Clinical Study Protocol

Phase III trial of CCNU/temozolomide (TMZ) combination therapy vs. standard TMZ therapy for newly diagnosed MGMT-methylated glioblastoma patients (CeTeG)

EUDRACT Number: 2009-011252-22

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PROTOCOL AUTHORIZATION

28.1.16
Date

Prof. Dr. med. Ulrich Herrlinger
Vertreter des Sponsors

28.1.16
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Participating centers

The multicenter CeTeG trial is performed at 17 centers throughout Germany. A comprehensive list of all participating centers with the responsible local principal investigators is part of appendix 4 and is continuously updated.

Financial Support

This trial is supported by a grant of the German Federal Ministry for Education and Research.

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SYNOPSIS

Study Title	Phase III trial of CCNU/temozolomide (TMZ) combination therapy vs. standard TMZ therapy for newly diagnosed MGMT-methylated glioblastoma patients (CeTeG)
Study population	Newly diagnosed patients with glioblastoma harbouring a methylated MGMT promoter
Rationale	The prognosis of patients with glioblastoma (GBM) is dismal. The addition of temozolomide (TMZ) to the treatment protocol has significantly improved the outcome from a median overall survival (mOS) of 12.5 months to a mOS of 14.6 months (Stupp et al., 2005). In a previous non-randomized bicentric phase II trial, primary combination chemotherapy with lomustine (CCNU) and TMZ was highly effective (mOS 23 months; UKT-03 trial; Herrlinger et al., 2006; Glas et al., 2009) and warrants further investigation. Thus, the CeTeG trial further investigates the efficacy of CCNU/TMZ in a randomized multicenter phase III setting against standard therapy. Since in the previous trial only patients with a methylated MGMT (mMGMT) promoter had benefit from CCNU/TMZ (mOS in the mMGMT group 34 months, in the non-mMGMT group 12.5 months; Glas et al., 2009) the trial is restricted to mMGMT patients.
Sponsor	Rheinische Friedrich-Wilhelm-University of Bonn, represented by the Faculty of Medicine of the University of Bonn, represented by the Dean of the Medical Faculty Prof. Prof. Dr. med. Nicolas Wernert, Sigmund-Freud-Str. 25, D-53105 Bonn
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Number of study centers	17
Study Design / Development phase	Prospective, open-label, randomized, multicenter phase III study
Objective	To analyze whether combined CCNU/TMZ therapy is superior to standard TMZ regarding efficacy as measured by overall survival
Number of subjects	To be assessed for eligibility n = 658 To be allocated to trial n = 141 To be analyzed n = 128 (ITT)
Investigational products	TMZ (Temozolomide) CCNU (Lomustine)
Treatment plan	After central neuropathology confirmation of glioblastoma and confirmation of a methylated MGMT status, patients are randomized into 2 arms: <u>Experimental arm (CCNU/TMZ arm):</u> 60 Gy standard radiotherapy (RT, 30 x 2 Gy) Six 42-day courses of oral CCNU 100 mg/m^2 (day 1) and oral TMZ 100 mg/m^2 (day 2-6), first CCNU application starting with the first day of RT CCNU/TMZ and radiotherapy start 2-5 weeks after diagnosis (day of surgery for glioblastoma (GBM)). In courses 2-6, TMZ dose are adjusted according to the hematotoxicity observed in the previous course and can be increased stepwise

	up to 200 mg/m^2/day Standard arm (TMZ arm): 60 Gy standard radiotherapy (RT, 30 x 2 Gy) and comcomitant TMZ therapy (daily TMZ 75 mg/m^2) starting with the first day of radiotherapy Six 28-day courses of TMZ (day 1-5) starting 4 weeks after completion of radiotherapy. In the first course TMZ is given at a dose of 150 mg/m^2/day, in case no toxicity is observed, the 2nd course is applied at a daily dose of 200 mg/m^2 Concomitant TMZ and radiotherapy start 2-5 weeks after diagnosis Follow-up per patient: Each patient will be followed until at least 36 months after randomization. Follow-up of all patients ends 36 months after the inclusion of the last patient. All patients in the trial are followed until this time point. Duration of intervention per patient: Experimental arm: 6 courses CCNU/TMZ à 42 days = 9 months Standard arm: 6 weeks radiotherapy + concomitant TMZ, 4 weeks treatment pause, 6 courses of TMZ à 28 days = 8.5 months
Duration of therapy for an individual patient	Experimental arm: A maximum of 6 six-week courses of CCNU/TMZ are applied, so that the duration of treatment for the individual patient ist 36 weeks. Within the trial, the patient is followed for at least 3 years. Standard arm: The concomitant phase of TMZ and RT takes 6 weeks, followed by 4 weeks without therapy, again followed by up to 6 four-weeks courses of standard adjuvant TMZ therapy (24 weeks). This sums up to an overall duration of therapy of 34 weeks. Within the trial, the patient is followed for at least 3 years.
Duration of the trial	The patients in this trial are recruited over a time of 2 years. With a treatment time of 34-36 weeks and a further follow-up time for a total of 3 years after inclusion, the trial will be closed 3 years after inclusion of the last patient. With 6 months time for preparation before inclusion of the first patient and 6 months for data analysis, the whole trial will take 71 months. First patient in to last patient in: ~~33~~ 35 months Duration of the entire trial: 81 71 months
Schedule of events for determination of toxicity and efficacy	• **Screening visit (week 1-3 after resection)**: informed consent for MGMT testing and for neuropathology reference testing • **Baseline visit (week 3 to 5 after resection)**: Informed consent for the trial, I/E criteria, medical history and demographics, vital signs, physical and neurological examination, concomitant medication, Karnofsky PS, Mini-Mental-Status evaluation and neurocognitive testing (NOA-07 test battery), quality of life questionnaire, MRI scan, ECG, spirometry, pregnancy test, complete blood count and CRP, serum chemistry and urine analysis, coagulation, evaluation of preexisting conditions in analogy to CTCAE, randomisation • **At the beginning of each course of CCNU/TMZ or TMZ**: vital signs, physical and neurological examination, concomitant medication, Karnofsky PS, complete blood count and CRP, serum chemistry and urine analysis, coagulation, CTCAE evaluation **Throughout all treatment courses of TMZ and CCNU/TMZ starting with radiotherapy, a differential blood count has to be determined weekly by the general practitioner of each patient. The results have to be faxed to the treating center for review.**

	• **MRI/ progression assessment visits every 12 weeks (+/- 5 days) after randomization during study treatment and follow up until end of study**: vital signs, physical and neurological examination, concomitant medication, Karnofsky PS, Mini-Mental-Status evaluation quality of life questionnaire, contrats-enhanced MRI scan; NOA-07 test battery (only every 24 weeks), complete blood count and CRP, ,serum chemistry and urine analysis, coagulation, CTCAE evaluation evaluation of progression
Primary Endpoint	• Overall survival (OS) as measured from the day of randomization until death
Secondary Endpoints	• Progression-free survival (PFS) as measured from the day of randomization until diagnosis of progressive disease determined by MRI (modified RANO criteria) • Best response rate determined by MRI (modified RANO criteria) • Frequency of delay of the next CCNU/TMZ or TMZ course by more than 2 weeks • Acute toxicity during radiotherapy and chemotherapy according to CTCAE V4.0 • Quality of life, determined by EORTC QLQ questionnaires • Evaluation of late neurotoxicity by MMSE and NOA-07 test battery
Inclusion criteria	• Written informed consent • Patients have to be in a cognitive state that allows them to understand the rationale and necessity of study therapy and procedures. • Newly diagnosed histologically proven GBM or gliosarcoma WHO Grad IV, histology confirmed by reference neuropathology (Insitute of Neuropathology, University of Bonn Medical Center, Prof. Dr. Pietsch). Histology obtained by complete resection, partial resection, open biopsy or stereotactic biopsy • Methylated MGMT promoter in the tumor as determined by MDxHealth using methylation-specific PCR • Males or females 18-70 years of age, estimated life expectancy of at least 12 weeks • Karnofsky Performance Score (KPS) ≥ 70% • Patient compliance and geographic proximity that allow adequate follow up • Male and female patients with reproductive potential must use an approved contraceptive method (intrauterine device, birth control pills, or barrier device) during and for 3 months after the trial (Pearl index <1%) • Pre-menopausal female patients with childbearing potential: a negative serum pregnancy test must be obtained prior to treatment start • Adequate organ function as described below: • Adequate bone marrow reserve: • white blood cell (WBC) count ≥3000/µl, • granulocyte count >1500/µl, • platelets ≥100000/µl, • haemoglobin ≥ 10 g/dl • Adequate liver function • bilirubin < 1.5 times above upper limit of normal range (ULN), • alanine transaminase (ALT/SGPT) and aspartate transaminase (AST/SGOT) < 3 times ULN • Adequate renal function: creatinine < 1.5 times ULN • Adequate blood clotting: • PT not below lower limit of normal range • PTT not above upper limit of normal range • Negative HIV test
Exclusion criteria	• Prior malignancy (unless adequately treated carcinoma in situ of the cervix or nonmelanoma skin cancer), unless the prior malignancy was diagnosed and definitively treated at least 5 years previously with no subsquent

	evidence of recurrence • Prior chemotherapy, systemic or local treatment with DNA-damaging agents, tyrosine kinase inhibitors or anti-angiogenic agents for any cancer • Prior RT to the brain • Concurrent administration of any other anti-tumor therapy not described in the protocol • Allergy or intolerance of temozolomide, dacarbazine, CCNU or other nitrosourea derivatives • Unable to undergo MRI • Past medical history of diseases with poor prognosis, e.g. severe coronary heart disease, heart failure (NYHA III/IV), severe poorly controlled diabetes, immune deficiency, residual deficits after stroke, severe mental retardation or other serious concomitant systemic disorders incompatible with the study (at the discretion of the investigator) • HIV infection, active Hepatitis B or C infection • Any active infection (at the discretion of the investigator) • Female patients that are pregnant or breastfeeding • Patients with reproductive potential who do not accept to use contraception during the trial and 3 months thereafter • Treatment in another clinical trial with therapeutic intervention or use of any other investigational agent during the trial or within the 30 days before enrollment • Any psychological, cognitive, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up scheduled visits (at the discretion of investigator)
Discontinuation rules	**Discontinuation of the whole trial** • The trial will be stopped in case of inacceptable toxicity. Inacceptable toxicity is found if more than 2 of the first 30 patients in one of the arms of the trial die from acute complications of therapy. • Additionally, the DMSB and/or the coordinating investigator as the designee of the sponsor can stop the trial transiently or permanently for any safety reason. • There is no interim analysis for efficacy. Thus there is no stopping rule based on efficacy parameters. **Discontinuation rules for an individual patient.** An individual patient will be discontinued from study therapy under the following circumstances: • There is MRI- defined progressive disease according to modified RANO criteria. • The patient requests discontinuation (as long as the patient consents explicitly for further follow-up): ▪ Non-compliance of the patient • The drugs exhibit unacceptable toxicity: Delay of the next course for 6 weeks or more due to hematological toxicity Any non-hematological CTCAE grade 3/4 toxicity attributable to CCNU or temozolomide. Those patients may receive temozolomide or CCNU monotherapy, respectively, if toxicity can be clearly attributed to one of the the agents • The patient becomes pregnant
Statistical analysis	Efficacy: Overall survival (OS) as primary efficacy parameter is measured from the day of randomization into one of the study arms until death. OS will be compared between the two treatment groups using a two-sided log-rank test at a level of 5% stratified for center and GBM recursive partitioning analysis (RPA) class. Description of the primary efficacy analysis and population: The primary analysis will be performed according to the intention to treat (ITT) principle. The intent-to treat (ITT) analysis includes all 128 patients who have been randomized in the trial and have started with the first dose of CCNU (experimental arm) or TMZ

	(standard arm). Dropouts will be evaluated as censored observations at the time of dropout. An additional per-protocol analysis includes all patients who have received two courses of CCNU/TMZ (experimental arm) or concomitant TMZ plus one course of adjuvant TMZ (standard arm).The results of both tests are expected to be consistent. Additionally, an analysis of the “as randomized” population will be performed. Safety: All patients randomized in the trial will be evaluated for safety. Adverse events are recorded by a standardized questionnaire for each course of chemotherapy. Long-term safety will be also evaluated by determining the rate of late neurotoxic sequelae through repeated neurocognitive testing using the NOA-07 test battery and repeated MRI. Secondary endpoints: Secondary endpoints are overall survival, response rate, rate of delay of the next CCNU/TMZ or TMZ course and quality of life/neurocognitive functioning. These parameters are analyzed for the ITT and the per protocol population

ABBREVIATIONS

AE	Adverse event
AP	Alkaline phosphatase
ALAT	Alanine transaminase
ANC	Absolute neutrophil count
ASAT	Aspartate transaminase
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
CCNU	Lomustine
CBC	Complete blood count
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTC	Common toxicity criteria
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
EDC	Electronic Data Capture
EORTC	European Organization for Research and Treatment of Cancer Quality of Life
GBM	Glioblastoma
GCP	Good clinical practice
ICH	International Conference on Harmonization
Investigator	A person responsible for the conduct of the clinical trial at a designated study center
ITT	Intention to treat
KPS	Karnofsky Performance Status
MGMT	O6-methylguanin-DNA-methyltransferase
mMGMT	methylated MGMT promoter
mPFS	Median progression-free survival
nmMGMT	non-methylated MGMT promoter
MMST	Mini Mental Status Test
MRI	Magnetic resonance imaging

NCI	National Cancer Institute
OS	Overall survival
PD	Progressive disease
PCV	Procarbacine, CCNU, Vincristine
PFS	Progression-free survival
PI	Principal investigator
PR	Partial response
QoL	Quality of life
SAE	Serious Adverse Event
SD	Stable disease
SOP	standard operational procedures
TMZ	Temozolomide
TTP	Time to progression
ULN	Upper limit of normal range
WBC	White blood cell

INVESTIGATOR AGREEMENT

I have read this protocol and the attached scientific/prescribing information about the study drug and agree that it contains all necessary details for carrying out this study.

I also agree to conduct the study according to Declaration of Helsinki, ICH GCP rules and national law as well as national guidelines/guidances.

I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug and the conduct of the study.

_____

Investigator's Signature* Date

_____

Name of Investigator (Typed or Printed)

_____

Institution, Address*

_____

Phone Number*

* If the address or phone number of the investigator changes during the course of the study, written notification will be provided by the Investigator to the Sponsor and will not require protocol amendment(s).

1. BACKGROUND, RATIONALE AND RISK/BENEFIT CONSIDERATIONS

1.1 Background

Since the time of the trials establishing RT as an efficient treatment strategy for glioblastoma (GBM; Walker et al., 1980; Green et al., 1983) there were indications that nitrosourea compounds may prolong survival in newly diagnosed GBM patients. However, there is no single phase III trial showing this conclusively. The MRC trial (MRC investigators, 2001) even clearly failed to detect a beneficial effect of PCV chemotherapy (including CCNU). Only in metaanalyses, nitrosourea chemotherapy significantly prolonged survival by 2 months (DeAngelis et al., 1998; GMT trialists, 2001). The addition of TMZ to radiotherapy as defined by the EORTC/NCIC intergroup trial (Stupp et al., 2005) has defined the current standard of therapy. The addition of TMZ has significantly improved mPFS from 5 months with RT alone to 7.9 months and mOS from 12.5 months alone to 14.6 months although these survival times leave patients with GBM still with a dismal prognosis.

Up to date, there is no regimen which has proven in a randomized phase III trial to be superior to standard TMZ therapy in newly diagnosed GBM. The results of the RTOG 0525/EORTC 26052-22053 phase III trial which randomized standard TMZ therapy against intensified TMZ chemotherapy are awaited but not yet published. However, preliminary data of a non-randomized phase II trial using an intensified TMZ regimen (Weiler et al., 2008) suggest that intensified TMZ therapy does not prolong survival compared to standard TMZ. There are also attempts to combine TMZ with antiangiogenic approaches in the first-line setting of GBM. So far, only data from non-randomized trials are available which suggest at most moderate effects for TMZ + cilengitide (PFS-6 65.4%; Stupp et al., 2007) or which cannot be evaluated due to small numbers. Preliminary reports of non-randomized US trials with combinations of bevacizumab and TMZ have been published in abstract form with promising results (mPFS 7-13 months; Lai et al., 2009; Vredenburgh et al., 2009; Nicholas et al., 2009; Gruber et al., 2009) but the final results have to be awaited.

A dramatic effect beyond TMZ monotherapy has been seen in the previous non-randomized bicentric phase II trial with CCNU (100 mg/m^2, day 1) and TMZ (100 mg/m^2, day 2-6; up to 6 6-week courses) therapy in newly diagnosed GBM patients. In this trial,

mOS was markedly extended to 23 months (Herrlinger et al., 2006) as opposed to the historical data from the EORTC/NCIC trial (mOS 14.6 months). The analysis of long-term survival after CCNU/TMZ (Glas et al., 2009) showed that 47.4% of patients survive 2 years and 18,5% of patients survive 5 years. In the most prevalent subgroup of patients belonging to the prognostically homogenous group of patients in the RPA class IV (recursive partitioning analysis; Scott et al. 1998), the 95% confidence intervals (95%CI) of the 2-year survival rate does not overlap between the patients treated with CCNU/TMZ (54%, 95%CI 34-74%, U. Herrlinger, unpublished data) and the patients treated with standard TMZ in the EORTC/NCIC trial (19%, 95%CI 15-24%; Mirimanoff et al., 2006) suggesting superiority of the CCNU/TMZ regimen. Already Hegi et al. (2005) have demonstrated that the outcome after TMZ chemotherapy in GBM is highly dependent on the promoter methylation status of the DNA reparation enzyme MGMT. Patients with a methylated MGMT promoter (mMGMT) survive significantly longer than patients with a non-methylated MGMT promoter (nmMGMT). In the previous phase II CCNU/TMZ trial (Herrlinger et al., 2006), patients with nmMGMT promoter did not significantly benefit from CCNU/TMZ (mOS 12.7 months, identical to standard TMZ therapy, Hegi et al., 2005), whereas patients with mMGMT had a very strong benefit (mOS 34.4 months, Glas et al., 2009). Thus, the present trial is designed only for patients with mMGMT.

The combination of CCNU and TMZ may have an at least additive antiproliferative and proapoptotic effect on GBM cells. Further *in vitro* analyses in primary GBM cell cultures regarding the particular mechanism of CCNU/TMZ combination chemotherapy are ongoing. The particular design of the regimen (single dose of CCNU, TMZ given on 5 consecutive days) appears to play a role for the success of the regimen. Our schedule that combines CCNU on day 1 with TMZ (100 mg/m^2/d) on the 5 consecutive days appears to be more effective than combinations of another nitrosourea compound, BCNU, and a single application of TMZ (550 mg/m^2) which was not substantially more active than TMZ alone in patients with recurrent GBM (Prados et al., 2004) and had only modest activity in newly diagnosed anaplastic glioma (Chang et al., 2004). In contrast, Barrié et al. (2005) reported that with a schedule (BCNU 150 mg/m^2 day 1 + TMZ 110 mg/m^2/d days 1-5) similar to our schedule, high objective response rates were seen in inoperable newly diagnosed GBM and a comparably long mOS (12.7 months) was observed in this prognostically unfavourable group.

Since the benefit of a new therapy is not only defined by efficacy in terms of survival prolongation but also by short-term and long-term side effects, it is important to know that acute hematotoxicity of the CCNU/TMZ regimen was tolerable and transient, albeit higher than with standard TMZ therapy: high-grade myelotoxicity occurred in 42% of patients and toxic death in 1/31 patients (Herrlinger et al., 2006). Fortunately, no unexpected organ toxicity was recorded: 3/31 patients experienced transient nitrosourea-associated organ toxicity (grade 2 lung fibrosis, grade 3 asymptomatic elevation of transaminases, grade 4 CCNU-induced hepatitis). The long-term evaluation of surviving patients in the phase II trial and in another pilot trial showed that none of the long-term surviving patients experienced late neurotoxicity impairing the performance score. Thus, the survival-prolonging effect of CCNU/TMZ is not associated with quality of life-reducing late neurotoxicity.

1.2 Rationale

The need to analyze the CCNU/TMZ combination in a randomized trial is defined by the very promising survival results obtained in the phase II trial and by the potential selection bias which is inherent in non-randomized phase II trials. If the major hypothesis is proven correct by the trial, i.e. overall survival is significantly prolonged by CCNU/TMZ in the context of acceptable acute toxicity and without quality of life-reducing late neurotoxicity, the results are very likely to profoundly change general medical practice: in this case, CCNU/TMZ has to be regarded as the new standard of therapy for patients with GBM with a methylated MGMT promoter. The trial has therefore the potential to become a landmark study for GBM therapy. All further patients with mMGMT GBM matching the inclusion criteria of the trial will then have the individual benefit of PFS prolongation by 50% in average which would be a substantial benefit. Also, the rate of long-term survival patients will increase (Glas et al., 2009).

1.3 Risk/benefit considerations

The regimen used for the experimental arm of this trial is well supported by previous phase II data (Herrlinger et al., 2006, Glas et al., 2009): In the phase II trial, mOS was markedly extended to 23 months (Herrlinger et al., 2006) as opposed to the historical data from the EORTC/NCIC trial (mOS 14.6 months). The analysis of long-term survival after CCNU/TMZ (Glas et al., 2009) showed that 47.4% of patients survive 2 years and 18,5% of patients survive 5 years. In the most prevalent subgroup of patients belonging

to the prognostically homogenous group of patients in the RPA class IV (recursive partitioning analysis; Scott et al. 1998), the 95% confidence intervals (95%CI) of the 2-year survival rate does not overlap between the patients treated with CCNU/TMZ (54%, 95%CI 34-74%, U. Herrlinger, unpublished data) and the patients treated with standard TMZ in the EORTC/NCIC trial (19%, 95%CI 15-24%; Mirimanoff et al., 2006) suggesting superiority of the CCNU/TMZ regimen.

According to the non-randomized phase II data, hematotoxicity of the CCNU/TMZ regimen was tolerable and transient, albeit higher than with standard TMZ therapy: high-grade myelotoxicity occurred in 42% of patients and toxic death in 1/31 patients (Herrlinger et al., 2006). Fortunately, no unexpected organ toxicity was recorded: 3/31 patients experienced transient nitrosourea-associated organ toxicity (grade 2 lung fibrosis, grade 3 asymptomatic elevation of transaminases, grade 4 CCNU-induced hepatitis). The long-term evaluation of surviving patients in the phase II trial and in another pilot trial showed that none of the long-term surviving patients experienced late neurotoxicity impairing the performance score. Thus, the survival-prolonging effect of CCNU/TMZ is not associated with quality of life-reducing late neurotoxicity.

Overall, the additional toxicity brought about by CCNU/TMZ combination therapy may by far be outweighed by the expected superior efficacy (approx. 50%+ in median progression-free and overall survival in the phase II trial). The patients in the control arm will undergo up-to date standard therapy without frequent and severe myelotoxicity. All trial participants will receive superior neurooncological care as compared to community standards, i.e. patients may realize benefits form participation in the trial even if they are randomized to the standard arm.

1.4 Investigational products

CCNU and TMZ are both commercially available drugs approved for marketing authorization in Germany. The SmPCs of CCNU/ Temozolomide are attached to the study protocol in Appendix 5. In this study CCNU is used in label. Temozolomide is only approved to be given in a monotherapy. Since in the experimental arm a combined therapy consisiting of Lomustine + Temozolomide is provided, Temozolomide in the experimental arm is used off label. This combined therapy has been used before in a non-randomized clinical trial leading to an improved survival by acceptable toxicity (Herrlinger et al 2006), thereby justifying the combination of both drugs and establishing the rational for this clinical trial (for details see chapter 1.1-1.3).

1.4.1 Temozolomide

Chemistry

TMZ (3, 4-dihydro-3-methyl-4-oxoimidazole [5,1-d-as-tetrazine-8-carboxamide]; $C_6H_6N_6O_2$, molecular weight 194.15) is an imidazotetrazinone compound that is spontaneously hydrolyzed under physiological conditions to yield the active metabolite, 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide (MTIC).

Pharmacodynamics

Temozolomide is a base-selective DNA-methylating agent with a preference for the N^7 and O^6 positions of guanine. Although methylation at O^6 accounts for no more than 5-10% of DNA lesions, O^6 methylation is considered a major mediator of TMZ cytotoxicity because it promotes the substitution of cytosine by thymine upon replication which triggers the DNA mismatch repair system. The DNA repair enzyme MGMT transfers methyl groups from the O^6 position of guanine to a cysteine moiety in its active center, but is thereby inactivated and consumed, and cannot be recovered. Accordingly, cells with high MGMT levels are predicted to resist TMZ cytotoxicity unless their MGMT activity is either depleted e.g. by continuous TMZ exposure or MGMT is inhibited pharmacologically. It is assumed that the futile attempts at DNA repair in cells lacking MGMT contribute to the overall cytotoxic effects of TMZ, but this has not been confirmed in a clinical setting (Friedman et al. 1998).

Pharmacokinetics and metabolism

TMZ has an oral bioavailability of almost 100% and does not require hepatic activation, resulting in reliable drug exposure after oral administration. The drug should be taken early in the morning prior to the first meal since concurrent meals reduce absorption by approximately 10% (Brada et al**.,**. 1999). The serum half-life is less than 2 h. TMZ is rapidly eliminated with a mean elimination half-life of 1.8 hours and exhibits linear kinetics over the therapeutic dosing range. TMZ has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weakly bound to human plasma proteins; the mean percent bound of drug-related total radioactivity is 15%. Blood brain barrier penetration is good, and the cerebrospinal fluid levels reach 20-40% of the serum levels (Ostermann et al. 2004). Drug accumulation has not been observed.

TMZ is spontaneously hydrolyzed at physiologic pH to the active species, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC) and to TMZ acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC), which is known to be an intermediate in purine and nucleic acid biosynthesis and to methylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC. Relative to the AUC of TMZ, the exposure to MTIC and ACI is 2.4% and 23%, respectively. About 38% of the administered TMZ total radioactive dose is recovered over 7 days; 37.7% in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is as unchanged TMZ (5.6%), AIC (12%), TMZ acid metabolite (2.3%), and unidentified polar metabolites(s) (17%). Overall clearance of TMZ is about 5.5 L/hr/m2

Side effects

Temozolomide can cause myelosuppression. Thrombocytopenia and lymphopenia might occur. Lymphopenia can lead to opportunistic infection, e.g. pneumocystis carinii pneumonia. Further, medication with temozolomide might lead to nausea and vomiting. Some patients suffer from diarrhea during the first applications. Rare side effects include headache, fatigue, obstipation, exanthema, fever and shivering, pain, vertigo, weight loss, dyspnea, dyspepsia, alopecia, abnormal tasting, paresthesia as well as allergic reaction including erythrodermia, urticaria and anaphylactic shock. Any specific toxictiy in distinct organs has not yet been reported. (Reversible) elevated liver enzymes have been described as potential side effect.

1.4.2 CCNU

Chemistry

CCNU (lomustine, 1-(2-chloroethyl)-3-cyclohexyl-1-nitosourea) is a nitrosourea compound that -in humans- undergoes biotransfomation to the geometric, monohydroxylated metabolites trans-4-hydroxy CCNU and cis-4-hydroxy CCNU. CCNU interacts with DNA by alkylation and carbamoylation (Lown et al., 1979), particularly with deoxyguanosine and deoxycytidine (Gombar et al., 1980), and carbamoylation of free amino groups of peptides and proteins (Wheeler et al., 1975).

Pharmaceutical interactions

CCNU is hydroxylized in the liver to active metabolites. Hydroxylation is dependent on cytochrome P450 enzymes. Thus, substances influencing cytochrome P450-dependent metabolism are likely to influence the metabolism of CCNU. Interactions of CCNU with activation of ifosfamid and cyclophosphamid are known (Chang et al., 1994). Of importance is a retrospective observational trial indicating a reduced survival in glioblastoma patients treated with CCNU when cytochrom P450 enzyme inducing antiepileptics (e.g. Phenytoin, Carbamazepin) were administered (Oberndorfer et al., 2005). Thus, the present trial requires to switch patients with EIADs on non-enzyme-inducing antiepileptics.

Distribution and pharmacokinetics

Because of the rapid chemical and biochemical decomposition and oxidative transformation of CCNU in plasma and tissues shortly after administration, distribution data, based on experiments with CCNU labeled with ^{14}C in either the ethylene, carbonyl, or cyclohexyl moieties refer to hydrolysis products rather than intact CCNU. After oral administration of variously labeled CCNU in man, radioactivity was demonstrated within 10 minutes in plasma, with peak levels in 1-6 hours (Sponzo et al., 1973). Significant quantities of radioactivity are found in all tissues including brain and cerebrospinal fluid within a short time and are similar regardless of position of label or route of administration. The decomposition of CCNU is markedly increased in the presence of proteins (Levin et al., 1978); the mechanism appears to be catalysis by serum albumin of the conversion of CCNU to reactive species. The cyclohexyl ring is subject to oxidation. Preferential distribution is to fat, liver, and brain (Oliverio et al., 1970; Litterst et al., 1974; Levin et al., 1978; Russo et al., 1984). Pharmacokinetic data have been published (Lee et al., 1985). It should be taken at least three hours after the last food intake.

Metabolism and excretion

CCNU rapidly disappears from plasma after oral or parenteral administration, and it has been assumed that its fate in vivo is similar to its decomposition in aqueous solution. Schemes for this decomposition, including suggested mechanisms for non-specific catalysis of decomposition by serum proteins have been published (Colvin et al., 1976) and these indicate the formation of chloroethyl carbonium ion as an alkylating agent, and cyclohexyl isocyanate as a carbamoylating agent. Excretion of radioactivity due to variously (ethylene, carbonyl, cyclohexyl) labeled CCNU is mainly in the urine. There is also some biliary excretion and reabsorption from the gastrointestinal tract in some species. Other urinary metabolites are cyclohexylamine and dicyclohexyl urea. In addition to these essentially hydrolytic products of CCNU metabolism, there has also been demonstrated in vitro monohydroxylation of the cyclohexyl ring by rat liver microsomes to yield cis- and trans- hydroxylated derivatives inposition 2, 3, and 4 of the cyclohexyl ring (Hilton and Walker, 1975). The same hydroxylation has been found after parenteral administration of CCNU (reviewed by Kohlhepp et al., 1981); major urinary excretion products among these are the cis-4- and trans-4-hydroxylated products and these have also been demonstrated in plasma after ingestion of CCNU in man (Lee et al., 1985). The properties of some of these derivatives have been studied; they appear to be more toxic than CCNU but have better therapeutic indices. Their carbamoylating and alkylating properties differ from each other and from CCNU, depending on the position of the hydroxyl group (Johnston et al., 1975; Wheeler et al., 1977; Heal et al., 1978). Other urinary products of metabolism are thiol conjugates (thiodiacetic acid, S-carboxymethyl cysteine) derived from the alkylating species (Kohlhepp et al., 1981).

Side effects

Adverse events in man mainly affect the hematopoietic system with thrombocytopenia, leucocytopenia and anaemia. Myelosuppression occurs delayed, mainly after 4-6 weeks and can be cumulative. Further, medication with CCNU might lead to nausea and vomiting, more rarely to diarrhea. Occasionally, moderate hepatic dysfunction has been observed. In rare cases, pulmonary fibrosis, alopecia, stomatitis and minor neurological dysfunctions, e.g. apathia, ataxia and desorientation. In a few cases, irreversible damage of the optic nerve has been described in the combination with radiotherapy. CCNU can have carcinogenic, mutagenic and teratogenic effects.

2. OBJECTIVES

2.1 Primary Objective

This phase III trial determines whether combined CCNU/TMZ chemotherapy plus standard radiotherapy is superior to TMZ monochemotherapy plus standard radiotherapy alone in patients with newly diagnosed mMGMT GBM patients regarding overall survival.

2.2 Secondary Objectives

Secondary objectives are to determine whether combined CCNU/TMZ/RT therapy is superior to standard TMZ/RT therapy regarding progression-free survival and time to treatment failure as well as to determine acute and late toxicity of CCNU/TMZ therapy including its effects such as the delay of subsequent courses due to acute toxicity.

2.3 End-points

Primary end-point:

- Overall survival (OS) as measured from the day of randomization until death

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Secondary endpoints:

- Progression-free survival (PFS) as measured from the day of randomization until diagnosis of progressive disease determined by MRI (modified RANO criteria)
- Best response rate determined by MRI (modified RANO criteria)
- Frequency of delay of the next CCNU/TMZ or TMZ course by more than 2 weeks
- Acute toxicity during radiotherapy and chemotherapy according to CTC AE V4.0
- Quality of life, determined by EORTC QLQ questionnaires
- Evaluation of late neurotoxicity by MMSE and NOA-07 test battery.
- Time to treatment failure

3. STUDY POPULATION

3.1 General Considerations

Newly-diagnosed patients with histologically proven glioblastoma or gliosarcoma and a methylated MGMT can be accrued for this trial. This accounts for 40-45% of the population of newly diagnosed GBM. Only patients without prior chemotherapy or radiotherapy may be included. Since the present trial compares experimental CCNU/TMZ with standard TMZ the inclusion/exclusion criteria are identical to the ones of the trial estblishing TMZ as standard therapy (Stupp et al., 2005). This also implies that only adult patients up to an age of 70 years can be accrued.

3.2 Inclusion Criteria

Patients meeting **all** the following criteria may be enrolled

- Written informed consent
- Patients have to be in a cognitive state that allows them to understand the rationale and necessity of study therapy and procedures.
- Newly diagnosed histologically proven GBM or gliosarcoma WHO Grad IV, histology confirmed by reference neuropathology (Insitute of Neuropathology, University of Bonn Medical Center, Prof. Dr. Pietsch). Histology obtained by complete resection, partial resection, open biopsy or stereotactic biopsy
- Methylated MGMT promoter in the tumor as determined by MDxHealth using methylation-specific PCR
- Males or females 18-70 years of age, estimated life expectancy of at least 12 weeks
- Karnofsky Performance Score (KPS) ≥ 70%
- Patient compliance and geographic proximity that allow adequate follow up
- Male and female patients with reproductive potential must use an approved contraceptive method (intrauterine device, birth control pills, or barrier device) during and for 3 months after the trial (Pearl index <1%)
- Pre-menopausal female patients with childbearing potential: a negative serum pregnancy test must be obtained prior to treatment start

- Adequate organ function as described below:
    - Adequate bone marrow reserve:
        - white blood cell (WBC) count ≥3000/µl,
        - granulocyte count >1500/µl,
        - platelets ≥100000/µl,
        - haemoglobin ≥ 10 g/dl
    - Adequate liver function
        - bilirubin < 1.5 times above upper limit of normal range (ULN),
        - alanine transaminase (ALT/SGPT) and aspartate transaminase (AST/SGOT) < 3 times ULN
    - Adequate renal function: creatinine < 1.5 times ULN
- Adequate blood clotting:
    - PT not below lower limits of normal range
    - PTT not exceeding the upper limit of normal range
- Negative HIV test

3.3 Exclusion Criteria

Patients meeting **one** of the following criteria **cannot** be enrolled:

- Prior malignancy (unless adequately treated carcinoma in situ of the cervix or nonmelanoma skin cancer), unless the prior malignancy was diagnosed and definitively treated at least 5 years previously with no subsquent evidence of recurrence
- Prior chemotherapy, systemic or local treatment with DNA-damaging agents, tyrosine kinase inhibitors or anti-angiogenic agents for any cancer
- Prior RT to the brain
- Concurrent administration of any other anti-tumor therapy not described in the protocol

- Allergy or intolerability of temozolomide, dacarbazine, CCNU or other nitrosourea derivatives
- Unable to undergo MRI
- Past medical history of diseases with poor prognosis, e.g. severe coronary heart disease, heart failure (NYHA III/IV), severe and poorly controlled diabetes, immune deficiency, residual deficits after stroke, severe mental retardation or other serious concomitant systemic disorders incompatible with the study (at the discretion of the investigator)
- Known HIV infection, active Hepatitis B or C infection
- Any active infection (at the discretion of the investigator)
- Female patients that are pregnant or breastfeeding
- Patients with reproductive potential who do not accept to use contraception during the trial and 3 months thereafter
- Treatment in another clinical trial with therapeutic intervention or use of any other investigational agent within the 30 days before enrolment
- Any psychological, cognitive, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up scheduled visits (at the discretion of investigator)

3.4 Distribution of gender

In the previous trial defining the standard for first-line treatment of glioblastoma (Stupp et al., 2005), 61% male and 39% female patients had been included. Since the present CeTeG trial uses the same inclusion criteria and thus addresses the same population, a similar distribution of gender can be expected. Gender is not a prognostically significant marker in glioblastoma so that there will be no stratification according to gender and no subgroup analyses according to gender. Population pharmacokinetic analysis indicates that women have an approximately 5% lower clearance adjusted for body surface area for temozolomide than men. Women have higher incidences of Grade 4 neutropenia and thrombocytopenia in the first cycle of therapy than men. Overall, the differences

between the two genders are so small that all patients receive TMZ doses irrespective of their gender.

3.5 Removal of subjects from study / Withdrawl of subjects

An individual patient will be discontinued from study therapy within the study but treated off-study and followed further under the following circumstances:

- There is MRI- defined progressive disease according to modified RANO criteria as determined by central reference neuroradiology
- The patient requests discontinuation.
- The drugs exhibit unacceptable toxicity defined as follows:
    - Delay of the next course for 6 weeks or more due to hematological toxicity
    - Any non-hematological CTCAE grade 3/4 toxicity attributable to CCNU or temozolomide. Those patients may receive temozolomide or CCNU monotherapy, respectively, if toxicity can be clearly attributed to one of the agents
- The patient becomes pregnant.
- Non-compliance

When a patient withdraws prior to completing the study, the reason for withdrawal is to be documented on the CRF and in the source document. Any clinically significant abnormalities persisting at withdrawal will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

All patients who are discontinued from study therapy for any reason have to be followed according to the study protocol with clinical and MRI investigations (see chapter 6.1.”Follow-up after completion of the study therapy or withdrawal (every 12 weeks)”) until the end of the follow-up-time of the whole trial 3 years after the inclusion of the last patient.

If a patient requests discontinuation of the study therapy and withdraws his/her consent for the trial, the patient is asked to consent to the performance and documentation of the follow-up visits according to the study protocol.

3.6 Patients Replacement

According to the patient number calculation, 136 patients have to be allocated and 128 of these allocated patients are expected to form the intention-to-treat (ITT) population which included all patients who are included in the trial and have received their first dose of chemotherapy. This implies that about 6% of the patients (n=8) included in the trial are anticipated to be drop-outs before starting chemotherapy. These drop-out patients are not replaced.

Any patient dropping out after receiving his first dose of chemotherapy is part of the ITT population and is not replaced.

4. TRIAL DESIGN

This is a multicenter, randomized, open-label phase III trial for newly diagnosed glioblastoma patients with methylated MGMT promoter in their tumor. The study includes the following steps:

Screening phase (1-3 weeks after resection)**:** Patients with previously untreated GBM are screened for the trial. After obtaining informed consent for determination of MGMT promoter methylation status and reference neuropathology, a block of paraffin-embedded tissue is sent for reference neuropathology review to the Department of Neuropathology, University of Bonn. From there, tissue is sent to MDxHealth, where the MGMT promoter methylation status is determined by methylation-specific PCR.

Baseline and randomization phase (week 3-5 after resection)**:** Baseline examinations are performed. After obtaining the MGMT promoter status and confirmation of GBM histology (for the form to submit reference neuropathology and MGMT testing see appendix 3) and obtaining informed consent for trial participation, inclusion/exclusion criteria are evaluated and documented, patients are randomized for standard TMZ chemotherapy or experimental CCNU/TMZ therapy, both in combination with standard RT. Therapy (i.e. RT) has to start within 2 weeks after randomization and 5 weeks after surgery. A 5 week interval is generally accepted for clinical trials in GBM and does not impair therapeutic efficacy (Blumenthal et al., 2008).

Treatment phase: The treatment phase as well as the follow-up phase of the trial is summarized in figure 1. The treatment phase should start not later than 5 weeks after surgery and not later than 2 weeks after randomization and baseline visit.

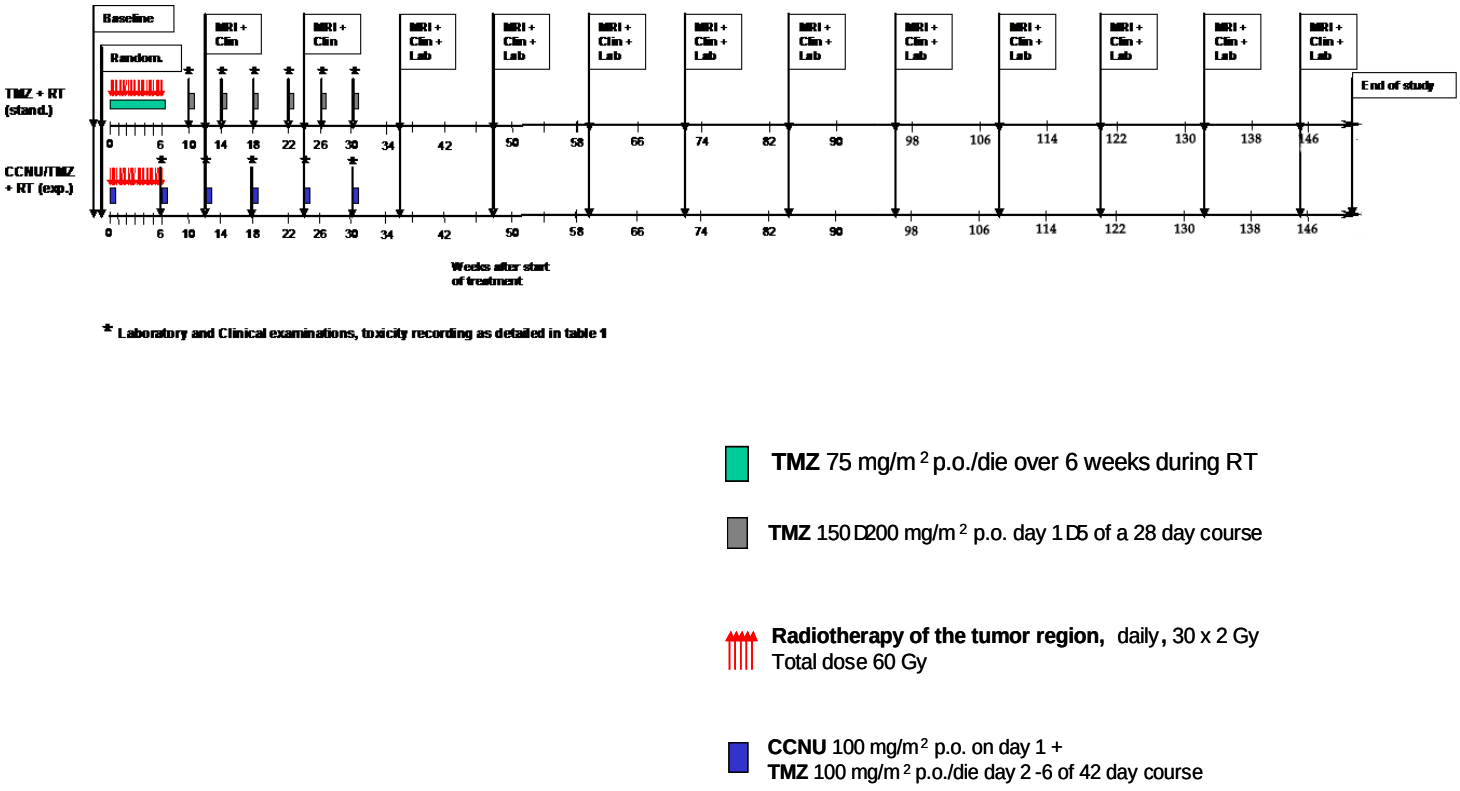
The trial includes two treatment arms:

Experimental arm (CCNU/TMZ arm; 50% of patients): the first course of CCNU (100 mg/m^2 day 1) and TMZ (100 mg/m^2/day, day 2-6) is started on the first day of RT (60 Gy in 2 Gy fractions, 5 days/week). The following 5 courses are applied 6 weeks after the start of the previous course. In the experimental arm, not more than 6 six week courses can be applied.

Standard arm (TMZ arm; 50% of patients): the first application of TMZ is given on the first day of RT (60 Gy in 2 Gy fractions, 5 days/week). During RT, TMZ is given on a daily base with 75 mg/m^2/day (including RT-free weekend days). RT with concomitant TMZ chemotherapy (6 weeks) is followed by a 4 weeks interval without therapy. In week 11 after the initiation of RT, the TMZ block chemotherapy ensues with 6 courses of TMZ 150-200 mg/m^2 day 1-5 of a 28 day course. It is recommended that TMZ chemotherapy is stopped after application of 6 courses (as suggested by Stupp et al., 2005).

Follow-up phase: After the end of the treatment phase, all patients will be followed by clinical examination and contrast-enhanced MRI every 12 weeks until 3 years after randomization. Follow-up of all patients ends 36 months after the inclusion of the last patient. All patients in the trial are followed until this time point.

Fig.1: Schematic overview of the study



5. THERAPEUTIC REGIMENS, DOSE MODIFICATIONS, CONCOMITANT MEDICATION

5.1. Therapeutic Regimens

5.1.1 Radiotherapy

Radiotherapy will consist of a conventionally fractioned regimen, delivering a total dose of 60 Gy in 6 weeks, in a fractionated focal irradiation at a dose of 2 Gy per fraction given once daily schedule five days per week (Monday through Friday) over a period of 2 Gy per fraction six weeks, for a total of 30 fractions dose of 60 Gy. Radiotherapy is performed as standard involved-field and will be delivered to the gross tumor volume with a 2-to-3-cm margin for the clinical target volume. Radiotherapy will be planned with dedicated computed tomography (CT) / MRI and three-dimensional planning systems; conformal radiotherapy will be delivered with linear accelerators with nominal energy of 6 MV or more, and quality assurance will be performed by means of individual case reviews. Radiotherapy will start after randomization and no later than day 35 after surgery. In case of interruptions further radiotherapy is to be performed as determined

by standard operation procedures of the department of radiotherapy. A delay of more than 5 days in continuation of radiotherapy will be regarded as a treatment failure; study therapy may nevertheless continue.

5.1.2 Chemotherapy dosing: general considerations

Deviations between calculated TMZ dose and dose applied of more than 5% are regarded as protocol violations Also, the body weight of the previous course can be used to calculate the body surface area of the next course if it does not differ by more than 5%. The chemotherapy doses of patients with a body surface area of more than 2.3 m^2 are all calculated with a body surface area of 2.3 m^2.

5.1.3 Experimental arm: chemotherapy with CCNU/TMZ

The experimental arm consists of six 42 day-courses of CCNU 100 mg/m^2/day (day 1) and TMZ 100 mg/m^2/day (day 2-6). The first course starts with the first day of RT. CCNU and TMZ are applied orally. TMZ and CCNU have to be taken on empty stomach meaning at least 2-3h hours after the last meal. At least 30 minutes earlier, a serotonin antagonist such as ondansetron or tropisetron have to be taken as antiemetic. TMZ and CCNU is applied on an outpatient base. The doses of CCNU and TMZ are justified by the previously published phase II trial (Herrlinger et al., 2006; Glas et al., 2009) which used the same doses and which provided the promising results that are the base for the present trial. The next course of CCNU/TMZ can only be started if WBC are >3000/µl, neutrophil counts are >1500/µl and platelets are >100000/µl and in case CTC grade < 2 toxicity. Treatment failure is assumed in case of a delay of more than 6 weeks for the start of the next course of CCNU/TMZ. After progression or treatment failure of a patient the further therapy is applied at the discretion of the treating physician.

5.1.3.1 Dose modifications of CCNU/TMZ

Dosing is based on adverse event (AEs) during the prior treatment cycle. If a patient experiences several adverse events, the recommended dose adjustment is to be based on the toxicity that requires the greatest dose reduction. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events Version

4.0 (CTCAE). In response to acute toxicity, the dosage of TMZ will be reduced according to the criteria outlined in this section. In any case of hematologic toxicity of grades 3 or 4, it is recommended to obtain RBC, platelets, WBC and a differential blood count at least twice weekly. Leucocytes, ANC and platelets have to be determined at least 7 days after the last G-CSF application or transfusion of platelets.

As in the previous phase II trial, the doses of CCNU and TMZ are individually adjusted in following courses according to white blood cell (WBC) and platelet nadirs during the previous course according to the following scheme:

- In case the nadir (WBC < 1500/µl or thrombocytes < 50000/µl) occurred after day 25, CCNU will be reduced by one dose level with the dose levels being 100%, 75% and 50% of the initial dose. In case of WBC <1500/µl thrombocytes <50000/µl at the dose level of 50%, CCNU has to be permanently discontinued.
- Depending on the nadirs during the first 25 days of the previous course TMZ will be decreased to the lower dose levels of 75 mg/m^2 or 50 mg/m^2 or increased stepwise to the higher dose levels of 120 mg/m^2, 150 mg/m^2 and 200 mg/m^2 according to the following schedule:
    - reduction by 1 dose level if WBC <1500/µl or platelets < 50 000/µl;
    - reduction by 2 dose levels if WBC <1000/µl or platelets < 25 000/µl;
    - increase by 1 dose level if RT was completed and WBC >2500/µl and platelets >100000/µl.
    - In case of WBC <1500/µl or thrombocytes <50000/µl at the lowest dose level of 50 mg/m2, TMZ has to be permanently discontinued.
- In case of any non-hematological toxicity CTCAE grade 3/4, the substance causing the toxicity will be withheld in further courses and therapy within the trail may continue with the substance not causing the toxicity.

Using this scheme, the individual dose adaptation in subsequent courses allows to apply the individually highest possible dose of chemotherapy which may differ greatly between different patients.

It is allowed to apply erythrocyte and/or thrombocyte transfusions to improve Hb and platelet values. The target Hb value and transfusion trigger value is defined by medical comorbidities at the discretion of the investigator. In case platelets counts or Hb values have been improved by transfusion of platelet or erythrocyte concentrates, the platelet and Hb values have to be stable or increasing for at least 7 days prior to the start of the next course.

5.1.4 Standard arm: concomitant and adjuvant chemotherapy with TMZ

TMZ chemotherapy in the standard arm is applied as described in TMZ product information and as described in the landmark publication by Stupp et al. (2005) which led to the approval of TMZ for first-line therapy in glioma.

Concomitant TMZ chemotherapy is started with the first day of radiotherapy at a dose of 75 mg/m² body surface area daily. The last day of radiotherapy is the last day of TMZ chemotherapy. TMZ is also given on weekends. TMZ can be administered as long as all of the following criteria are fulfilled:

> neutrophils ≥1500/µl, thrombocytes ≥100000/µl, non-hematological toxicity ≤ grade 1 CTC (except alopecia, nausea and vomiting).

In case of CTC grade 2 toxicity, neutrophils between 500 and 1500/µl and/or thrombocytes between 10000 and 100000/µl TMZ has to be interrupted until all of the above mentioned criteria are fulfilled again. Temozolomide has to be discontinued in case of CTC grade 3/4 toxicity, neutrophils <500/µl and/or thrombocytes <10.000/µl. The adjuvant phase of temozolomide therapy will then be started with the lower dose of 100 mg/m2 and increased in subsequent courses in steps of 25 mg/m2/day if nofurther grade 3/4 hematotoxicity ensues.

In the ***adjuvant*** phase starting 4 weeks +/- 5 days from the last day of radiotherapy, 6 courses of standard adjuvant TMZ chemotherapy is applied with 150-200 mg/m²/day for 5 days of a 28-day course (standard defined by Stupp et al., 2005). If toxicity has already occurred during the combined therapy, TMZ has to be applied at doses of 100mg/m²/day (dose stage -1). Generally, during the first course of monotherapy 150mg/m²/day temozolomide (dose stage 0) has to be administered, during courses 2-6 200mg/m²/day (dose stage 1), if no toxicity occurred (neutrophils ≥ 1500/µl, thrombocytes ≥ 100000/µl and CTC ≤ 2 except alopecia, nausea, vomiting). Temozolomide has to be reduced by one dose stage (dose steps are: 75 mg/m², 100 mg/m², 125 mg/m², 150 mg/m² and 200 mg/m²) if neutrophils < 1000/µl, thrombocytes < 50000/µl and/or non-hematological toxicity CTC=3 attributed to TMZ. Temozolomide has to be discontinued if intolerable toxicity persists despite dose stage 1 is administered or grade 3 toxicity persists even after dose reduction.

Treatment failure is assumed in case of a delay of more than 6 weeks for the start of the next course of TMZ. After progression or treatment failure of a patient the further therapy is applied at the discretion of the treating physician.

5.2 Supply, package, storage and labelling of investigational products

CCNU and TMZ are both commercially available drugs approved for marketing authorization in Germany. Therefore the capsules are prescribed by the treating physician and provided by the local pharmacy. Drugs are to be kept in an appropriate, secure, locked area at the pharmacy of the participating center and are supplied on the day of intake by the pharmacy. CCNU will be taken by the patient in the hospital under supervision of study personnel. TMZ (day 2-6 of each course) is distributed by the trial center and taken on an outpatient base. The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of all drugs received using the Drug Accountability Record form. Since this is an open study and drugs are approved for marketing authorization no labelling will be performed. In this study CCNU is used in label. Temozolomide is only approved to be given in a monotherapy. Since in the experimental arm a combined therapy consisiting of Lomustine + Temozolomide is provided, Temozolomide in the experimental arm is used off label. This combined therapy has been used before in a non-randomized clinical trial leading to an improved survival by acceptable toxicity (Herrliger et al 2006), thereby justifying the combination of both drugs and establishing the rational for this clinical trial (for details see chapter 1).

Temozolomide

TMZ is supplied in capsules of the following p.o. dosage strengths: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg and 250 mg. Each capsule contains drug substance in combination with lactose, colloidal silicon dioxide, sodium starch glycolate, tartaric acid, and stearic acid. The capsule shells contain gelatin, titanium dioxide, and sodium lauryl sulfate. The capsules should be stored as indicated in the valid SmPC. Capsules are stable for at least 24 months when stored in amber glass bottles at this temperature.
Patients are supplied with TMZ by the local investigator. TMZ as well as the combination of TMZ and CCNU are taken on an outpatient base. If vomiting occurs

during the course of treatment, no redosing of the patient is allowed before the next scheduled dose. The capsules should be taken on an empty stomach, therefore a minimum of 3 hours after a meal and with no food ingestion for 1 hour after TMZ and CCNU administration.

CCNU

Compound name: Cecenu®. A capsule contains 40 mg CCNU in combination with wheat starch, lactose, talcum, magnesiumstearat, gelatine, titanium dioxide and indigocarmin. The capsules should be stored as indicated in the valid SmPC.. Capsules are stable for 36 months when stored in amber glass bottles at this temperature. Cecenu® is manufactured by Medac. Patients will be instructed to swallow the capsules whole, in rapid succession, without chewing them. If vomiting occurs during the course of treatment, no redosing of the patient is allowed before the next scheduled dose. The capsules are recommended to be taken before nighttime or 3 hours after a meal.

5.3 Concomitant therapy

5.3.1 Premedication

Corticosteroids are administered at the treating physician's discretion. This could be important, because the relevance of "edema" will be taken into consideration by the neuroradiologist. Steroid dose must be stable within 14 days prior to study registration or decreasing 5 days prior to registration.

5.3.2 Prophylaxis

Antiemesis

A prophylactic standard antiemetic regimen using a serotonin antagonist (e.g. ondansetron, tropisetron) prior to administration of the chemotherapeutic agents CCNU and TMZ is mandatory.

Lymphocytopenia

In case of lymphopenia <500/µl during CCNU/TMZ or the adjuvant therapy phase of TMZ monotherapy, prophylactic treatment with trimethoprim and sulfamethoxazol (e.g Cotrim forte®) should be started with Trimethoprim 160 mg, Sulfamethoxazol 800 mg

(e.g. Cotrim forte®) three times a week. Additionally, prophylactic trimpethorim/sulfamethoxazol therapy according to this regimen is mandatory during standard daily concomitant TMZ therapy.

Neutropenia

Afebrile Neutropenia

In case of ANC < 500 / µl without fever or infection, prophylactic antibiotic therapy with ciprofloxacin should be started, in case of rapid decrease of ANC prophylaxis could be started before the threshold of 500 / µl. Patients with neutropenia < 500 / µl lasting more than 7 days should be given additional antimycotic prophylaxis with itraconazol-suspension 5 mg/kg twice daily (as long as neutrophile counts are < 1000 / µl). Particular attention should be payed to potential contraindications of a treatment with itraconazol, e.g. drugs prolonging QT-interval. Patients with neutropenia <500/µl should also receive G-CSF (e.g. Granocyte®) 19,2 Mio IE (150 µg) /m^2/day until neutrophil counts reach 1500/µl.

Febrile Neutropenia

In case of neutrophile counts < 500 / µl with fever and/or infection patients should be admitted to the hospital and treated with piperacillin 4g and tazobactam. Septic patients should be given gentamicin (Refobacin®) 3 mg/kg additionally (ototoxicity and nephrotoxicity to be considered) once a day. Hematopoietic colony-stimulating factors like Lenograstim (e.g. Granocyte®) 19,2 Mio IE (150 µg) /m^2 should be given once a day until neutropenia is resolved (ANC >1500/µl). In case of persisting fever and absent detection of pathogens, antibiotic therapy should be switched to meropenem (Meronem ®) 1 g t.i.d.. Vancomycin 1 g b.i.d. might be added. Patients with neutropenia < 500 / µl lasting more than 7 days should be given additional antimycotic prophylaxis with itraconazol-suspension (see above). In case of lymphocyte counts < 500 / µl Trimethoprim 160 mg, Sulfamethoxazol 800 mg (e.g. Cotrim forte®) three times a week.

5.3.3 Other concomitant medication

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed, provided their use is documented in the patient records and on the appropriate CRF. All concomitant medications,

received from 30 days prior to study entry until completion/early withdrawal, will be recorded in the CRF at each visit. The information should include the name of the drug, indication for use in this patient, daily dose, and the start and stop date(s) of administration.

The administration of any other anticancer agent is NOT permitted. This also applies to agents with hypothetical anticancer effects such as St John's wort extracts, high-dose vitamin therapy, Boswellia acids, any sort of immunotherapy. Similarly, the use of other investigational drugs, experimental radiotherapy beyond standard radiotherapy (stereotactic boost, hyperfractionated radiotherapy) or hyperthermia is not allowed. Patients may receive, at the discretion of the investigator, appropriate medical and surgical treatment that is not specifically prohibited by this protocol. If a patient has or develops hypertension, therapy with an angiotensin converting enzyme inhibitor or angiotensin II antagonist is recommended. Patients with liver enzyme-inducing antiepileptic agents are encouraged to switch to non-enzyme-inducing agents (levetiracetam, gabapentin, lamotrigin). Treatment with steroids should be registered (dose, day).

5.4 Duration of Therapy

Treatment cycles will be repeated until progression or unless unacceptable toxicity is encountered. A maximum of 6 cycles of CCNU/TMZ will be administered. After the completion of CCNU/TMZ therapy with a maximum of 6 courses, the patient will be followed by neurological examination and MRI every 3 months. In case of recurrent disease, salvage therapy is chosen at the discretion of the treating physician.

If a patient progresses while on treatment further therapy is at the discretion of the treating physician.

6. CLINICAL EVALUATION, LABORATORY TESTS, FOLLOW-UP

6.1 Study procedures

The attached Time and Events Schedule (Table 2) summarizes the frequency and timing of the various investigations and safety measurements. The neuroradiologic evaluation of response must be performed by contrast-enhanced MRI. A deviation of more than 5 days regarding the defined timepoints for each visit is regarded as a

protocol violation. This does not apply to the delay of chemotherapy courses due to prolonged toxicity in the previous course. The therapeutic options for patients who progress during study treatment are not determined by this protocol, but according to our previous experiences (Herrlinger et al., 2006), intensified TMZ chemotherapy according to the one week on/off schedule (Wick et al., 2007) is recommended. To ensure reproducibility of MRI evaluation, all MRIs have to be reviewed by the reference neuroradiologist Prof. Dr. E. Hattingen, Division of Neuroradiology, Department of Radiology, Sigmund-Freud-Str. 25, 53105 Bonn. The MRIs have to be sent blinded (only labelled with Pat.-ID) to the reference neuroradiologist to ensure unbiased progression assessment.

In particular, the study visits include the following items:

- **Screening visit (week 1-3 after resection)**:
    - Written informed consent for neuropathology reference testing and for MGMT testing

- **Baseline visit (week 3 to 5 after resection)**:
    - Written informed consent for the trial
    - Inclusion/exclusion criteria (including MGMT and reference neuropathology test result)
    - Medical history and demographics
    - Vital signs
    - physical and neurological examination
    - concomitant medication
    - Karnofsky PS
    - Mini-Mental-Status evaluation and neurocognitive testing (NOA-07 test battery)
    - quality of life questionnaire
    - baseline contrast enhanced MRI scan (all post surgery MRIs not older than 3 weeks can be taken as baseline MRI (ideally early post surgery (72h))
    - ECG
    - spirometry
    - pregnancy test for women with reporductive potential
    - complete blood count and CRP
    - Blood sampling for translational studies

- serum chemistry and urine analysis
- coagulation
- Documentation of preexisting conditions in analogy to CTCAE
- Randomisation

- **At the beginning of each course of CCNU/TMZ or TMZ**:
  (Standard arm (TMZ): visit can be done within 5 days before start of cycle;
  Experimental arm (CCNU/TMZ): visit has to be done on day of cycle start.
  Before start of chemotherapy (concomitant TMZ or first cycle CCNU/TMZ: blood analysis obtained in Baseline can be used if not longer than 5 days old)
  - Assessment of survival
  - vital signs,
  - physical and neurological examination,
  - concomitant medication,
  - Karnofsky PS,
  - complete blood count and CRP,
  - serum chemistry and urine analysis,
  - coagulation,
  - CTCAE evaluation

Throughout all treatment courses of TMZ and CCNU/TMZ starting with radiotherapy a differential blood count has to be determined weekly by the general practitioner of each patient. The results have to be faxed within 24 hours to the treating center for review. In case pathological laboratory values are regarded by the local investigator to have medical consequences (e.g. grade 4 neutropenia requiring prophylactic antibiotic treatment) the differential blood count has to be repeated at the study center.

- **MRI/ progression assessment visits every 12 weeks (+/- 5 days) after randomization during study treatment and follow up until end of study**
- (Follow-up of all patients ends 36 months after the inclusion of the last patient. All patients in the trial are followed until this time point.)
  - vital signs
  - physical and neurological examination

- concomitant medication (all medication during the treatment phase, during follow-up this includes only the tumor-related medication)
- further tumor-directed therapy (surgery, radiotherapy, chemotherapy): day of start of further therapy, day of progression for each therapy
- Karnofsky PS
- Mini-Mental-Status evaluation
- quality of life questionnaire
- contrast-enhanced MRI scan
- NOA-07 test battery (only every 24 weeks)
- complete blood count and CRP
- Blood sampling for translational studies
- serum chemistry and urine analysis
- coagulation
- CTCAE evaluation
- Assessment of progression/survival

Table 2: Schedule of Study procedures

	Screening visit Week 1-3	Base-line visit Week 3-5 [2]	Treatment phase		After 6 courses of CCNU/TMZ or TMZ
			At the beginning of each course of CCNU/TMZ or TMZ	MRI/progression assessment visit every 12 weeks[1]	MRI/progression assessment visit every 12 weeks[1]
Clinical examination					
Informed consent for MGMT and reference neuropathology [3][3]	**x**				
Informed Consent for trial participation		**x**			
Results of MGMT testing and ref. neuropathology		**x**			
I / E criteria, demographics and medical history		**x**			
Evaluation of preexisting conditions in analogy to CTCAE		**x**			
Vital signs: BP, P, T, height, weight [1]		**x**	**x**	**x**	**x**
Physical and neurological examination		**x**	**x**	**x**	**x**
Concomitant medication		**x**	**x**	**x**	**X5**
Karnofsky PS		**x**	**x**	**x**	**x**
MMSE		**x**		**x**	**x**
NOA-07 test battery		**x**		**x (every 24 weeks)**	**x (every 24 weeks)**
QoL: EORTC QoL C30 and BN20		**x**		**x**	**x**
CTCAE evalutation		**x**	**x**	**x**	**x**
MRI and response assessment					
Gd-MRI		**x**		**x**	**x**
Progression/survival				**x**	**x**
Laboratory Testing					
Spirometry		**x**			
Serum pregnancy test [4]		**x**			
CBC with differential and CRP		**x**	**x**	**x**	**x**
Serum chemistry [5] and urinanalysis, coagulation		**x**	**x**	**x**	**x**
Blood sampling for translational studies		**x**		**x**	**x**

Abbreviations: BP = blood pressure, CTCAE = common terminology criteria for adverse events, ECG = electrocardiogramm, Gd = gadolinium-enhanced, I/E = inclusion/exclusion criteria, MRI = magnetic resonance imaging, MMSE =Mini Mental State Examination, NOA-07 test battery short neuropsychological test, PS = performance score, T = temperature

Comments: (1) Within 5 days before or after scheduled visit. (2) Baseline assessment to be performed ≤ 21 days prior to start of RT. (3) for trial, MGMT testing and reference neuropathology ≤ 21 days prior to start of study treatment. (4) For women with reproductive potential ≤ 14 days prior to enrollment. (5) Including ASAT, ALAT, gammaGT, AP, amylase, lipase, creatin kinase, total bilirubine, C-reactive protein, creatinine, Na, K, Ca, TSH.(5) Only tumor-directed comedication

6.2 Efficacy Evaluations

6.2.1 Definition of Efficacy Criteria

Response and progression will be evaluated using the response criteria defined by the Response Assessment in Neuro-Oncoloy Working Group (RANO, Wen et al., 2010) The measure of "size" of contrast-enhancing lesions on T1-weighted scans is the largest cross-sectional area (largest cross-sectional diameter x largest diameter perpendicular to it). Measurable lesions are defined as lesions with two perpendicular diameters of at least 10 mm, visible on two or more axial slices. The cystic or surgical cavity should not be measured in determining response. In case of multiple lesions, a maximum of five of the largest lesions may be measured.

T2 and/or FLAIR hyperintensities are also evaluated for response and progression. T2/FLAIR hyperintensities are only graded as “decreasing”, “stable” or “increasing” and are, according to the RANO criteria, not formally quantified. In general, “increasing” T2/FLAIR hyperintensities qualifying for progressive disease can only be diagnosed if it may be attributed to tumor growth (e.g. mass effect such as sulcal effacement, thickening of the corpus callosum, infiltration of the cortical ribbon or location outside the radiation field) AND other causes for increased T2/FLAIR hyperintensities are unlikely such as radiation effects, decreased corticosteroid dosing, demyelination, ischemic injury, infection, seizures, postoperative changes or other treatment effects. In unclear cases, a repeat MRI 4 weeks later is recommended.

Clinical criteria such as neurological status and steroid usage are also taken into account to determine response and progression. The neurological status is graded as “improving”, “stable” or “worsening”. Steroid usage is not taken into account for the definition of progressive disease (PD). In general, to label the neurological status as “worsening”, it should be unlikely that the deterioration of the neurological status is caused by comorbid events such as radiation therapy, reduction or termination of steroid dosage, comedication adverse events, cerebrovascular events, complications of therapy, infection, seizures, postoperative changes or other treatment effects. Clinical worsening has to be present for 7 days or more. Clinical progression should be always

further substantiated by demonstration of progressive contrast.-enhancing lesions on MRI.

The RANO criteria are in general as follows:

- ***Complete Response (CR):*** Disappearance of all measurable contrast enhancing lesions in magnetic resonance imaging at least 4 weeks apart, T2/FLAIR lesions stable or decreasing, without steroids and neurologically stable or improved.
- ***Partial Response (PR):*** At least 50% reduction in the size of all measurable contrast enhancing lesions in magnetic resonance imaging at least 4 weeks apart, T2/FLAIR lesions stable or decreasing, steroids stable or reduced, and neurologically stable or improved.
- ***Stable disease:*** Less than 50% reduction or less than 25% increase in the size of a solid mass or all contrast enhancing lesions in magnetic resonance imaging, with no escalation of steroid treatment and no neurological deterioration.
- ***Progression:*** At least 25% increase in the size of measurable contrast enhancing lesions in magnetic resonance imaging OR clear increase of a non-measurable lesion or the appearance of a new lesion OR significantly increasing T2/FLAIR hyperintensities (only if other causes for increased T2/FLAIR hyperintensities are unlikely such as radiation effects, decreased corticosteroid dosing, demyelination, ischemic injury, infection, seizures, postoperative changes or other treatment effects) OR clear and significant worsening of the neurological status not attribuable to other causes apart from the tumor (see above)

For the interpretation of the study´s results we introduced some modifications of the RANO criteria (refered to as “modified RANO criteria”) as the following restrictions in the RANO response assessment apply to MRI and clinical controls in the early phase of the treatment:

- It is important to note that due to the tendency of MGMT-methylated GBMs to develop pseudoprogression (Brandes et al., 2008), progression of contrast-enhancing lesions or T2/FLAIR lesions in the first MRI after completion of radiotherapy (scan scheduled for week 12) or in any unscheduled clinical and/or MRI examination up to 12 week after completion of radiotherapy is only regarded as progressive disease (PD) if one of the following criteria apply
    - new enhancement outside the radiation field (i.e. beyond the 80% isodose)

- unequivocal evidence of viable tumor on histopathologic sampling (after re-surgery)

- Since in some cases treated with CCNU/TMZ (Stuplich et al., in preparation), pseudoprogression may even ensue later than 12 weeks after the end of radiotherapy, i.e. up to the second scheduled clinical and MRI control examination 24 weeks after randomization, PD can only be diagnosed between week 12 after the end of radiotherapy and the scheduled clinical and MRI examination visit 24 weeks after randomization inclusively if progression according to the RANO criteria given above is confirmed in a scan 4 to 6weeks after the scan suggesting progression. Therapy within the trial has to continue until confirmation of progression in the MRI scan 4 weeks later. If PD is confirmed, the earliest timepoint at which the criteria for PD had been fulfilled will be taken as the timepoint to calculate progression-free survival.

In any case PD is diagnosed in the local center according to the criteria given above, all MRIs starting with the baseline MRI have to be immediately sent to the reference neuroradiologist Prof. Dr. Elke Hattingen, Division of Neuroradiology, Department of Radiology, Sigmund-Freud-Str. 25, 53105 Bonn. The MRIs have to be sent blinded (only labelled with Pat.-ID) to the reference neuroradiologist to ensure unbiased progression assessment. Therapy within the trial has to continue until confirmation of progression in the MRI scan by the reference neuroradiologist.

6.2.2 Definition and evaluation of efficacy endpoints

Overall survival (Primary endpoint): Survival is defined as the duration from randomization to the date of death due to any cause.

Progression-free survival: The progression-free survival is defined as the time from randomization to the first documented evidence of progression of disease according to the modified RANO criteria.

Overall Response: The overall response rate is defined as the relative proportion of patients with complete and partial responses.

Time to Treatment Failure: Time to treatment failure is defined as the duration from the day of diagnosis (surgery obtaining histology) to any of the following:

- Death for any reason
- relapse or progressive disease (PD) during or after study treatment,
- discontinuation of combined CCNU/TMZ treatment for any reason before the completion of 3 cycles CCNU/TMZ

Frequency of delay of the next CCNU/TMZ or TMZ course by more than 2 weeks

Quality of Life: The EORTC QoL questionnaire modules QLQ-C30 and BN20 will be used to assess the quality of life. These assessments will be performed on the visits specified in the Time and Events Schedule. Patients will be given these questionnaires to complete by a study center staff member. The staff member will collect each completed assessment and check it for completeness before giving the patient the next assessment to complete.

The European Organization for Research and Treatment of Cancer (EORTC) QoL (Quality of Life Questionnaire) – BN20 is a well validated and internationally recognized questionnaire designed to reflect the core dimensions of patients' QoL. The 30 item questionnaire incorporates five functional scales: general physical symptoms, physical functioning, psychological distress, social functioning, and fatigue/malaise. Most items are rated on a 4 point Likert scale ranging from "not at all" to "very much". Seven questions regarding physical functioning/evaluation of activities of daily living are in a simple dichotomous yes/no format. Two global QoL questions complete the questionnaire and are arranged in visual analogue format with superimposed numbers ranging from 1-7. The questionnaire is designed to be self-administered following a brief explanation of its purpose and format. It takes approximately 10 minutes to complete the questionnaire both in the pretreatment setting as well as while the patients are on treatment. The questionnaire has demonstrated validity in different cancer populations as well as in different disease stages and their associated treatments. Test-retest reliability of the core questionnaire tested within a four day period ranged from good to excellent for all functional scales with Pearson's r values ranging from 0.72 to 0.91. The EORTC QoL-BN20 has been used successfully in several clinical trials.

Assessment of treatment-related neurotoxicity: T2-weighted MRI imaging will be used to detect leukencephalopathic changes. To detect neurotoxicity-associated cognitive deficits, a written assessment of treatment-related cognitive dysfunction (NOA-07 test battery) will be performed. The computer-based test battery comprises subtests for attention, working memory, viseoperceptive performance and verbal fluency. This test is already in use in another neurooncological trial (NOA-07).

6.3 Safety Evaluations

Safety is monitored continuously throughout the trial as detailed in Table 2 “Time and Schedule of Events”. The study will include the following evaluations of safety and tolerability:

Adverse Events: Adverse events will be reported throughout the study at each visit. Adverse events will be followed by the investigator.

Clinical Laboratory Tests: Laboratory tests at each visit will be performed at the Laboratory of the treating University Medical Center. Between visits, weekly laboratory testings are performed by the general practitioner or oncologist of the patients and results are to be faxed within 24 hours to the local investigator. All laboratory reports will be reviewed by the investigator. This review must be documented, and any clinically relevant changes occurring during the study must be recorded in the adverse event section of the CRF.

Vital Signs

Physical and neurologic examination: Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

Karnofsky performance score: Karnofsky performance score is outlined in appendix 1

NOA-07 test battery: the NOA_07 test battery is outlined in section 9.2.7.

MMST: The MMST is outlined in appendix 2

General safety monitoring: The management of SAE within the study group will be according to ICH GCP, i.e. depending on the criteria expected/unexpected, suspected/

not suspected, dead/alive SAEs have to be announced to the sponsor within the legal time frame. Similarly, the sponsor will announce SAEs to the authorities within the legal time frame. For details see chapter 7 (adverse event reporting). Safety is independently monitored by the Data monitoring and safety board as detailed below.

6.4 Data monitoring and safety board (DMSB)

The trial is supervised by an independent Data Monitoring and Safety Board (DMSB). The tasks of the DMSB in the CeTeG trial are the following:

- The DMSB will review all serious adverse advents (SAE) of all patients so far recruited to the trial every half a year.
- In case of more than 1 patient with toxic death per 20 patients recruited, all safety information is provided to the DMSB independently of the 6 months turn for SAE reviewing.
- The coordinating PI (LKP) can ask the DMSB at any time to review any data from the trial and to decide whether to procede with the trial without changes, to modify the trial or to stop the trial entirely. It may be for example necessary to modify the trial if during the ongoing trial the results of another randomized trial define a new standard of primary GBM therapy which will have impact on the standard arm of the ongoing trial. The data provided to the DMSB for review may include so far unmonitored data. In case a decision has to be made regarding the stopping or continuation of the trial, an extra monitoring visit has to monitor the data relevant for this decision.
- All amendments for the trial protocol are provided to the DMSB.
- The DMSB is free to suggest any modifications regarding the trial (e.g. stopping of the trial, modifications of the protocol). The DMSB will convene by telephone conference every 6 months to discuss whether any action has to be taken. The last DMSB telephone conference on the 6 months schedule will be held about 1 year after the inclusion of the last patient, i.e. 4 months after the end of any trial-associated chemotherapy.

Set up, members and tasks of the DSMB are outlined in detail in the DMSB manual.

7. ADVERSE EVENT REPORTING

The definitions and reporting requirements of ICH Guideline for Clinical Safety Data, Management, Definitions and Standards for Expedited Reporting, Topic E2 will be adhered to. This is briefly described below.

7.1 Definitions

7.1.1 Adverse event definitions and classifications

Adverse Events

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event includes any unfavorable and unintended sign including an abnormal finding, symptom, or disease temporally associated with the study treatment as well as any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures including laboratory test abnormalities whether or not related to the product.

The clinical manifestation of any failure of expected pharmacological action is not recorded as an adverse event. If, however, the event fulfils any of the criteria for a “serious” adverse event, it must be recorded and reported as such. Investigators should also report signs and symptoms when ever present that are associated with the progressive disease.

The ZKS Cologne as the institution responsible for data management collects all adverse events data and is responsible for SAE handling, documentation and reporting to the authorities.

Serious adverse event

A serious adverse event is any untoward medical occurrence with the study treatment at any dose that meets any of the following conditions:

- results in death excluding death due to progression of disease unless related to study treatment. Exception: if the investigator deems the tumor progression to be related to the use of the study drug.

- is life-threatening at the time of the event i.e. immediate risk of dying
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- results in congenital anomaly or birth defect
- is considered significant and serious by the investigator for any other reason

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations; for example, important medical events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. Any adverse event is considered a serious adverse event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Life-threatening:

The term “life-threatening” in the definition of “serious” refers to an adverse event in which the patient was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.

Hospitalization:

Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as serious, UNLESS at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours.

OR

- The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study).

OR

- The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care).

It should be noted that invasive treatment during any hospitalization may fulfill the criteria of 'medically important' and as such may be reportable as a serious adverse event dependant on clinical judgement. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability:

Means a substantial disruption of a person's ability to conduct normal life functions.

Unexpected adverse event

An unexpected adverse event, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or the package insert/summary of product characteristics for an approved product). Also, reports which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected adverse events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered "unexpected".

Association with the use of the drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable or very likely by the definitions listed in Section 13.1.2.

Suspected unexpected serious adverse reaction (SUSAR)

The suspicious case of an unexpected serious adverse reaction is defined as Suspected Unexpected Serious Adverse Reaction (SUSAR) as EU-Directive 2001/20/EC.They require very rapid notification of the Competent Authorities. Is the SUSAR fatal or life-threatening the Ethics Committee and Regulatory Agency will be notified (e.g. by telephone, facsimile transmission, or in writing) as soon as possible but no later than 7 calendar days after first knowledge by the sponsor that a case qualifies, followed by as complete a report as possible within 8 additional calendar days. This report will include an assessment of the importance and implication of the findings.

All other suspected unexpected serious ADRs, which are not fatal or life-threatening, must be reported as soon as possible but no later than 15 calendar days after first knowledge by the sponsor that the case meets the minimum criteria for expedited reporting.

The initial reports submitted will contain at least: randomization number, a suspect medicinal product, an identifiable reporting source, description of SAE, and for which there is a reasonable suspected causal relationship, the sponsor's unique case identifier and the study protocol or EudraCT number. Follow-up information will be actively sought and submitted as it becomes available.

7.1.2 Documentation and assessment of adverse events

Adverse events contain as defined all diseases, clinical signs or symptoms, which appear after randomization of patients.

The **type** is determined as followed:
- continuous
- intermittent

The **maximum intensity** is defined as
- mild
- moderate
- severe

The **relationship to the trial medication** has to be described as
- certain
- probable
- possible
- unlikely

The **outcome is described** as follows:
- recovered
- improved
- unchanged
- worsened
- death
- unknown

7.2 Procedures

7.2.1 All adverse events

All adverse events that occur between the first study-related procedure and 30 days following the last study-related procedure (excluding follow-up) and medical conditions prevalent prior to the first study-related procedure will be recorded. All adverse events

must be followed to satisfactory resolution or stabilization of the events. Any adverse event meeting the definition of SAE must be reported using the SAE form.

All adverse events, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as “upper respiratory infection”. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The coordinating principal investigator as the designee of the sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities and to the appropriate IEC/IRB. This includes the second assessment concerning seriousness, relatedness and expectedness regarding SAEs. Additionally the sponsor is responsible for the continuous evaluation of the risk/benefit ratio of the trial. Changes in the risk/benefit ratio have to be reported to the regulatory authorities and to the appropriate IEC/IRB within in 15 days of awareness.

Patients (or their designee, if appropriate) must be provided with a “study card” indicating the name of the investigational product, the study number, the investigator’s name and a 24-hour emergency contact number.

7.2.2 Serious Adverse Events

Reporting of Serious Adverse Events

All serious adverse events occurring during clinical studies and within 30 days following the last study-related procedure must be reported by the investigator **within 24 hours** of their knowledge of the event by fax to the following address:

ZKS Cologne
Gleueler Str. 269, 50935 Cologne
Telefon: 0221- 478 - 88137
Fax: 0221- 478 - 7984

The ZKS Cologne is responsible for SAE handling and documentation, SAE quality assurance, SAE- reporting to BfArM / CA / investigators and development of SAE database.

A serious adverse event form must also be completed within 24 hours of the awareness and forwarded to the above mentioned address. Each serious adverse event must be followed up until resolution or stabilization, by submission of updated reports. All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the patient's participation in the study, must be followed until any of the following occurs:

- the event resolves
- the event stabilizes
- the event returns to baseline, if a baseline value is available
- the event can be attributed to agents other than the study drug or to factors unrelated to study conduct, or
- when it becomes unlikely that any additional information can be obtained (patient or health care practitioner refusal to provide additional information, lost to follow up after demonstration of due diligence with follow-up efforts)

Reporting of pregnancy

In the event of a pregnancy occurring in a patient or in a partner of a male patient after the first dose of the trial medication was applied has to be recorded on a pregnancy

form. This form must be reported by the investigator **within 24 hours** of their knowledge of the event by fax to the following address:

ZKS Cologne
Gleueler Str. 269, 50935 Cologne
Telefon: 0221- 478 - 88137
Fax: 0221- 478 – 7984

Monitoring of the patient will be continued until the conclusion of the pregnancy.

Development Safety Update Report – DSUR (former Annual Safety Report)

Once per year, the sponsor or PCI will supply a report on the safety of trial subjects with all available relevant information concerning patient safety during the reference period to the competent supreme federal authority and the competent authorities of all other member states of the EU or EEA where the trial is being conducted. This report will also be supplied to the responsible ethics committee.

The annual safety report will be compiled according to the corresponding ICH guideline E2F „Development Safety Update Report – DSUR“
The data-lock point for the patient data to be included and analyzed refers to the 11.06.2010 as day of clinical trial approval by the competent authority (BfArM).
The sponsor or PCI will supply the report within 60 days of one year after the reference date (data-lock point).

8. REFERENCE CENTERS

8.1 Neuropathology Reference Center

Before inclusion in the trial, the histological diagnosis of glioblastoma has to be confirmed by reference neuropathology. After obtaining informed consent for reference neuropathology and MGMT analysis a block of paraffin-embedded tissue has to be sent for reference neuropathology review to the following address.

Prof.Dr.T.Pietsch
Department of Neuropathology
University of Bonn Medical School
Sigmund-Freud-Str. 25, 53105 Bonn
Fax: 0228 2871 4331
Tel.: 0228 2871 6602

The result of reference histology is communicated to the local center within 10 days. Furthermore, the reference neuropathology center also sends part of the tissue to MDxHealth for MGMT promoter methylation status determination.

8.2 Central determination of MGMT status

MGMT promoter analysis is performed by

MDxHealth S.A. / HistoGeneX
Campus Middelheim
Laboratory building
Lindendreef 1
2020 Antwerpen
BELGIUM
T: +32 (0) 32181910
F: +32 (0) 32300265

The test is performed on DNA from paraffin-embedded tissue using methylation-specific PCR. All analyses are performed according to internal SOPs. Tissue blocks are sent from the Department of Neuropathology to MDxHealth for MGMT testing. Sending of tissue blocks directly from the local centers to MDxHealth is not necessary. The results of the MGMT promoter analysis is communicated by email to the local treating center within 6 days after receiving the tissue block. In case of a non-methylated test result i.e. with a ratio of <2, the patient is not eligible for study treatment, cannot be randomized and is excluded from the the trial. Local testing of MGMT methylation status is discouraged.

8.3 Neuroradiology Reference Center

In case of progressive disease determined by the local neuroradiologist, contrast-enhanced MRIs showing progression as well as all previous MRIs have to be sent to the reference neuroradiologist for reference analysis:

Prof. Dr. Elke Hattingen

Division of Neuroradiology, Department of Radiology, University of Bonn Medical Center

Sigmund-Freud-Str. 25, 53105 Bonn

Phone: +49-228-2871 6389, Fax: +49-228-2871 4321,
Email: susanne.greschus@ukb.uni-bonn.de

The MRIs should be sent as electronic files on CD. The MRIs have to be sent blinded (only labelled with Pat.-ID) to ensure unbiased progression assessment. MRIs have to be accompanied by the Neuroradiology reference form (appendix 4). Results will be communicated within 5 working days. Study therapy is only discontinued if progressive disease is confirmed by reference neuroradiology. After the end of the study-specific follow-up of 3 years it is nevertheless mandatory to further follow-up the patient with contrast-enhanced MRI every 3 months until death.

9. STATISTICS

9.1 Sample Size Consideration

The trial has to accrue 128 evaluable patients (64 evaluable patients per arm). The sample size calculation is based on the following facts:

- The EORTC/NCIC trial (Hegi et al., 2005) showed that patients with a methylated MGMT promoter treated with standard TMZ chemotherapy (identical regarding inclusion criteria and therapy to the patients in the standard arm of the proposed CeTeG trial) have a 2 year overall survival rate of 48.9%
- The UKT-03 trial (Herrlinger et al., 2006; Glas et al., 2009) showed that patients with a methylated MGMT promoter treated with CCNU/TMZ (identical regarding inclusion criteria and therapy to the patients in the experimental arm of the proposed CeTeG trial) have a 2 year overall survival rate of 75%.

Overall survival (OS) is the primary outcome parameter on which power and sample size calculations for the CeTeG trial are based. It is expected that in the CeTeG trial the experimental CCNU/TMZ therapy can increase the 2 year survival rate from 48.9% in the standard arm to 70% in the experimental arm (slightly less than the 75% observed in the previous phase II trial). Assuming this increase in overall and assuming exponentially distributed survival times, a constant recruitment of 64 patients per treatment group over two years with a follow-up of additional three years will result in a power of 80% for the intended two-sided log-rank test (level of 5%). This timepoint has been delayed from 24 months in previous versions of the protocol to 36 months.The reasons for this delay were as follows:

The assumptions for the initial planning of the trial match to event (death) rates of 0.356 and 0.176 events per patient year and result in an expected number of 68 events after two years of recruitment and two years of follow-up. . A blinded analysis of the overall survival time 14 months after last-patient-in (36 months after first-patient-in) showed that there is an overall mean risk for the event “death” of 0.1994/patient year due to an unexpected low number of events at this time and indicating a low number of events at the end of the intended follow-up-time which might result in a power lower as expected. With the observed actual event rate and an assumed OR of 2 as planned, the 68 events required for an analysis with a sufficient power of 80% can be reached by a prolongation of the follow-up time to April 2017, i.e. 36 months after last-patient-in. The sample size calculation was performed using the “PS” power and sample size program (Dupont and Plummer, 1997) and additional simulation analysis. Assuming that 6% of patients may not be analyzable for the primary endpoint OS due to non-compliance or loss to follow-up before the start of chemotherapy, additional 8 patients adding up to a total of 136 MGMT-methylated patients have to be randomized for the trial. Dropout patients and patients lost for follow-up after the start of chemotherapy will be evaluated as observations censored at the time of dropout. The figure of approx. 6% patients who may be non-compliant and/or lost for follow-up for the ITT evaluation of the pimary endpoint may be overestimated. In the previous bicentric phase II trial with CCNU/TMZ (Herrlinger et al., 2006; Glas et al., 2009), none of the 31 patients included was lost for follow-up or non-compliant. This corresponds to experiences of most centers with other trials for untreated GBM such as the so far not published phase II cilengitide trial. In experienced neurooncological centers as the ones taking part in the CeTeG trial, the lost-to-follow-up rate ist very low. The long-term analysis of the EORTC/NCIC trial

defining the CeTeG standard arm shows that only 9 of the 573 patients (1.6%) randomized refused further involvement in the trial (Stupp et al., 2009). The situation in the EORTC/NCIC trial can well be transferred to the situation in the CeTeG trial since some of the centers in the CeTeG trial have already participated in the EORTC/NCIC trial. To have nevertheless an adequate safety margin it appears to be prudent to calculate with a higher, i.e. 6% non-compliance rate until the start of chemotherapy. Since the ITT evaluation comprises all patients that have receive a first dose of chemotherapy (labelled as censored observations) the expectedly low rate of malcompliance and loss for follow-up rate after the start of chemotherapy is not important for the adequate analysis of the trial.

A methylated MGMT status and confirmation of GBM histology by the neuropathology reference center are the major inclusion criteria which are not yet available during the screening visit but which have to be fulfilled for randomization. Thus, it has to be taken into account that also a few patients with a non-methylated MGMT promoter and mMGMT patients with local GBM histology but reference diagnoses other than GBM (reference neuropathology is performed after MGMT testing) are screened for the trial. According to the German Neuropathology Reference Center at the Department of Neuropathology, University of Bonn, which is also serving as reference center for this trial, approx. 7% of the local diagnoses of GBM cannot be confirmed by the reference center (T. Pietsch, personal communication). Thus, if 136 patients have to be randomized, reference neuropathology has to be performed on 145 patients. Assuming that only 45% of newly diagnosed GBM patients have a mMGMT tumor (Hegi et al., 2005), for 145 patients evaluated in reference pathology, 322 patients with newly diagnosed GBM and matching inclusion/exclusion criteria have to be screened and analyzed for MGMT promoter methylation status (“patients screened for eligibility”).

9.2 Randomization

Randomization is carried out as central fax randomization. The randomization form (appendix 3) has to be faxed to the following address:

Clinical Study Core Unit, SZB
Institute of Clinical Chemistry and Chlincal Pharmacology
University of Bonn

Fax: 0228 2871 16039

Phone (in case of any problems): 0228 2871 16040

Randomziation is carried out according to a predefined randomization list for each center provided by the Institut für Medizinische Biometrie, Informatik und Epidemiologie (IMBIE), University of Bonn**.** Due to the different schedules for application of CCNU/TMZ (6 week courses) and standard TMZ (4-week courses), blinding of patients and of the treating physician is not possible. However, the reference neuroradiologist determining the day of progression on MRI will be blinded to the treatment protocol.

Randomization is stratified per participating center. Since age (<50 vs. ≥50 years), performance score (WHO performance score 0 vs. 1 or 2), extent of surgery (complete or partial resection vs. biopsy only) and mental state (MMSE ≥27 vs. <27) are strong prognostic factors in patients with newly diagnosed GBM (Gorlia et al., 2008), it would be desirable to also stratify randomization according to these parameters. With an average number of 10 patients recruited per center this does not appear to be feasible. Therefore, randomization is only stratified by center and the other prognostic factors are taken into account in the prespecified data analysis. The above mentioned prognostic factors have been implemented in 3 prognostic classes of GBM patients that have been developed by recursive partitioning analysis (RPA, Curran et al., 1993), validated in further trials (Scott et al., 1998) and further modified and validated using the data of the EORTC/NCIC trial (Mirmanoff et al., 2006) which defines the standard arm of CeTeG. The confirmatory analysis of the CeTeG trial will therefore analyze the primary endpoint OS not only stratified by center but also stratified by RPA class.

9.3 Statistical and Analytical Methods: Efficacy parameters

Statistical analysis starts 36 months after the inclusion of the last patient Statistical analysis will be performed at the Institute of Medical Biometry, Informatics and Epidemiology (IMBIE) at the University of Bonn Medical Center (Dir.: Prof. Dr. Matthias Schmid). OS, the primary parameter, will be compared between treatment groups using a two-sided log-rank-test at a level of 5% stratified for center and for RPA class. Centers contributing less than 3 patients for one arm of the treatment arms are pooled in this analysis.The primary confirmatory analysis will be based on the intention-to-treat (ITT) population. The ITT population contains all patients who have received a first dose

of chemotherapy (CCNU in the experimental arm and TMZ in the standard arm). Dropouts will be evaluated as censored observations at the time of dropout. An additional comparison will be made based on the per protocol population. The results of both analyses should be consistent. The per-protocol analysis includes all patients who have received two courses of CCNU/TMZ in the experimental arm or concomitant TMZ plus one course of adjuvant TMZ in the standard arm. Additionally, an analysis of the "as randomized" population will be performed.

The following secondary efficacy endpoints are also determined:

- Progression-free survival (PFS) determined by MRI (modified RANO criteria)
- Best response rate determined by MRI (modified RANO criteria)
- Frequency of delay of the next CCNU/TMZ or TMZ course by more than 2 weeks
- Acute toxicity during radiotherapy and chemotherapy according to CTC AE V4.0
- Quality of life, determined by EORTC QLQ questionnaires
- Evaluation of late neurotoxicity by MMSE and NOA-07 test battery

Survival parameters are measured in days starting from the day of start of treatment (first day of RT). Surviving patients and patients lost for follow-up are censored for the Kaplan-Meyer analysis. Overall survival and progression-free survival will be summarized by Kaplan-Meier curves. Median time estimates as well as associated 95% confidence intervals will be reported. In addition Cox regression analyses adjusted and unadjusted for stratification factors such as age, performance score, extent of resection will be performed in an exploratory manner. The analysis will be based on the intent-to-treat population and repeated for the per-protocol population.

A plan for the complete analysis of the collected data will be developed before the end of the data collection. All additional analyses such as subgroup analyses (PFS and OS according to resection status) will be purely descriptive.

9.4 Safety Analysis

Patients who did not receive at least one dose of any study medication will be excluded from the analysis of safety. Tables of adverse event incidence (preferred term classification) and individual incidence will be produced. A complementary analysis of adverse events by severity of event and by relationship to trial treatment will also be performed. Dose reductions, delay of therapy in subsequent courses ("Frequency of

delay of the next CCNU/TMZ or TMZ course by more than 2 weeks" as secondary endpoint) and premature withdrawals will also be described.

9.5 Assessment of Quality of life and late neurotoxicity

Quality of life (QoL) is recorded through the standardized an validated EORTC QLQ-C30 and BN20 questionnaires (Osoba et al., 1996). These questionnaires contain a total of 30 QoL-related questions which are scored on a nominal scale (0-5 points); the result of each question is recorded for computerized examination and the questions relating to the same dimension of QoL (e.g. emotional well-being) are taken together for an overall score of this dimension. The scores for the different dimensions will be compared between repeated assessments throughout the trial and between the two arms of the trial.

MMSE is recorded as a point score with a maximum of 30 points. Values above 26 points are regarded as normal. The short neuropsychological test *The NOA-07 test battery* tests the performance in the 4 following neuropsychological dimensions:
1. Attention as measured by the Trail Making test B (Lezak et al. 1995), 2. Working memory as determined by the module "figure repeating" of the HAWIE-R test (Tewes et al., 1994), 3. viseoperceptive performance as determined by the Trail making test A (Lezak et al., 1995) and 4. alphabetic (controlled Oral Word association Test COWA, Benton eand Hamsher, 1989) and semantic verbal fluency (Lezak et al., 1995).
The scores for the different dimensions will be compared between repeated assessments throughout the trial.

10. INVESTIGATIONAL PRODUCT LOGISTICS

CCNU and TMZ are both commercially available drugs approved for marketing authorization in Germany. Therefore the capsules are prescribed by the treating physician and provided by the local pharmacy. Drugs are to be kept in an appropriate, secure, locked area at the pharmacy of the participating center and are supplied on the day of intake by the pharmacy. CCNU will be taken by the patient in the hospital under supervision of study personnel. TMZ (day 2-6 of each course) is distributed by the trial center and taken on an outpatient base. The health insurance will be charged for the standard treatment whereas the chemotherapy given in the experimental arm will be covered by the trial organisation. The investigator, or a responsible party designated by

the investigator, will maintain a careful record of the inventory and disposition of all drugs received using the Drug Accountability Record form. Since this is an open study and drugs are approved for marketing authorization no labelling will be performed.

11. ETHICAL AND REGULATORY ASPECTS

The patients in the standard arm receive the current standard therapy of primary GBM therapy. The regimen used for the experimental arm is well supported by previous phase II data (Herrlinger et al., 2006, Glas et al., 2009). According to the non-randomized phase II data, the patients in the experimental CCNU/TMZ arm may have more myelotoxicity which may be balanced by the expected superior efficacy. The patients in the standard arm will undergo up-to date standard therapy without frequent and severe myelotoxicity. All trial participants will receive superior neurooncological care (e.g. frequent MRI and clinical follow-up by an experienced team) as compared to community standards, i.e. patients may realize benefits form participation in the trial even if they are randomized to the standard arm.
All investigators are responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory requirements.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have originated in the Declaration of Helsinki, and that the clinical study data are credible.

11.1 Independent Ethics Committee (IEC)

Documented approval from appropriate Ethics Committee(s) will be obtained for all participating centers prior to study start, according to ICH GCP, local laws, and regulations. The trial starts only after an uinconditional approval of the leading Ethics committee at the University of Bonn has been obtained. Each participating center can start the trial if the local Ethics Committee has approved the local center and the local investigators as suitable for conducting this trial.

11.2 Ethical Conduct of the Study

The procedures set out in this protocol, regarding conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide the Good Clinical Practice Guidelines and the guiding principals detailed in the Declaration of Helsinki. The trial will also be carried out in keeping with applicable local law(s) and regulation(s). This may include an inspection by sponsor-representatives and/or Regulatory Authority representatives at any time. The investigator must agree to the inspection of study-related records by the Regulatory Authority/sponsor representatives, and must allow direct access to source documents to the Regulatory Authority/sponsor representatives.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties.

11.3 Regulatory Authority Approvals/Authorisations

Regulatory authority approvals/authorisations/notifications, where required, will be in place and fully documented prior to study start.

11.4 Insurance

All subjects participating in the study will have insurance coverage by the sponsor, which is in line with applicable laws and/or regulations.

Adress of insurance:
Ecclesia mildenberger Hospital GmbH
Klingenbergstraße 4
32754 Detmold
Fax: 05231-603-440
Insurance Number: 5701032303010

11.5 Informed Consent

Each patient must give written consent according to local requirements after the study has been fully explained. The consent form must be signed before performance of any

study-related activity. The consent form that is used must be approved by both the sponsor and by the reviewing IEC. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before entry into the study, the local investigator must explain to potential patients the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort it may entail. Patients will be informed that their participation is voluntary and that they may withdraw consent to participate at any time for any reason. They will be informed that choosing not to participate or to withdraw their consent will not affect the care they will receive for the treatment of his/her disease. Patients will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a patient identification register for the purposes of long-term follow-up if needed and that their records may be accessed by competent authorities and authorized sponsor staff without violating the confidentiality of the patient, to the extent permitted by the applicable law(s) or regulations. By signing the informed consent form the patient is authorizing such access. During the written informed consent process, the patients are informed about their obligations in case of any problem which may be relevant for the insurance.

The patient will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry to the study, consent should be appropriately recorded by the patients` dated signature. After having obtained the consent, a copy of the informed consent form must be given to the patient.

If the patient is unable to read or write, an impartial witness should be present for the entire informed consent process which includes reading and explaining all written information and personally date and sign the informed consent form after the oral consent of the patient is obtained.

Written informed consent in the CeTeG trial is obtained in two steps. First, at the screening visit, patients are asked to consent to reference neuropathology and MGMT testing. In the second step after obtaining the results of reference neuropathology and MGMT promotor methylation analysis, patients are asked to consent to participation in the trial.

In case the patient wants to withdraw from study treatment he will be asked to consent to continuation of monitoring of disease progression every 12 weeks as planned in this study and as standard in routine patient care.

11.6 Data handling and record keeping

The collection and processing of personal data from patients enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational product(s) used in this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

The coordinating principal investigator as the designee of the sponsor ensures that the personal data are

- processed fairly and lawfully
- collected for specified, explicit, and legitimate purposes and not further processed in a way incompatible with these purposes
- adequate, relevant, and not excessive in relation to said purposes
- accurate and, where necessary, kept up to date

Explicit consent for the processing of personal data will be obtained from the participating patient before collection of data. Such consent will also address the transfer of the data to other entities such as regulatory authorities.

The patient has the right to request through the investigator access to his/her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps should be taken to respond to such request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental

loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study patients confidential.

The plausibility of the data will be ensured by an GCP-conform data management (ZKS Cologne).

11.7 Financing

The trial is supprted by a grant form the German Ministry of Education and Research (BMBF). This covers all costs for the trial (organization, management, case payments, data and adverse event processing and analysis, communication with regulatory authorities) including medication in the experimental arm. All trial procedures that are part of standard therapy for glioblastoma first-line therapy are paid for by the health insurance companies of the pariticipating patients. For example, this includes medication in the standard arm, contrast-enhanced MRI every 12 weeks and weekly laboratory tests.

12. REGULATORY DOCUMENTATION

12.1 Patient Identification Register and Patient Screening Log

The local principal investigator agrees to complete a patient identification register to permit easy identification of each patient during and after the study.

The patient identification register will be treated as confidential and will be filed by the investigator in the Trial Center File. To ensure patient confidentiality, no copy will be made. All reports and communications relating to the study will identify patients by assigned number only.

The investigator must also complete a Patient Screening Log, which reports on all patients who were seen to determine eligibility for inclusion in the study.

12.2 Case Report Form Completion

CRF are provided for each patient in paper format.

All data obtained in this study are source data. The clinical site study staff members will record the data on source documents immediately, except for data that are available on

original printouts or as data files. The study data will be transcribed by study personnel from the source documents, i.e. hospital records, into CRF

All data relating to the study must be recorded in CRF. The investigator verifies that all data entries in the CRF are accurate and correct.

The study file and all source data should be stored until notification by the principle investigator.

12.3 Data Processing and Data management

IT-Infrastructure and personnel for data management will be provided by the Clinical Trial Centre Cologne (ZKS Köln). The clinical trial database will be developed and validated at the ZKS according to their Standard Operating Procedures (SOPs).

The data management system is based on a validated commercial Clinical Data Management System study software. Data is stored in a database. Changes of the data will be documented and saved in an audit trail. The Clinical Data Management System provides a study-specific user and role concept. The database is integrated in a general IT-infrastructure system with firewall and backup system. The data is saved daily.

After completion of data entry and resolving all outstanding queries, the database will be closed and the data will be exported for statistical analysis. All documentation forms are registered and checked for completeness by the Clinical Trial Centre Cologne (ZKS Köln). Data will be entered doubly by two independent data admissioners and aligned in a validated study database. Additionally, there will be checks of plausibility. Data discrepancies and implausibilities will be clarified with the study center in written form (queries). Queries will be answered timely by the study center. Details will be defined in a data management manual.

All correspondence related to this clinical study should be kept in appropriate study files. Records of patients, source documents, CRFs, and IRB/IEC pertaining to the study must be kept on file. All original patient, laboratory, and study drug inventory records relating to the study shall be retained for not less than 2 years.

12.4 Safe-Keeping of Trial Documents

Original documents will be safely kept in the trial managing office at least for 15 years after finishing of the final trial report.

The principal investigator will take care about all administrative data (exchange of letters with Ethics Committee(s), regulatory authority and trial coordination), patients' informed consent, patient's identification list, copies of the study documentation (protocol, amendments) for above mentioned time period.

Original patient's data are kept for the study center current archival storage period, but not less than 15 years.

13. ADMINISTRATIVE REQUIREMENTS /QUALITY ASSURANCE

13.1 Protocol Modifications

All protocol amendments must be issued by the sponsor, signed and dated by the coordinating principal investigator, and cannot be implemented without prior IEC approval and, if applicable, competent authority authorization, except where necessary to eliminate immediate hazards to the patients or when the changes involves only logistical or administrative aspects of the study (e.g., typographical errors, inconsistencies).

In situations requiring a deviation from the protocol, the deviation must be authorized by the coordinating principal investigator. CRFs and source documents have to describe any deviation from the protocol and the circumstances requiring it.

13.2 Adherence to standard operating procedures (SOPs)

All physicians involved in this trial will adhere to their local SOPs for the conduct of clinical trials. Also, the guidelines of the Deutsche Gesellschaft für Neurologie (DGN)

and the Neuroonkologische Arbeitsgemeinschaft in der Deutschen Krebsgesellschaft (NOA) are observed.

13.3 Monitoring

According to the ‚Good Clinical Practice' (GCP) and in order monitoring of the trial will be accomplished.

Objectives of the monitoring visits are to verify that:

- The rights and well-being of human subjects are protected,
- the reported trial data are accurate, complete, and verifiable from source documents and
- the conduct of the trial is in compliance with the currently approved protocol / amendment(s), with GCP, and with the applicable regulatory requirement(s).

Monitoring will be done by the ZKS Cologne according to the actual present ZKS Cologne-SOP's. The monitoring concept is based upon the ADAMON criteria (TMF project "GCP conform monitoring in IITs, http://www.tmf-ev.de/site/DE/int/AG/MKS/Projekte/IIT-Monitoring/c_Monitoring.php). Monitoring details are described in a trial specific monitoring manual.

The monitor is authorized to compare the trial documentation sheets and the source documents in consideration of data protection rights. Thus, the monitor has to have direct access to source documents during his on site activities.

13.4 On-Site Audits/Inspections

Representatives of the regulatory authorities such as the BfArM or Regierungspräsidum may visit the site to carry out an audit of the study in compliance with regulatory guidelines. Such inspections will require access to all study records, including source documents, for inspection and comparison with the CRF. Patient privacy must, however, be respected. Sufficient prior notice will be provided to allow the investigator to prepare properly for the audit.

14. FINAL REPORT AND PUBLICATION

The results of the study will be reported in a Clinical Study Report generated by the coordinating principal investigator. The coordinating principal investigator will have the right to publish such data and information without approval from the sponsor. Authorship of publications resulting from this study will be based on generally accepted criteria for major medical journals. Participating center qualify for at least one co-authorship if the center accrues at least 5% of the patients of the ITT study population.

According to the AMG and ICH all data will be published as soon as possible.

15. TRANSLATIONAL INVESTIGATIONS

The trial also includes the following translational investigations:

1. Measuring of tumor perfusion on an additional MRI sequence

One of the main problems of alkylating chemotherapy in patients with MGMT-methylated GBM is the differentiation between true tumor progression and pseudoprorgression. It can be hypothetized that tumor perfusion will be increased in true progression but decreased in pseudoprogression. Therefore, selected centers of the CeTeG may additionally measure permeability (DCE) as a measure of tumor perfusion at each time point when an contrast-enhanced MRI is performed (Baseline, every 12 weeks and any unscheduled MRI). The additional MRI sequence requires an additional 8 minutes of MRI measuring time but no additional appliciation of a contrast-enhancing agent.

2. Molecular analyses

Tumor material and patient's blood will be analyzed for factors associated with the development and/or progression of the tumor, response to treatment and the reaction of the immune system against the tumor. This requires the following measurements:

- Collection of paraffin-embedded tumor blocks and, if available, fresh frozen tissue for molecular analyses after the end of patient recruitment
- Collection of two 10 ml vials of serum and one vial of EDTA blood at baseline and at each MRI control visit every 12 weeks (to be stored at -80°C)

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17. APPENDICES

APPENDIX 1: Karnofsky performance scale

Scale	Karnofsky perfomance
100 %	Normal; no complaints; no evidence of disease
90 %	Able to carry on normal activity; minor signs or symptoms of disease
80 %	Normal activity with effort; some sign or symptoms of disease
70 %	Cares for self; unable to carry on normal activity or do active work
60 %	Requires occasional assistance, but is able to care for most personal needs
50 %	Requires considerable assistance and frequent medical care
40 %	Disabled; requires special care and assistance
30 %	Severely disabled; hospitalization is indicated, although death not imminent
20 %	Very sick; hospitalization necessary; active support treatment is necessary
10 %	Moribund; fatal processes progressing rapidly
0 %	Dead

.

APPENDIX 2: MINI MENTAL Status EXAMINATION

(Vorname/Nachname) Punktwert	Datum (Tag/Monat/Jahr)
_____/_____	_____/_____/_____ _____

1. Orientierung

Zeit (z. B. Welchen Tag haben wir heute?)	1. Jahr	__/(1)
	2. Jahreszeit	__/(1)
	3. Datum	__/(1)
	4. Wochentag	__/(1)
	5. Monat	__/(1)
Ort (z.B. Wo sind wir?)	6. Land/Staat)	__/(1)
	7. Bundesland	__/(1)
	8. Stadt/Ortschaft	__/(1)
	9. Klinik/Praxis	__/(1)
	10. Stockwerk	__/(1)
	Summe (max. 10)	[__][__]

2. Merkfähigkeit

Der Untersucher nennt folgende drei Gegenstände und fordert den Patienten auf, die Begriffe zu wdh. 1 Punkt für jede richtige Antwort. Der Untersucher wdh. Die Wörter so lange, bis der Patient alle drei gelernt hat (höchstens sechs Wdh.)	1. >Auto<	__/(1)
	2. >Blume<	__/(1)
	3. >Kerze<	__/(1)
	Summe (max. 3)	[__]

3. Aufmerksamkeit und Rechenfähigkeit

Von 100 an sind jeweils 7 abzuziehen. Falls ein Rechenfehler gemacht wird und die darauf folgenden Ergebnisse „verschoben“ sind, wird nur ein Fehler gegeben.	1. >93<	__/(1)
	2. >86<	__/(1)
	3. >79<	__/(1)
	4. >72<	__/(1)
	5. >65<	__/(1)
ODER		
Falls der Patient die Aufgabe nicht durchführen kann/will, „RADIO“ rückwärts buchstabieren lassen.	1. >O<	__/(1)
	2. >I<	__/(1)
	3. >D<	__/(1)
	4. >A<	__/(1)
	5. >R<	__/(1)
	Summe (max. 5)	[__]

4. Erinnerungsfähigkeit

Der Untersucher fragt nach den drei zuvor genannten Wörtern.

1. >Auto< __/(1)
2. >Blume< __/(1)
3. >Kerze< __/(1)

Summe (max. 3) [__][__]

5. Sprache

Der Untersucher zeigt 2 Gegenstände und fordert den Patienten auf, diese zu benennen.

1. >Armbanduhr< __/(1)
2. >Bleistift< __/(1)

Nachsprechen.

3. >Sie leiht ihm kein Geld mehr.< __/(1)

Der Untersucher lässt den Patienten folgende Aufgabe ausführen.

4. >Nehmen Sie dieses Blatt in die rechte Hand. __/(1)
5. Falten Sie es in der Mitte.< __/(1)
6. >Legen Sie es auf den Boden.< __/(1)

Der Untersucher bittet den Patienten,

7. die Anweisung auf der nächsten Seite zu befolgen. __/(1)

Der Untersucher bittet den Patienten,

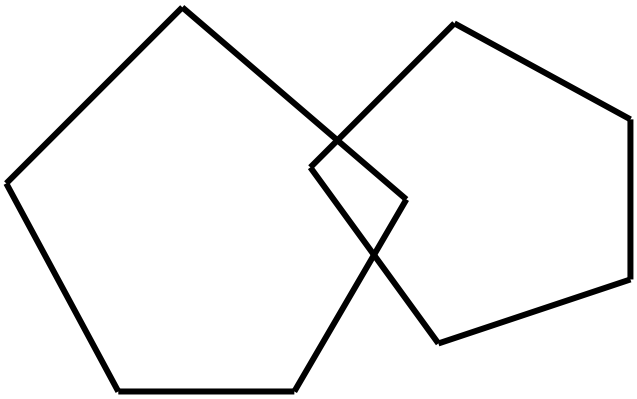
8. einen vollständigen Satz zu schreiben. __/(1)

Der Untersucher lässt den Patienten die auf der nächsten Seite vorgegebene Figur malen (1 Punkt, wenn alle Seiten und Winkel stimmen und die sich überschneidenden Linien ein Viereck bilden.)

9. Nachzeichnen __/(1)

Summe (max. 9) [__]

Bitte schließen Sie die Augen!



APPENDIX 3: EORTC QLQ-C30 Version 3.0) und EORTC QLQ-BN20

Studienennummer / Blatt |__|__|__|__| / |__|__| / |__|__|__|

Bitte tragen Sie Ihre Initialen (Vorname / Nachname) ein: |__|__|

Ihr Geburtstag (Tag, Monat, Jahr): |__|__| . |__|__| . |__|__|__|__|

Das heutige Datum (Tag, Monat, Jahr): |__|__| . |__|__| . |__|__|__|__|

	überhaupt nicht	**wenig**	**mässig**	**sehr**
1. Bereitet es Ihnen Schwierigkeiten, sich körperlich anzustrengen (z.B. eine schwere Einkaufstasche oder einen Koffer zu tragen)?	1	2	3	4
2. Bereitet es Ihnen Schwierigkeiten, einen <u>längeren</u> Spaziergang zu machen?	1	2	3	4
3. Bereitet es Ihnen Schwierigkeiten, eine <u>kurze</u> Strecke ausser Haus zu gehen?	1	2	3	4
4. Müssen Sie tagsüber im Bett liegen oder in einem Sessel sitzen?	1	2	3	4
5. Brauchen Sie Hilfe beim Essen, Anziehen, Waschen oder Benutzen der Toilette?	1	2	3	4
Während der letzten Woche:	**überhaupt nicht**	**wenig**	**mässig**	**sehr**
6. Waren Sie bei Ihrer Arbeit oder bei anderen tagtäglichen Beschäftigungen eingeschränkt?	1	2	3	4
7. Waren Sie bei Ihren Hobbys oder anderen Freizeitbeschäftigungen eingeschränkt?	1	2	3	4
8. Waren Sie kurzatmig?	1	2	3	4
9. Hatten Sie Schmerzen?	1	2	3	4
10. Mussten Sie sich ausruhen?	1	2	3	4
11. Hatten Sie Schlafstörungen?	1	2	3	4
12. Fühlten Sie sich schwach?	1	2	3	4

Patientennummer / Blatt |_|_|_|_| / |_|_| / |_|_|_|

Während der letzten Woche:	**überhaupt nicht**	**wenig**	**mässig**	**sehr**
13. Hatten Sie Appetitmangel?	1	2	3	4
14. War Ihnen übel?	1	2	3	4
15. Haben Sie erbrochen?	1	2	3	4
16. Hatten Sie Verstopfung?	1	2	3	4
17. Hatten Sie Durchfall?	1	2	3	4
18. Waren Sie müde?	1	2	3	4
19. Fühlten Sie sich durch Schmerzen in Ihrem alltäglichen Leben beeinträchtigt?	1	2	3	4
20. Hatten Sie Schwierigkeiten, sich auf etwas zu konzentrieren, z.B. auf das Zeitunglesen oder das Fernsehen?	1	2	3	4
21. Fühlten Sie sich angespannt?	1	2	3	4
22. Haben Sie sich Sorgen gemacht?	1	2	3	4
23. Waren Sie reizbar?	1	2	3	4
24. Fühlten Sie sich niedergeschlagen?	1	2	3	4
25. Hatten Sie Schwierigkeiten, sich an Dinge zu erinnern?	1	2	3	4
26. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Familienleben beeinträchtigt?	1	2	3	4
27. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung Ihr Zusammensein oder Ihre gemeinsamen Unternehmungen mit anderen Menschen beeinträchtigt?	1	2	3	4
28. Hat Ihr körperlicher Zustand oder Ihre medizinische Behandlung für Sie finanzielle Schwierigkeiten mit sich gebracht?	1	2	3	4

Bitte kreuzen Sie bei den folgenden Fragen die Zahl zwischen 1 und 7 an, die am besten auf Sie zutrifft.

29. Wie würden Sie insgesamt Ihren Gesundheitszustand während der letzten Woche einschätzen?

1	2	3	4	5	6	7
sehr schlecht						ausgezeichnet

30. Wie würden Sie insgesamt Ihre Lebensqualität während der letzten Woche einschätzen?

1	2	3	4	5	6	7
sehr schlecht						ausgezeichnet

Patientennummer / Blatt |_|_|_|_| / |_|_| / |_|_|_|

Während der letzten Woche:	**überhaupt nicht**	**wenig**	**mässig**	**sehr**
31. Fühlten Sie sich unsicher in Bezug auf die Zukunft?	1	2	3	4
32. Hatten Sie das Gefühl, gesundheitliche Rückschläge erlitten zu haben?	1	2	3	4
33. Waren Sie besorgt, dass Ihr Familienleben gestört werden könnte?	1	2	3	4
34. Hatten Sie Kopfschmerzen?	1	2	3	4
35. Hat sich Ihre Einstellung zur Zukunft verschlechtert?	1	2	3	4
36. Haben Sie doppelt gesehen?	1	2	3	4
37. Haben Sie verschwommen gesehen?	1	2	3	4
38. Hatten Sie Schwierigkeiten beim Lesen?	1	2	3	4
39. Hatten Sie Anfälle?	1	2	3	4
40. Hatten Sie ein Schwächegefühl auf einer Körperseite?	1	2	3	4
41. Bereitete es Ihnen Mühe, die richtigen Worte zu finden, um sich auszudrücken?	1	2	3	4
42. Hatten Sie Schwierigkeiten beim Sprechen?	1	2	3	4
43. Bereitete es Ihnen Mühe, anderen Ihre Gedanken mitzuteilen?	1	2	3	4
44. Fühlten Sie sich tagsüber schläfrig?	1	2	3	4
45. Hatten Sie Koordinationsprobleme?	1	2	3	4
46. Machte Ihnen Haarverlust zu schaffen?	1	2	3	4
47. Machte Ihnen Hautjucken zu schaffen?	1	2	3	4
48. Hatten Sie ein Schwächegefühl in beiden Beinen?	1	2	3	4
49. Fühlten Sie sich unsicher auf den Beinen?	1	2	3	4
50. Hatten Sie Mühe Ihre Blase zu kontrollieren?	1	2	3	4

APPENDIX 4: List of participating centers

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