functioning supports the notion of a long-term net clinical benefit mediated by lomustine-temozolomide and encourages the use of this combination in therapy in patients with glioblastoma with methylated *MGMT* promoter.

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Introduction

Glioblastoma is the most common brain tumour and has a dismal prognosis. Patients with a tumour with a methylated *MGMT* promoter are more amenable to alkylating chemotherapy than are those without methylation, leading to a significantly longer overall survival in patients with this alteration treated with alkylating chemotherapy.[1–3] The randomised, phase 3 CeTeG/NOA-09 trial[4] showed that patients with a methylated *MGMT* promoter had further increased survival with the application of an intensified alkylating regimen: with combined lomustine–temozolomide therapy, median overall survival was increased from 31·4 months with standard temozolomide to 48·1 months with the combination (hazard ratio [HR] 0·60 [95% CI 0·35–1·03]). Tolerability of the combined lomustine–temozolomide was good, despite moderately increased haematotoxicity and slightly increased nausea, alopecia, and neurological symptoms.[4]

However, therapy for patients with glioblastoma remains far from curative. Therefore, any extension of survival must be carefully weighed against the potential negative treatment effects on the patient's independence and health-related quality of life (HRQOL).[5] Furthermore, neurocognitive functioning is increasingly recognised as an important outcome measure and might be negatively affected by treatment and the tumour itself.[6] An intensified alkylating treatment could result in reduced tolerability[7] and potential long-term neurocognitive sequelae. There-fore, the effect of combined lomustine–temozolomide combination therapy on patients' HRQOL and neuro-cognitive functioning was a secondary endpoint of the CeTeG/NOA-09 trial. Here, we present the results of HRQOL assessments and neurocognitive functioning in CeTeG/NOA-09, documented over the whole course of the disease.

Methods

Study design and participants

The CeTeG/NOA-09 study design has been previously published.[4] Briefly, this randomised, multicentre, open-label, phase 3 trial enrolled patients from 17 university hospitals in Germany (appendix p 15) aged 18–70 years with newly diagnosed, histologically confirmed, chemotherapy-naive, *MGMT*-methylated glioblastoma, and a Karnofsky performance score (KPS) of at least 70%. The trial protocol is available online. All patients provided written informed consent and the study was approved by the ethics committees of all participating centres. All trial activities adhered to the principles of the Declaration of Helsinki and the guidelines for Good Clinical Practice.

See **Online** for appendix

For the **trial protocol** see https://neurologie.uni-bonn.de/sektionen/klinische-neuroonkologie/therapiestudien.htm

Randomisation and masking

Patients were randomly assigned (1:1) to receive either combined lomustine–temozolomide chemotherapy or standard temozolomide chemotherapy. As previously described,[4] the randomisation list was generated using SAS (Rolf Fimmers, Institute for Medical Biometry, Informatics, and Epidemiology, University Hospital Bonn, Bonn, Germany) and kept at the Clinical Study

Core Unit of the Study Center Bonn without access for any personnel involved in patient treatment at the local sites, including the principal investigator (PI) or any personnel from the trial site in Bonn. Randomisation was done with a block size of six and was stratified for centre by allocating complete blocks to a centre. The trial sites contacted the team of the Clinical Study Core Unit by fax for randomisation. This team checked crucial inclusion and exclusion criteria listed on the randomisation fax form, then the trial site received a fax with the randomisation details, including allocation to treatment group. Every randomisation was documented, including the person who did the randomisation at the Clinical Study Core Unit. Because of the different schedules for application of combined lomustine–temozolomide (6-week courses) and standard temozolomide (4-week courses), the masking of patients, treating physicians, and investigators was not possible. The only part of the trial that was masked was the final analysis of MRIs for the assessment of progression.

Procedures

All patients were planned to receive standard focal radiotherapy (60 Gy in 2 Gy fractions). Patients additionally received either standard oral temozolomide (concomitant with radiotherapy daily 75 mg/m² followed by six courses of 150–200 mg/m² for 5 days, every 4 weeks),[9] or six 6-week courses of oral combined lomustine–temozolomide (lomustine 100 mg/m² on day 1, temozolomide 100–200mg/m², on days 2–6). Rules for dose adaptation and premature removal of patients from the study have been described previously.[4] Briefly, the temzolomide dose was escalated stepwise from 100 mg/m² per day to 120 mg/m² per day, 150 mg/m² per day, and 200 mg/m² per day in subsequent courses, if no substantial haematological or organ toxicity had ensued in previous courses. Patients were taken off study therapy in case of a delay of the next course for more than 6 weeks or non-haematological grade 3 or 4 toxicity (according to the Common Terminology Criteria for Adverse Events, version 4.0). All patients were followed up with clinical examination and contrast-enhanced MRI every 3 months.

HRQOL was measured at baseline and every 3 months throughout the trial, irrespective of disease progression and further second-line therapies, using the German translation of the validated European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire core 30 (QLQ-C30; items were global health, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties) and the EORTC brain tumour module (BN20; items were future uncertainty, visual disorder, motor dysfunction, communication deficit, headache, seizure, drowsiness, itchy skin, hair loss, weakness of legs, and bladder control).[10–12] These paper-based questionnaires were completed by patients without assistance before seeing the physician and discussing examination results, treatments, and perspectives. The items were scaled and scored according to the algorithm described in the EORTC scoring manual.[13] Raw scores were aggregated and transformed to a linear scale from 0 to 100. A higher score represents a higher level of functioning on function scales and a higher burden of symptoms on symptom scales. Differences of at least ten points were judged to be clinically meaningful.[14,15]

To screen for general cognitive function deficits, the Mini-Mental State Examination (MMSE) was used every 3 months to assess orientation, memory, attention, recall, language, and visual construction, with a maximum total score of 30 points.[16] Although developed for detecting dementia in older people and deemed less adequate for patients with brain tumours, MMSE was used to provide longitudinal screening data quickly.[6] Following previous reports, an MMSE score of 26 or lower was the cutoff for impaired function.[17] Differences of at least three points were regarded as clinically meaningful.[17,18]

More detailed neurocognitive testing was done with a set of standardised psychometric instruments used previously (NOA-07 battery).[19] Trail Making Tests (TMTs; parts A and B) were used to measure visual exploration, speed of processing, mental flexibility, and executive functions.[20] Working memory was measured with the digit span forward and backward from the Wechsler Adult Intelligence Scale–revised (German version).[21] The German version of the Controlled Oral Word Association (COWA) test was used to measure lexical verbal fluency and the Regensburger Wortflüssigkeitstest was used for the analysis of semantic verbal fluency (using the categories animals and food items).[22] The raw scores were measured in seconds for TMT parts A and B, number of digits for digit span forward and backward, and number of words for COWA and semantic fluency. Raw scores were transformed into *Z* scores using normative data from a healthy control population (mean 0, SD 1) matched for age and sex. Higher *Z* scores indicated better performance. Detailed neurocognitive testing was done every 6 months throughout the trial.

KPS, a 100-point scale grading performance of activities of daily life, as rated by the treating physician or study nurse, was recorded as a general parameter that was associated with physical functioning and assistance needed in daily life. KPS was scored at baseline and at least every 3 months during the whole period of the study, irrespective of disease progression and further second-line therapies.

Outcomes

The primary endpoint, overall survival, and secondary endpoints of progression-free survival, best response as measured by modified Response Assessment in Neuro-Oncology criteria in patients with incomplete tumour resection and documented post-operative

residual disease, frequency of delay of the next chemotherapy course by more than 2 weeks, and acute toxicity have already been reported.[4] Additional secondary endpoints reported here are assessment of differences between the two treatment groups over time in HRQOL by EORTC-QLQ-C30 and EORTC-BN20, and in neurotoxicity by MMSE and the NOA-07 battery.

Statistical analysis

The sample size was calculated on the basis of the assumption that combined lomustine–temozolomide could increase 2-year overall survival from 48·9% to 70·0%; the trial thus had to recruit 128 eligible patients.[4] The trial was not powered for the secondary endpoints reported here.

The analyses of HRQOL and neurocognitive functioning endpoints reported here were prespecified secondary analyses to generate hypotheses on the long-term effect of therapy on HRQOL and neurocognition. The assessment in changes in KPS was added as a post-hoc analysis. Stratification factors for multivariable time-to-event analyses were recursive partitioning analysis (RPA) class and centre.[8] The primary target population for analysis, the modified intention-to-treat population (mITT), included all randomly assigned patients who received at least one dose of study chemotherapy. An analysis regarding the characteristics of patients for whom no HRQOL data were available at baseline (selection bias analysis) was done post-hoc.

To assess differences between the two treatment groups over time regarding HRQOL, KPS, MMSE score, or neurocognitive data, a linear mixed-model analysis based on mean change from baseline (post-hoc decision) was done using treatment group and time-to-treatment interaction as fixed effects and patient and respective item as random effects. P values were derived from the test on treatment to time interaction in the linear mixed model analysis. The threshold for significance was set at $p<0·05$. An additional Hochberg procedure to adjust for multiple testing was done post-hoc for results obtained from ten items of interest. These ten items were selected post-hoc and included six HRQOL items: global health, physical functioning, social functioning, cognitive functioning, communication deficit, and motor dysfunction. These items are the same as those that had been selected for the analysis of the GLARIUS trial and included five items that were selected in AVAGlio to facilitate comparison.[23,24] The items also included KPS, MMSE, and two items from neurocognitive testing, TMT-B and COWA. Further exploratory linear mixed model analyses also investigated the changes in these parameters over the first year after randomisation when acute adverse events that are potentially attributable to chemotherapy could occur.

Time to first deterioration (defined as the time from randomisation to the timepoint with a decrease of function scale score or increase of symptom scale score by at least ten points from baseline without further improvement)[24] was assessed for HRQOL as a post-hoc analysis. Death for any reason was regarded as an event but tumour progression alone, as assessed by central neuroradiological assessment, was not. For neurocognitive testing, KPS, and MMSE, time to first deterioration analysis is not well established and therefore, was not done. Time to first deterioration was analysed as univariable Cox regression analysis and, as a sensitivity analysis, as multivariable Cox regression analysis with RPA class, centre, and the interaction between the two, as additional covariates to achieve consistency with the primary endpoint survival analysis. P values were calculated with a Wald χ^2 test of the regression parameter in the Cox regression analysis. All analyses were done using SAS (version 9.4). This study is registered with ClinicalTrials.gov, NCT01149109.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. After database lock, UH, NS, JW, and RF had access to all trial data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between June 17, 2011, and April 8, 2014, 141 patients were enrolled and randomly assigned (69 to temozolomide and 72 to combination lomustine–temozolomide) and followed up until April 8, 2017 (the planned end of the trial). 129 patients received at least one dose of study treatment: 63 in the temozolomide group and 66 patients in the combined lomustine–temozolomide group (figure 1). Patient characteristics and analysis of survival parameters and safety have already been published.[4] Briefly, baseline characteristics were similar between treatment groups and most patients in both groups had favourable prognostic factors, such as a KPS of 90% or higher (49 [78%] of 63 in the temozolomide group and 57 [86%] of 66 patients in the lomustine–temozolomide group) and macroscopic complete resection (40 [63%] patients in the temozolomide group and 39 [59%] in the lomustine–temozolomide group).

Compliance for the assessment of HRQOL and neurocognitive functioning was high at baseline and decreased over time (appendix pp 2, 6–8). For the clinician-rated KPS, data were available for 128 (99%) of 129 patients at baseline and for 70% or more patients over 4 years (appendix p 2). For HRQOL questionnaires, the proportion of surviving patients providing HRQOL data remained above 60% for 2 years, eventually decreasing slightly below 50% after 3·5 years (appendix p 2). HRQOL questionnaire compliance was similar between treatment groups. For cognitive screening with MMSE, availability was 126 (98%) of 129 patients at baseline, decreasing to 68 (62%) of 110 patients after 1 year and remaining

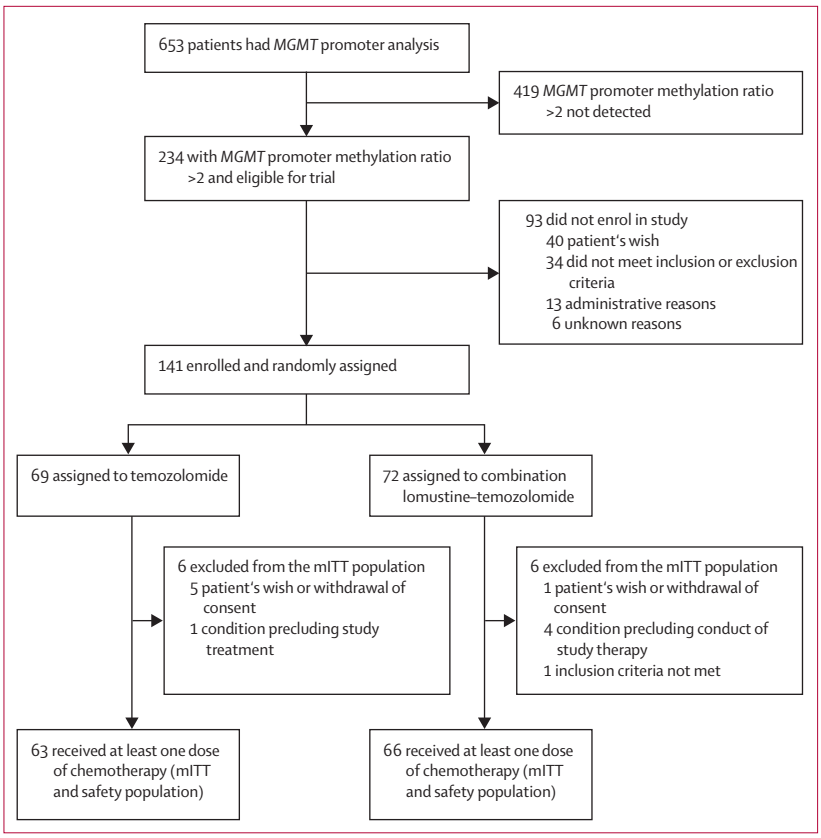

Figure 1: **Trial profile**
mITT=modified intention to treat population (all patients as randomised who received at least one dose of study chemotherapy).

around 50% from year 2 to 4 (appendix p 2). Compliance for detailed neurocognitive testing was lower: 120 (93%) of 129 patients at baseline, 72 (60%) of 121 at 6 months, and 63 (57%) of 110 at 12 months contributed. From month 30 after randomisation, both groups had about 30% compliance of expected assessments (appendix p 2). Median follow-up for HRQOL (the item global health) was 19·4 months (IQR 7·8–38·6), for MMSE was 15·3 months (4·1–29·6), and for COWA was 11·0 months (0–27·5). The median follow-up time for each of the 35 items is summarised in the appendix (p 9).

The characteristics of patients (eg, extent of resection, *IDH* status, RPA class) who did not complete baseline HRQOL and neurocognitive functioning testing did not significantly differ from those of patients who did contribute (appendix p 10). Of 12 patients who were randomly assigned but were excluded from the mITT population (figure 1), six (50%, three per treatment group) had HRQOL and neurocognitive functioning baseline data but none provided any data beyond baseline. Thus, sensitivity analyses of HRQOL and neurocognitive functioning in the ITT population were not done.

Mean changes from baseline in scores of the ten selected items (post-hoc selection) of interest (KPS; the HRQOL items global health, physical functioning, social functioning, cognitive functioning, communication deficit, and motor dysfunction; MMSE, neurocognitive functioning items TMT-B and COWA) over a period of 4 years is shown in figure 2. Additionally, the appendix (pp 3–5) shows the developement of the absolute scores of all 26 HRQOL domains, KPS, MMSE, and seven items of neurocognitive functioning.

MMSE scores decreased from baseline for patients in the lomustine–temozolomide group at three timepoints (12, 21, and 39 months) but not for patients in the temozolomide group (figure 2). Three patients had very low scores at these timepoints (1, 7, and 5); all three patients were in the lomustine–temozolomide group and had progressive disease at the time of MMSE testing and two of three patients died because of tumour progression within 4 months after the last measurement. Both treatment groups had average results from detailed neurocognitive testing below the average level of healthy controls (ie, level 0 in the neurocognitive functioning items [appendix p 5]) at baseline and at most follow-up timepoints.

The results of the linear mixed-model analysis for the ten items of interest are shown in table 1. For KPS, the six HRQOL items, as well as the neurocognitive functioning items TMT-B and COWA, no significant differences between treatment groups were observed. For MMSE scores, an advantage in favour of the temozolomide group, with a difference of of 0·11 points (95% CI 0·03–0·19) per 3 months; however, this difference was no longer significant after accounting for multiple testing (table 1). Applying the Hochberg procedure to account for multiple testing, the difference in MMSE score development between treatment groups was not significant (p=0·0058, adjusted alpha significance level 0·0050). The differences in MMSE scores were not clinically relevant since they did not meet the threshold (1·76/30 points over the observation time of 4 years).[17,18]

The results of the linear mixed model analysis of all other items are summarised in the appendix (p 11) and were studied on an exploratory basis at 5% significance level without adjustment for multiple testing. Of these, only the difference between groups (in favour of the lomustine–temozolomide group) for the domain pain reached an extent that can be associated with clinical relevance (19·4/100 points over 4 years).

In an exploratory, post-hoc, univariable analysis, we also assessed the time to first deterioration for the six HRQOL items of interest (table 2) and the other 20 HRQOL items (appendix p 12). In all HRQOL dimensions of the EORTC-QLQ-C30 and BN20 questionnaires, we found no significant differences regarding time to first deterioration (ie, a 10-point increase in symptom scores or decrease in functioning scores) between the two treatment groups in the univariate analysis. Multivariable analyses with

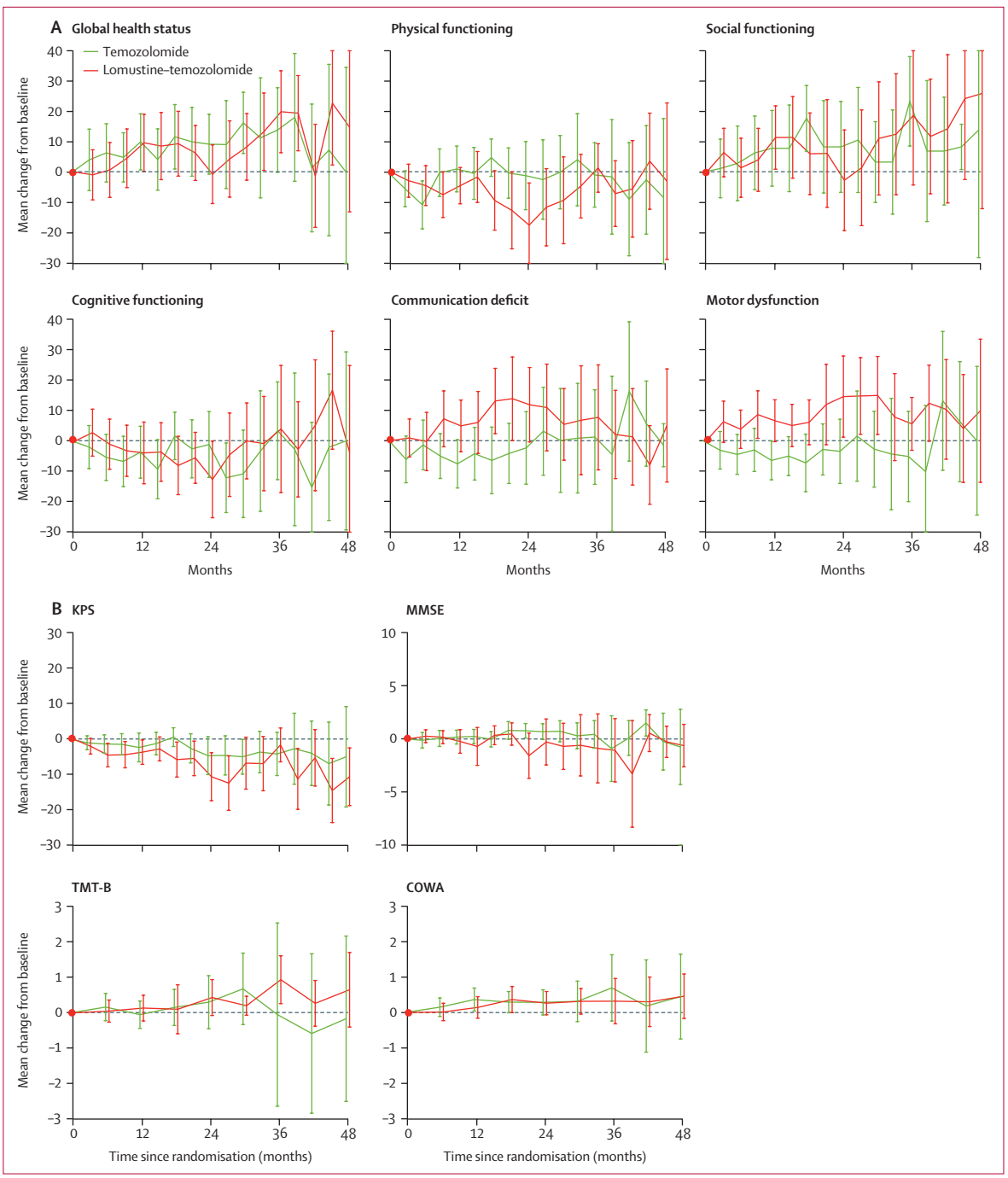

Figure 2: **Change from baseline of selected QOL domains during 4 years after randomisation**
(A) Selected items from the EORTC-QLQ-C30 and the EORTC-BN20 HRQOL questionnaires. (B) KPS, MMSE, TMT-B, and COWA. Error bars are standard deviation. For symptom scores (communication deficit and motor dysfunction), a high score represents a high symptom burden; for all other scores, including KPS, MMSE, TMT-B, COWA, and functional scores, a high score represents a high functional level. EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer quality of life questionnaire core-30. BN20= brain cancer module. KPS=Karnofksy performance score. MMSE=Mini Mental State Examination. TMT-B=Trail Making Test B. COWA=Controlled Oral Word Association.

stratification for centre and RPA class and their interaction were done in analogy to the primary end-point survival analysis[4] and supported these findings (appendix p 13).

In an exploratory, post-hoc analysis to assess changes in HRQOL and neurocognitive functioning during the first year when compliance was highest and the immediate influences of acute toxicity due to

	Slope			p value	α level*
	Temozolomide	Lomustine–temozolomide	Difference (95% CI)		
KPS	−0·45	−0·64	−0·19 (−0·46 to 0·08)†	0·17	0·025
Global health	−0·32	−0·02	0·30 (−0·23 to 0·83)‡	0·26	0·030
Physical functioning	0·01	−0·37	−0·39 (−0·89 to 0·12)†	0·13	0·015
Cognitive functioning	−0·50	−0·43	0·07 (−0·52 to 0·66)‡	0·82	0·050
Social functioning	−0·15	−0·07	0·08 (−0·58 to 0·74)‡	0·82	0·045
Communication deficit	0·79	0·63	−0·17 (−0·68 to 0·35)‡	0·53	0·035
Motor dysfunction	0·68	0·78	0·10 (−0·44 to 0·64)†	0·72	0·040
MMSE	0·08	−0·03	−0·11 (−0·19 to −0·03)†	0·0058	0·0050
TMT-B	−0·12	−0·04	0·08 (−0·02 to 0·17)‡	0·12	0·010
COWA test	−0·06	−0·02	0·04 (−0·01 to 0·09)‡	0·14	0·020

The analysis was done considering all data obtained throughout the trial: KPS, six EORTC quality-of-life questionnaire C30 and BN20 HRQOL domains, MMSE, and two domains of neurocognitive functioning. Slope is the change in points per 3 months (for KPS, MMSE, and HRQOL items) and change in *Z* score per 6 months (for TMT-B and COWA tests). EORTC=European Organisation for Research and Treatment of Cancer. HRQOL=health-related quality of life. KPS= Karnofsky performance score. MMSE=Mini Mental State Examination. TMT-B=Trail Making Test B. COWA=controlled oral word association. *Respective significance level adjusted for multiple testing. †Advantage for temozolomide group. ‡Advantage for lomustine–temozolomide group.

Table 1: **Linear mixed model analysis based on mean changes from baseline for ten selected items**

	Median time to deterioration (months)		Cox regression analysis		
	Lomustine–temozolomide (95% CI)	Temozolomide (95% CI)	Hazard ratio (95% CI)	p value	α level*
Global health status	29·3 (20·5–40·5)	23·9 (16·2–33·6)	0·91 (0·59–1·42)	0·68	0·017
Physical functioning	19·4 (9·6–27·5)	23·9 (15·7–31·3)	1·08 (0·70–1·66)	0·73	0·025
Social functioning	25·2 (15·8–32·5)	22·6 (11·1–28·8)	0·83 (0·54–1·28)	0·41	0·0083
Cognitive functioning	16·6 (9·5–26·7)	19·3 (8·4–23·9)	0·94 (0·62–1·44)	0·79	0·033
Communication deficit	4·8 (2·9–9·3)	6·0 (2·9–11·4)	1·04 (0·69–1·55)	0·86	0·042
Motor dysfunction	4·4 (2·9–6·6)	5·7 (3·2–9·0)	0·99 (0·66–1·47)	0·94	0·050

The analysis included six selected items from the EORTC quality-of-life questionnaire core 30 and the EORTC brain tumour module (BN20) health-related quality of life items. EORTC=European Organisation for Research and Treatment of Cancer. *Respective significance level adjusted for multiple testing.

Table 2: **Time to deterioration analysis of quality of life**

chemotherapy could be seen (duration of chemotherapy about 9 months), we did a linear mixed model analysis based on mean changes from baseline. In the group of ten items of interest and after adjustment for multiple testing, we found a significant difference between treatment groups only for the item physical functioning in favour of the temozolomide group (table 3). The difference (7·24 points) did not reach clinical relevance, which would require a difference of at least 10·0 points.[14,15] For all other items of HRQOL and neurocognitive functioning, we found significant differences (without correction for multiple testing) in two items (fatigue, digital span forward) in favour of the lomustine–temozolomide group and in four items (role functioning, insomnia, appetite loss, and drowsiness) in favour of the temozolomide group (appendix p 14).

Discussion

The analysis of the long-term changes of HRQOL, KPS, and neurocognitive functioning throughout the CeTeG/NOA-09 trial did not reveal systematic significant or clinically relevant differences between the patients who received combined lomustine–temozolomide and those who received temozolomide alone.

In linear mixed model analyses of six selected items of HRQOL, we found no long-term negative effect of intensified combined lomustine–temozolomide chemotherapy on HRQOL. Overall, this finding supports the notion that the life-prolonging treatment effect of the combination therapy does not come at the expense of a deterioration of patient-reported HRQOL. Notably, the complementary time to first deterioration (without subsequent improvement) analysis also did not reveal differences between the two groups of the trial. Taken together, the results of the linear mixed model using all values obtained throughout the trial (planned analysis of HRQOL) and the time to first deterioration analysis (exploratory analysis) showed that the combination treatment with combined lomustine–temozolomide did not adversely affect HRQOL. The broad distribution of 95% CI

	Slope			p value	α level*
	Temozolomide	Lomustine–temozolomide	Difference (95% CI)		
KPS	1·93	0·09	−1·85 (−3·66 to −0·03)†	0·048	0·010
Global health	2·88	1·85	−1·02 (−5·74 to 3·70)†	0·67	0·040
Physical functioning	9·97	2·73	−7·24 (−11·16 to −3·32)†	0·00040	0·0050
Cognitive functioning	−1·72	−1·26	0·46 (−2·69 to 3·61)‡	0·78	0·050
Social functioning	8·59	3·05	−5·54 (−11·21 to 0·12)†	0·057	0·015
Communication deficit	−3·85	0·23	4·08 (−0·86 to 9·02)†	0·11	0·020
Motor dysfunction	−2·14	0·02	2·16 (−2·55 to 6·87)†	0·37	0·035
MMSE	0·36	0·09	−0·26 (−0·69 to 0·16)†	0·23	0·025
TMT-B	-0·08	−0·02	0·07 (−0·44 to 0·58)‡	0·80	0·045
COWA test	0·07	0·08	0·01 (−0·31 to 0·33)‡	0·95	0·050

This analysis was restricted to year 1 after randomisation and based on mean changes from baseline for ten selected items: six items from the EORTC quality-of-life questionnaire core 30; the BN20 HRQOL domains KPS and MMSE; and two domains of neurocognitive functioning. Slope is the change in points per 3 months (for KPS, MMSE, and HRQOL items) and change in *Z* score per 6 months (for TMT-B and COWA tests). EORTC=European Organisation for Research and Treatment of Cancer. HRQOL=health-related quality of life. KPS=Karnofsky performance score. MMSE=Mini Mental State Examination. TMT-B=Trail Making Test B. COWA=Controlled Oral Word Association. *Respective significance level adjusted for multiple testing. †Advantage for the temozolomide group. ‡Advantage for the lomustine–temozolomide group.

Table 3: **Linear mixed model analysis for changes from baseline during the first year after randomisation**

values in the linear mixed model analyses suggests that for most domains of HRQOL (except for physical functioning), even a substantial increase of patient numbers would probably not have led to significant effects.

Long-term neurocognitive functioning, as measured by linear mixed model analysis, was also not reduced in the lomustine–temozolomide group in a clinically relevant manner. In-depth neurocognitive testing did not show any significant differences. The MMSE results showed differences that were in favour of the temozolomide group; however, they were not significant when adjusted for multiple testing and were also not clinically relevant, because even over the time course of 4 years the differences between the groups would only add up to 1·76/30 points and clinically significant results would require a difference of more than 3/30 points.[17,18]

The exploratory, post-hoc analysis of HRQOL and neurocognitive functioning in the first year after randomisation—ie, during ongoing radiotherapy and chemotherapy—was done to investigate whether changes existed in HRQOL domains that might reflect adverse events reported during that time. In the lomustine–temozolomide group, there was a moderate increase in the number of adverse events related to haematotoxicity and CNS dysfunction.[4] The finding of a worse HRQOL for the domain physical functioning in the lomustine–temozolomide group compared with the temozolomide group might give an indication that some short-term negative influence on physical functioning can be detected by adverse event documentation as well as results from HRQOL questionnaires. Unsurprisingly, the increased haematotoxicity is not mirrored in HRQOL changes in the first year after randomisation because haematotoxicity has little effect on HRQOL unless requiring medical intervention (eg, in case of infection). The proportion of adverse events from infections, however, was not clearly increased in the lomustine–temozolomide group.[4] The summary of the data on HRQOL in the first year after randomisation and adverse events suggests that a transient effect of combined lomustine–temozolomide on CNS dysfunction is possible. These parameters were not affected in long-term mixed model analyses nor in time to first deterioration analyses because an event in the time to first deterioration analysis requires the absence of a further complete re-improvement and transient deteriorations would thus not qualify as an event. A potential transient increase of CNS dysfunction could be related to undetected late and prolonged pseudo-progressions associated with higher cytotoxic efficacy of the combined lomustine–temozolomide regimen.[4,25] This issue will need particular attention in future studies of lomustine–temozolomide combination therapy.

Our HRQOL and neurocognitive functioning analyses have limitations. First, the trial is a relatively small phase 3 trial, as extensively discussed in the previous publication on survival parameters.[4] Second, after 3·5 years' follow-up, approximately 50% of expected HRQOL forms were missing. This finding urges careful interpretation of the data on the long-term follow-up and reduces generalisability because the linear mixed model analysis might be less precise and more biased as missing data increases. Notably, the compliance of surviving patients for providing HRQOL data after more than 12 months was higher than was that of other large glioblastoma trials,[24,26,27] and similar to that of low-grade glioma trials.[28] This finding might allow a robust and reliable interpretation of the HRQOL assessment in the CeTeG/NOA-09 trial. Nevertheless, patients with better prognostic factors and treatment response are inevitably

overrepresented at later timepoints. Because non-reporting patients might have had a different HRQOL than that of reporting patients, some degree of selection bias is likely.[29] Third, the problem of missing values is accentuated for the neurocognitive functioning measurements because compliance was much lower for neurocognitive functioning assesment than it was for HRQOL and lower than in a previous glioblastoma study.[26] Nevertheless, neuro-cognitive functioning assessments were available for 4 years, which is a long time for a glioblastoma trial. More frequent testing might have been beneficial to increase awareness for neurocognitive functioning testing in study sites, but might have introduced more influence of practice effects because we did not use alternative test versions. Overall, although missing data might impede our ability to individually predict HRQOL and neurocognitive risk for future patients treated with combined lomustine–temozolomide or temozolomide monotherapy, such gaps are unlikely to affect our conclusion regarding no difference between the groups because the amount of missing data was similar for both treatment groups. Fourth, as is typical for analyses of HRQOL and neurocognitive functioning, the multiplicity of the items is another limitation. Similar to previous publications on HRQOL in patients with glioma,[24,26–28] we tried to solve this problem by selecting items of particular interest. Nevertheless, this was a post-hoc selection, thus reducing our ability to make strong conclusions. Fifth, HRQOL and neurocognitive functioning are secondary endpoints and no confirmatory analysis was intended. Analyses of HRQOL and neurocognitive functioning were not done to provide further data on efficacy of the combined lomustine–temozolomide regimen but were rather part of an extended safety analysis looking for indications of late HRQOL-reducing neurotoxicity. In that regard, these analyses were primarily meant to generate hypotheses for further studies, particularly the analyses of time to first deterioration and HRQOL 1 year after randomisation, which were introduced post-hoc and therefore preclude strong conclusions. Sixth, the strength that CeTeG/NOA-09 is able to provide HRQOL and neurocognitive functioning data over a time span of 4 years, much longer than that of other glioblastoma trials, might also introduce a limitation. With a median progression-free survival time of about 17 months, HRQOL and neurocognitive functioning might be substantially influenced by second-line therapies as confounding factors.

Overall, we conclude that the addition of lomustine to temozolomide in patients with newly diagnosed *MGMT*-methylated glioblastoma is associated with a clear long-term net clinical benefit and our data provide a good rationale for the trial regimen as a treatment option for these patients. Nevertheless, changes in HRQOL during the first year after beginning treatment needs further exploration in future studies.

Contributors

UH, MS, RF, CC, and MG were responsible for the design of the trial. JW, TT, FM, JPS, US, PH, DK, OG, RG, OB, MU, CS, GT, SB, LB, NG, CS, SK, WS, MS, MG, UH, and NS contributed to patient recruitment, treatment, and data collection. CC provided administrative support. JW, RF, UH, and NS did the data analysis and writing of the first drafts. All authors approved the final version of the manuscript.

Declaration of interests

JPS reports grants from Merck; personal fees and other support from Roche, Medac, and Bristol-Myers Squibb; and personal fees from Boehringer and Mundipharma, outside of the submitted work. US reports other support from Medac, Schering Plough, Roche, Novocure, GlaxoSmithKline, and Novartis, outside of the submitted work. PH reports personal fees and non-financial support from Medac; and personal fees from AbbVie, Bristol-Myers Squibb, and Novocure, outside of the submitted work. OG reports personal fees from Roche and Gilead Sciences; and personal fees and non-financial support from MagForce and Bristol-Myers-Squibb, outside of the submitted work. CS reports personal fees from Roche, outside of the submitted work. GT reports personal fees from Bristol-Myers Squibb, Novocure, and Medac, outside of the submitted work. LB reports personal fees and non-financial support from Bristol-Myers Squibb; personal fees from Novartis, Jazz Pharmaceuticals, and Pfizer; grants and personal fees from Sanofi; and non-financial support from Amgen, outside of the submitted work. MG reports personal fees from Novartis, Bayer, Novocure, Medac, Kyowa Kirin, Roche, Abbvie, and Daiichi Sankyo, outside of the submitted work. UH reports grants from the German Federal Ministry of Education and Research, during the conduct of the study; grants and personal fees from Roche; personal fees and non-financial support from Medac and Bristol-Myers Squibb; personal fees from Novocure, Novartis, Daichii Sankyo, Riemser, Noxxon, AbbVie, and Bayer, outside of the submitted work. NS reports personal fees and other support from Roche, outside of the submitted work. All other authors declare no competing interests.

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