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Intergroup Study (EORTC-1709-BTG)

A phase III trial of marizomib in combination with standard temozolomide-based radiochemotherapy versus standard temozolomide-based radiochemotherapy alone in patients with newly diagnosed glioblastoma

MIRAGE

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Coordinating Group:	EORTC Brain Tumor Group
Collaborating Groups:	Canadian Cancer Trials Group (CCTG)
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Warning:

This is an Intergroup study coordinated by the EORTC. The present protocol is written according to the EORTC template and is fully applicable to all collaborative groups (with the exception of EORTC specific sections or other collaborative group(s) specific appendix and unless otherwise specified).

The chapters 19 to 21 and the PIS/IC are fully applicable to EORTC investigators only.

Corresponding items and contact addresses for non EORTC investigators are provided in their Group specific appendix that supersedes the contents of chapters 19-21 (unless otherwise specified).

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Protocol summary

Title of the Study	A phase III trial of marizomib in combination with standard temozolomide-based radiochemotherapy versus standard temozolomide-based radiochemotherapy alone in patients with newly diagnosed glioblastoma - MIRAGE
Objective(s)	The primary objective of this study is to compare overall survival (OS) in patients receiving marizomib in combination with standard treatment (temozolomide (TMZ) with concomitant radiotherapy (RT), followed by TMZ maintenance therapy: TMZ/RT→TMZ) with patients receiving standard treatment only (TMZ/RT→TMZ). The testing strategy is defined to assess this objective in both the whole population and the subgroup of unmethylated MGMT (O-6-methylguanine-DNA methyltransferase) patients with adequate statistical power. Secondary objective is to compare progression free survival (PFS) in the two treatment arms in the whole population. Further secondary objectives are: • To assess the safety and tolerability of marizomib combined with TMZ/RT→TMZ. • To assess objective and self-perceived neurocognitive function and quality of life of patients treated with this approach. • Descriptive and correlative translational research. • To evaluate pharmacokinetics in the MRZ arm
Methodology	This is a multicenter, randomized, controlled, open label phase III superiority trial with an early stopping rule for futility. After signing the informed consent form and upon confirmation of the patient eligibility, patients will be randomized 1:1 to the experimental arm (addition of marizomib to the standard treatment) or the standard arm. Stratification factors are: Institution; Age (≤55, >55 years); Karnofsky performance status (70/80, 90/100); Extent of surgery (partial/open biopsy, gross total).
Number of patients Number planned (Statistical design) Number analyzed	For this study, we assumed that in the whole trial population, the standard treatment plus marizomib presents with a superior OS efficacy compared to the standard treatment alone estimated by a hazard ratio equal to 0.74 (26% reduction of the hazard of death). This corresponds to a median OS of 16 months in the standard treatment alone compared to 21.6 months for standard treatment plus MRZ. We also assume that at the time of final analysis, the MGMT methylation status will be distributed 60% unmethylated, 30% methylated and 10% undetermined. We also hypothesized that the MRZ effect would be mainly present in the unmethylated MGMT subgroup where it would display a HR=0.70 (median OS of 13 months in the control arm and compared to 18.6 months for marizomib). The effect in the methylated MGMT subgroup would be HR>0.80 and in the undetermined cases which are assumed to be a balanced mixture of unmethylated and methylated MGMT cases the effect would be in the line with the overall population, i.e. HR=0.74. Based on the network of institution, it should be possible to recruit 400 patients/year (150 patients in the first year, and then 400 patients per year).

	For the primary endpoint OS, the formal statistical testing is based on comparisons between two treatment groups in both ITT population and unmethylated subgroup. We will use a graphical method to control overall Type 1 error at one-sided 2.5%. We have to recruit 750 patients to show the OS difference with 86% power (taking into account the interim analysis for futility) and overall one-sided 1.5% significance in the whole population and with 80.7% power and one sided 1% significance in the unmethylated MGMT subgroup (uMGMT). We will recruit these patients in about 30 months and will follow them up for about 19 months, the time necessary to observe the required 488 deaths (320 in uMGMT). We will perform the test in the ITT population and in the uMGMT subgroup simultaneously. If one of them is significant, we will attribute the assigned alpha to the other. At the final analysis, we will provide treatment effect estimates in the uMGMT and in the methylated MGMT (mMGMT) subgroups. In order to avoid exposing too many patients to a possibly ineffective and/or toxic treatment, a non-binding futility analysis will be conducted on the whole population.

Diagnosis and main criteria for inclusion	**Inclusion Criteria**
	
	• Histologically confirmed newly diagnosed glioblastoma (WHO grade IV)
	• Tumor resection (gross total or partial), or open biopsy only (no stereotactic biopsy)
	• Availability of FFPE tumor block or 24 unstained slides for MGMT analysis
	• Patient must be eligible for standard TMZ/RT→TMZ
	• Karnofsky performance score (KPS) ≥ 70
	• Recovered from effects of surgery, postoperative infection and other complications of surgery (if any)
	• The patient is at least 18 years of age on day of signing informed consent
	• Stable or decreasing dose of steroids for at least 1 week prior to inclusion
	• The patient has a life expectancy of at least 3 months
	• Patient has undergone a brain MRI within 14 days of randomization but after intervention (resection or biopsy)
	• The patient shows adequate organ functions as assessed by the specified laboratory values within 2 weeks prior to randomization defined as adequate bone marrow, renal and hepatic function within the following ranges:
	
	  • WBC ≥ 3×10^9/L
	  • ANC ≥ 1.5×10^9/L
	  • Platelet count of ≥ 100×10^9/L independent of transfusion
	  • Hemoglobin ≥ 10 g/dl
	  • Total Bilirubin ≤ 1.5 ULN
	  • ALT, AST, alkaline phosphatase (ALP) ≤ 2.5 × ULN
	  • Serum creatinine < 1.5 x ULN or creatinine clearance (CrCl) > 30 mL/min (using the Cockcroft-Gault formula)
	
	• Women of child bearing potential (WOCBP) must have a negative urine or serum pregnancy test within 7 days prior to randomization
	• Patients of childbearing / reproductive potential must agree to use adequate birth control measures, as defined by the investigator, during the study

	treatment period and for at least 6 months after the last study treatment. A highly effective method of birth control is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly. Patients must also agree not to donate sperm during the study and for 6 months after receiving the last dose of study treatment. • Women who are breast feeding must agree to discontinue nursing prior to the first dose of study treatment and until 6 months after the last study treatment. • Ability to take oral medication • Ability to understand the requirements of the study, ability to provide written informed consent and authorization of use and disclosure of protected health information, and agree to abide by the study restrictions and return for the required assessments. • Before patient registration/randomization, written informed consent must be given according to ICH/GCP, and national/local regulations. **Exclusion Criteria** • Patients with known IDH mutation (IDH mutation testing should be conducted for younger patients (<55years old), patients with tumors with atypical features, or with history or present concurrent lower grade gliomas. • Prior treatment for glioblastoma other than surgery; prior RT to brain and/or prior chemotherapy for lower grade glioma. Placement of BCNU wafer during surgery is not allowed Planned additional treatment with Tumor-Treating Fields • Known hypersensitivity to the active substance or any of the excipients in the IV formulation • History of thrombotic or hemorrhagic stroke or myocardial infarction in past 6 months • Congestive heart failure (New York Heart Association Class III to IV), symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention, and myocardial infarction within 6 months prior to first dose • Concurrent severe or uncontrolled medical disease (e.g., active systemic infection, diabetes, hypertension, coronary artery disease, psychiatric disorder) that, in the opinion of the investigator, would compromise the safety of the patient or compromise the ability of the patient to complete the study • Known history or current evidence of active Hepatitis B (e.g., positive HBV surface antigen) or C (e.g., HCV RNA [qualitative] is detected) • Known or current evidence of Human Immunodeficiency Virus (HIV) (positive HIV-1/2 antibodies) • Prior or second invasive malignancy, except non-melanoma skin cancer, completely resected cervical carcinoma in situ, low risk prostate cancer (cT1-2a N0 and Gleason score ≤ 6 and PSA < 10 ng/mL), either totally resected or irradiated with curative intent (with PSA of less than or equal to 0.1 ng/mL) or under active surveillance as per ESMO guidelines Other cancers for which the

	subject has completed potentially curative treatment more than 3 years prior to study entry are allowed. • Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.
Treatment Test product, dose and mode of administration Duration of treatment	Experimental arm: Standard radiotherapy (RT)(60 Gy in 30 fractions over 6 weeks) + TMZ 75 mg/m^2 p.o. daily for 6 weeks (during radiotherapy) and marizomib (MRZ) dose 0.8 mg/m^2 IV at days 1, 8, 15, 29 and 36. This is followed, after 4-week break, by up to 6 cycles of maintenance TMZ 150-200 mg/m^2 p.o. on days 1-5 of a 28-day cycle and up to 18 cycles of maintenance MRZ treatment (0.8 mg/m^2 IV) at days 1, 8, 15 of a 28-day cycle until disease progression, unacceptable toxicity or withdrawal of consent. Standard arm: Standard radiotherapy (RT) (60 Gy in 30 fractions over 6 weeks) + TMZ 75 mg/m^2 p.o. daily for 6 weeks (during radiotherapy) then (after 4-week break) up to 6 cycles of maintenance TMZ 150-200 mg/m^2 p.o. on days 1-5 of a 28-day cycle. All patients will have regular follow-up by MRI, 4 weeks after the end of radiotherapy (RT), then every 8 weeks thereafter until progression. Once patients stop study treatment, they will be followed as per institution's standard.
Criteria for evaluation Efficacy Safety	Response and progression will be assessed by RANO criteria as determined by the local investigator. OS is defined as the number of days from date of randomization to the date of death due to any cause. If a patient has not died, the data will be censored at the last date documented to be alive. PFS is defined as the number of days from date of randomization to the date of earliest disease progression or to the date of death due to any cause, if disease progression does not occur. MMSE is a brief, standardized tool to grade patients' neurocognitive function. It is an 11-question measure that tests five areas of neurocognitive function: orientation, registration, attention and calculation, recall, and language. This study will use the International Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, for adverse event reporting.

Statistical methods	We will conduct all efficacy analyses in the intent-to-treat (ITT) population. In the primary analyses, differences between the treatment groups in OS will be assessed by a stratified LogRank test adjusted for the stratification factors assessed at randomization (except institution). We consider this test as confirmatory and will perform it at a 1-sided significance level α=0.015 in the ITT population and α=0.01 in the uMGMT subgroup. If one of them is significant, the assigned alpha will be transferred to the other and the overall Type 1 error will be controlled at one-sided 2.5% by graphical method. Kaplan-Meier survival curves will be presented by treatment group, in the ITT population and by MGMT subgroup, together with a summary of associated statistics including the corresponding two-sided 95% confidence intervals. The hazard ratio (including two sided 97% and 95 % confidence interval in the ITT population and two sided 98% and 95 % confidence interval in the uMGMT subgroup) of the Marizomib group over the control group will be calculated by Cox's proportional hazards model stratified by the stratification factors assessed at randomization (except institution). A re-randomization-test analysis will be performed to support the primary analysis in the ITT population and in uMGMT. Secondary analyses of efficacy are supportive and will be analyzed in a non-confirmatory sense. Therefore no adjustments for multiplicity will be done. The following analyses will be performed. For PFS, the same analyses as for OS will be performed in the ITT population. For PFS and OS, Kaplan-Meier estimates will be calculated and unstratified Cox's proportional hazards model will be fit for various subgroups. Forest Plot will be displayed with a subgroup by treatment interaction test. The distribution of the MMSE at each time point of evaluation will be described on the two treatment arms separately using means and their associated standard error (a graphical display will be considered). Median and range will also be provided. The proportion of patients with 'normal' and 'impaired' MMSE score at baseline and at key timepoints of evaluation will also be displayed. Longitudinal analysis might also be performed and detailed in the SAP.

Translational research	FFPE tumor tissue will be prospectively collected for central testing of the MGMT status. Since MGMT status will be used in the primary OS analysis to determine if there is a difference in treatment effect which is dependent on this variable, this initial tumor tissue is a mandatory requirement within this protocol. We will also collect mandatory plasma and serum samples at study entry, after completion of RT and, every 3 cycles and at progression, as well as plasma samples for extracellular vesicle isolation (optional) for biomarker discovery. In this study, we plan to investigate the proteasomal activity in patients with sufficient amount of tissue available for these analyses. We have 2 objectives: firstly, we would like to confirm baseline proteasome activity and clinical response (PFS and OS), and secondly we want to see if the proteasome activity is modulated by marizomib in patients with tissue at baseline and at salvage surgery. To perform proteasome activity measurement, frozen tumor tissue, at study entry and after salvage surgery, should it occur, will be collected. Moreover, proteasomal activity will also be measured in PBMCs, collected at study entry, after completion of RT and, every 3 cycles and at progression. Future research might include isolation of ctDNA and gDNA from plasma. Depending on the study results, we may look for soluble factors in the serum which may be of interest as potential biomarkers. The ultimate goal of such work would be to define a tumor specific signature in the peripheral blood which could be used to monitor and predict response to therapy. Exploratory research may also include evaluation of a multigene signature to predict benefit from marizomib. FFPE samples will be stored at the EORTC BTG Tissue Repository (Rotterdam, NL) and blood derivates will be stored at the Intergrated BioBank Luxembourg (Luxembourg, LU).
Quality of Life	The main objective of QOL assessment within this trial is to determine the impact of addition of marizomib to temozolomide (TMZ) and radiation therapy (RT) on five chosen domains being primarily global QOL, with fatigue, physical function, neurocognitive function, communication and motor dysfunction as secondary QOL outcomes. It is expected that these are likely to be most affected in patients, based on the toxicity profiles and information of previous studies. Quality of life will be assessed through the EORTC Quality of Life Questionnaire (QLQ-C30) version 3 and the EORTC Brain Cancer module (QLQ-BN20), designed for use in brain tumor patients undergoing protocol treatment or radiotherapy. They will be collected every 16 weeks (± 7 days) until death, end of study, start of new anticancer treatment or lost to follow-up whichever comes first

Trial organization

- This trial is an intergroup trial, jointly conducted by the Canadian cancer trials group (CCTG)
- Each participating group is the Sponsor for their participants (unless otherwise agreed).

In summary:

Country	Recruiting group(s)	Sponsor
US & Canada	CCTG	CCTG
Europe	EORTC	EORTC

- The EORTC is the coordinating group in this trial and therefore centrally manage trial design and activation, attribution of duties and responsibilities between participating research groups, data collection and quality control of data, statistical analysis and publication.
- Each Sponsor locally manages the notification/submission of all necessary documents to their regulatory bodies and receives the confirmation of the review by IRB/IEC following the applicable national law.
- This protocol is to be followed by all participating groups. Chapters 1 to 18 are fully applicable to all groups. Chapters 19-21 are specific to the EORTC participants (members of the EORTC covered by the sponsorship of the EORTC). All particularities of participation of each individual group are included is the Group Specific Appendixes annexed at the end of the protocol.
- The patient information sheet and informed consent templates are applicable as such only for participants under the sponsorship of the EORTC (participants under a different sponsorship should refer to the corresponding Group Specific Appendix or to their group).
- The participation to this trial is only possible through one of the participating clinical cancer research groups. For contacts and addresses please refer to the Group Specific Appendix of the group of your membership on which behalf you are going to participate (see below).
- Investigators members of several groups participating to the trial should select one of these groups for the framework of this trial and have to include all patients through this group. In some cases, because of the national legal framework the choice may be imposed. For EORTC members all patients will be accounted for the membership independently from the group they choose to participate through (see EORTC Policy 10). In case of any difficulties in a group selection, please contact the EORTC Headquarters.
- The investigational drug Marizomib will be supplied by the industry

This trial is an academic trial with an educational grant support from the industry.

1 Background and introduction

The group of gliomas is divided into World Health Organisation (WHO) grades I-IV (Ref. 28). Glioblastoma, a grade IV glioma, is not only the most malignant but also the most common primary brain tumor in adults. Glioblastoma is a tumor thought to be of neuroglial origin, typically characterized by astrocytic differentiation and additional histological features such as microvascular proliferation and necrosis. Glioblastomas are diagnosed throughout all age groups with a median age at diagnosis of approximately 64 years. According to age-adjusted analyses, the incidence of glioblastoma is continuously increasing from young to old subjects with a highest incidence rate in patients aged 75 to 84 years (Ref. 32).

Mutations of the isocitrate dehydrogenase *IDH1* and *IDH2* genes are frequent in WHO grade II and III gliomas (Ref. 57). Furthermore, they are present in nearly all glioblastomas that have progressed from grade II or III tumors. Accordingly, these tumors have been called "secondary glioblastomas". Since IDH mutations are the best way to define the occurrence of a glioblastoma from a less malignant precursor lesion, these tumors are now separately classified in the 2016 WHO classification and called "IDH-mutated glioblastomas" which represent approximately 5% of all glioblastomas. IDH-mutated glioblastomas have a better prognosis than their IDH wild-type counterparts (Ref. 22). The clear majority of glioblastoma arise de novo which means that no lower-grade precursor lesion has been known. These tumors, sometimes also referred to as "primary glioblastoma", typically harbor no IDH mutation and have been named “IDH-wildtype glioblastoma” in the 2016 WHO classification (Ref. 28). Accordingly, the updated WHO classification indicates that IDH-mutant glioblastoma should be considered a distinct entity.

The median survival of glioblastoma patients is in the range of one year in population-based studies (Ref. 20) and is in the range of 15-16 months in clinical trial populations (Ref. 8, Ref. 17). Glioblastomas are paradigmatic for their propensity to deeply infiltrate adjacent brain areas, precluding definitive surgical resection and limiting the efficacy of other local therapies. The results achieved with traditional cancer therapies are poor because of defects in the apoptotic machinery of glioma cells, accounting for their resistance to irradiation and chemotherapy.

Younger age, better performance status and extent of resection have repeatedly been shown to be positive prognostic factors in glioblastoma patients. Furthermore, data from the EORTC 26981/22981-NCIC CE3 trial indicate that a Mini-Mental State Examination (MMSE) score of 27 or higher is associated with better outcome (Ref. 19). The majority of glioblastomas does not harbor molecular factors associated with a better prognosis in gliomas such as IDH mutation or 1p/19q co-deletion (Ref. 50). The DNA repair protein O-6-methylguanine-DNA methyltransferase (MGMT) removes the alkylation at the O^6-position of guanine induced by alkylating agents. Thereby, MGMT confers resistance to alkylating chemotherapeutic drugs such as nitrosoureas or temozolomide. MGMT is expressed if the gene promoter is unmethylated. In contrary, a methylated MGMT promoter leads to gene silencing and is associated with sensitivity to alkylating agents (Ref. 23). In glioblastoma patients who are treated with alkylating drug chemotherapy, MGMT promoter methylation is associated with prolonged progression-free and overall survival (Ref. 42; Ref. 29; Ref. 54).

Biopsy or surgical resection is mandatory to allow for a histopathological characterization of the tumor tissue. The emergence of various molecular markers stresses the importance of having sufficient amount of tissue in order to be able to perform all desired analyses. Results obtained in various retrospective analyses stress the hypothesis that gross total resection results in prolonged survival in glioblastoma patients (Ref. 7). Furthermore, data from prospective trials which took advantage of the fluorescent dye, 5-aminolevulinic acid (5-ALA), or intraoperative MRI in order to improve the extent of resection, showed that patients with more complete resections of malignant gliomas had an improved progression free survival (Ref. 40, Ref. 39).

Radiotherapy has been a standard treatment for patients with newly diagnosed glioblastoma for decades. Data from a prospective trial comparing best supportive care alone with best supportive care and additional

radiotherapy demonstrated prolonged progression free survival (PFS) and overall survival (OS) with the administration of radiotherapy (Ref. 25). Since 2005, patients with newly diagnosed glioblastoma aged 70 years or younger are treated with maximal safe surgery followed by involved-field radiotherapy (RT) with concomitant temozolomide (TMZ) therapy followed by up to 6 cycles of maintenance temozolomide therapy (TMZ/RT→TMZ) according to results of the EORTC 26981/22981-NCIC CE3 trial (Ref. 42, Ref. 51). The situation is similar in elderly patients with newly diagnosed glioblastoma but only a fraction of patients might be eligible for combined radiochemotherapy (Ref. 33). Patients not considered eligible for combined modality treatment, e.g. frail subjects, may be treated based on the O-6-methylguanine-DNA-methyltransferase (MGMT) promoter methylation status with radiotherapy alone or temozolomide alone (Ref. 54, Ref. 29).

Since 2005, various attempts have failed to further improve the outcome of patients with newly diagnosed glioblastoma. Dose intensification of TMZ during the maintenance part using a regimen consisting of 21 days of temozolomide administration out of 28 days did not result in prolonged survival (Ref. 18). Several retrospective analyses also suggest that there is no clinical benefit from the extended administration of maintenance TMZ beyond 6 cycles (Ref. 3; Ref. 21). Efforts to improve overall survival results obtained with TMZ/RT-->TMZ have also failed, including the addition of antiangiogenic compounds such as bevacizumab (Ref. 17, Ref. 8) or cilengitide (Ref. 41) which were explored in randomized phase 3 trials. More recently, the vaccine rindopepimut, the first immunotherapeutic approach in the treatment of brain cancers, was assessed in a randomized, placebo-controlled phase 3 trial in patients with newly diagnosed glioblastoma harboring a mutation in the epidermal growth factor receptor (EGFR) gene called EGFRvIII. The addition of rindopepimut to TMZ/RT-->TMZ did not improve PFS or OS compared to placebo-treated patients (Ref. 50). Tumor-Treating Fields (TTFields) are alternating electric fields delivered through transducer arrays directly applied onto the scalp of patients. TTFields are supposed to exert anti-tumor effects by targeting dividing tumor cells while sparing other cells in the brain that are not undergoing division. The addition of TTFields to maintenance temozolomide has resulted in prolonged survival in patients with newly diagnosed glioblastoma (Ref. 43*)*. This trial, however, enrolled only patients who had stable disease after completion of radiotherapy. Several questions on how to potentially incorporate this novel treatment modality which is not yet reimbursed in many countries into standards of care remain unanswered.

1.1 Proteasome inhibitor - Marizomib

The proteasome is a central cellular structure for the turnover of proteins. Its activity is constituted by multiple proteases assembled in a large multi-protein complex. Cancer cells often exhibit enhanced proteasome activity and inhibition of proteasome activity may preferentially affect the viability of cancer cells, including glioblastoma cells (Ref. 48, Ref. 49, Ref. 36).

Marizomib displays a unique pharmacologic profile among proteasome inhibitors characterized by high potency and irreversible pan-proteasome inhibition. It inhibits all 3 major catalytic activities of the 20S core particle by rapidly entering cells and covalently binding to all three active enzyme sites (Ref. 27). Preclinically, marizomib has been shown to induce apoptotic cell death in stable human glioma tumor cell lines and in glioma stem cells, as well as in intracranial glioblastoma models in vivo (Ref. 4; Ref. 30;
Ref. 12). In vitro studies indicate that glioma stem (tumor-initiating) cells are rather resistant to irradiation and chemotherapeutic agents such as temozolomide, but are still sensitive to proteasome inhibitors, whereas neural stem cells are sensitive to irradiation and temozolomide, but resistant to proteasome inhibitors (Ref. 4).

Proteasome inhibition though knockdown of the PSMA1 component of the core 20S proteasome radiosensitizes non-small cell lung cancer cells, resulting in impairment of radiation-induced DNA double strand break repair, and the combination of proteasome inhibition by PSMA1 knockdown with irradiation enhanced tumor control in vivo (Ref. 10). In glioblastoma, proteasome inhibition by bortezomib enhanced apoptosis in combination with temozolomide (Ref. 47) and with irradiation (Ref. 31) as shown for several glioma cell lines. These data demonstrate that proteasome inhibition through a variety of modalities (e.g. bortezomib, marizomib, and gene

silencing) consistently results in anti-glioma activity. Together, these data suggest that proteasome inhibition should result in synergistic activity against various glioma cells when combined with temozolomide or irradiation. Bortezomib has been assessed in phase 1 and 2 trials in patients with recurrent glioblastoma. However, there was no clear signal of clinical activity, most likely because the drug does not cross the blood brain barrier (BBB) (Ref. 34; Ref. 16). In contrast, data from several preclinical studies demonstrate the unique ability of marizomib to cross the blood brain barrier (BBB). In a study measuring the 20S proteasome activity in mouse whole brain lysates with either marizomib or bortezomib, brain proteasome activity was inhibited by marizomib from 41-52% to 94-98% (peak), while bortezomib had no effect on brain proteasome activity (Ref. 56). Second, in a quantitative whole-body autoradiography study in rats, after a single intravenous dose of radiolabeled marizomib, radioactivity was found throughout the central nervous system (CNS) (cerebrum, cerebellum, and medulla) from 2 min to 24 h after injection (Ref. 12). Thirdly, the proteasome activity in the prefrontal cortex of monkeys was reduced by 26-28% after once- or twice weekly oral doses of marizomib (MRZ) (Ref. 12). Finally, biweekly intravenous administration of marizomib to mice bearing intracranial glioma xenografts significantly prolonged survival in comparison with vehicle-treated controls (Ref. 12). Taken together, the clinical and preclinical data strongly support the conclusion that marizomib is brain penetrant. In clinical studies with MRZ IV, the duration of MRZ administration varied from 1 to 120 min over the dose range 0.025 to 0.9 mg/m^2. MRZ exhibited similar PK properties in both once and twice-weekly infusion studies, with a short $t_{1/2}$ (generally ranging from 3 to 15 min), a very high volume of distribution, and a very high clearance rate. Together, these parameters account for the observation that little-to-no accumulation of MRZ is observed with repeat dosing. Generally, dose-proportional increases in MRZ exposure are noted with increased dose. The pharmacodynamic effects of MRZ on subunit-specific activity of the proteasome were measured in whole blood samples and mononuclear cells collected from patients with solid and hematologic malignancies across several clinical trials. Partial or complete inhibition of all three proteasome subunits [CT-L (chymotrypsin-like, β 5); T-L (trypsin-like, β 2) and C-L (caspase-like, β 1)] was achieved with both once- and twice-weekly MRZ dosing, with the rank order of sensitivity (CT-L > T-L > C-L) consistent with the biochemical potency of MRZ (Ref. 46). For CT-L activity, both initial on Cycle 1, Day 1 (C1D1) and peak proteasome inhibition was dose-dependent, with complete (100%) inhibition of CT-L activity in packed whole blood (PWB), and maximal (60 to 80%) inhibition of CT-L activity in peripheral blood mononuclear cells (PBMC), within the first dosing cycle. In contrast, C-L and T-L activities were unchanged or increased in the first cycle of MRZ dosing, suggesting compensatory hyperactivation in response to effective blockade of CT-L activity. Importantly, this response was overcome by further treatment with MRZ, with inhibition of T-L and C-L activity noted across dose levels with repeated dosing. These data suggest that initial potent inhibition of CT-L activity leads to a compensatory hyperactivation of the C-L and T-L subunits. As CT-L activity becomes fully inhibited by the irreversible activity of MRZ, progressive inhibition of the hyperactivated C-L and T-L subunits occurs, ultimately resulting in robust pan-proteasome inhibition within 2 cycles in the majority of patients (Ref. 27). As of 01 August 2018, a total of 451 subjects have received one or more doses of MRZ in 7 Phase 1 and Phase 1/2, dose-escalating clinical studies evaluating MRZ as a single agent or in combination with other anticancer drugs, including 171 subjects in Phase 1b and Phase 1/2 clinical studies for newly diagnosed and recurrent glioblastoma, respectively. In patients with *recurrent glioblastoma*, marizomib was administered (10 minute infusion) as a single agent or in combination with bevacizumab (Study MRZ-108, NCT02330562); the study was conducted in 4 parts. In all 4 parts of the study, patients were at their second or third relapse and were required to have had documented progressive disease and no prior therapy with bevacizumab. Part 1 evaluated MRZ at escalating doses, in order to establish the recommended dose, in combination with BEV (Cohorts 1 to 3) with an expansion cohort (Cohort 4) in subjects with relapsed GBM. The Part 2 portion of the study explored the activity of single-agent MRZ (Cohort 5) at the recommended dose of 0.8 mg/m^2. Upon evaluation of the efficacy data in conjunction with the safety data from Cohorts 1 to 4, the decision was taken to attempt an intrapatient dose-escalation of MRZ in order to evaluate higher doses in combination with BEV in the Part 3 portion of the study (Cohort 6) in the same patient population. Part 4 of the study was added to assess the feasibility of enterally-administered MRZ.

In Parts 1 and 3 of the study, in subjects with MRZ administered a dose up to 0.8 mg/m^2 in combination with bevacizumab, the best overall response by RANO criteria is 34.3%, with 23 of 67 subjects achieving a best response of CR (n = 2) or PR (n = 21), as well as a progression free survival rate at 6 months (PFS6) of 28.8% in all patients. Overall survival rates at 9 months (OS9) was 51.6%; in 37 patients with MGMT promoter-unmethylated tumors OS9 was 40.5%, and 70.2% in 21 patients with MGMT promoter-methylated tumors. Results as of 01 Aug 2018 indicate progression-free (PFS) and overall survival (OS) at the high end of any bevacizumab monotherapy study (Ref. 44). In the Taal *et al.* study, PFS6 and OS9 were 16% and 38%, respectively, for bevacizumab alone group.

In Part 2 of Study MRZ-108 (30 patients included), marizomib was administered as a single agent at the recommended phase II dose (RP2D) of 0.8 mg/m^2 as a 10-minute intravenous infusion on days 1, 8, 15 every four weeks. Single agent MRZ activity was clearly observed but was limited: Eight subjects (26.7%) had SD (duration ranging from 0.7 to 9.5 months for 7 subjects; 1 subject discontinued prior to PD). Four subjects clearly benefited from single-agent treatment with MRZ, including the 1 subject with a confirmed PR, and 3 subjects with durable clinical stabilization (1 subject for 8 cycles, another 2 subjects for 12 cycles). The median PFS was 1.8 months and the median OS was 11.4 months.

In the ongoing Study MRZ-108 in recurrent GBM, at MRZ doses ranging from 0.55 to 0.8 mg/m^2 in combination with BEV (n=67) and 0.8 mg/m^2 in the monotherapy arm (n=30), the most common treatment emergent adverse events (TEAEs) in both arms are fatigue, nausea, headache, vomiting, hallucination, hypertension, constipation and insomnia. Grade 3 and higher MRZ related TEAEs occurred in 51 subjects (76%) in the combination arm and in 17 subjects (57%) in the monotherapy arm with the majority of events occurring in the system organ classes (SOCs) of nervous system disorders, and psychiatric disorders and vascular disorders. The incidence of serious adverse events (SAEs) in combination therapy at MRZ doses up to 0.8 mg/m^2 and in subjects for MRZ monotherapy was 40% and 33%, respectively.

Based on these encouraging observations, a phase Ib trial of marizomib in combination with standard doses and schedules of TMZ/RT→TMZ in newly diagnosed glioblastoma has been ongoing (Study MRZ-112, NCT02903069) which explores safety and tolerability of this triple combination and which forms the basis for dosing for further clinical trials in newly diagnosed glioblastoma. During the dose escalation part of the study (MRZ dose levels of 0.55, 0.7, 0.8, and 1.0 mg/m^2), patients were enrolled in parallel to the concomitant modality cohort (TMZ/RT + MRZ on D1, 8, 15, 29, and 36 – these patients may continue with TMZ + MRZ in the adjuvant setting) and the adjuvant cohort (TMZ + MRZ on D1, 8, and 15).

After the RP2D had been determined in the dose-escalation part of the study for the concomitant treatment and adjuvant treatment arms, respectively, additional patients were enrolled in the dose expansion part of the study and were to be treated at the RP2D to confirm the safety and assess the preliminary activity for the combination of MRZ+TMZ+RT (concomitant treatment) followed by MRZ+TMZ (adjuvant treatment). An additional cohort was added to evaluate the safety of the combination of MRZ+TMZ+Optune as adjuvant treatment.

As of 01 Aug 2018, 63 subjects have been enrolled in Study MRZ-112 (35 in the concomitant treatment arm, 18 in the adjuvant treatment arm, and 10 in the Optune arm). Of the 35 subjects enrolled in the concomitant treatment arm, 25 of these subjects also continued to receive adjuvant treatment.

In the on-going study MRZ-112, the most common TEAEs (more than 1/3 patients) are fatigue, nausea, vomiting, hallucination, constipation, headache and confusional state. Grade 3 and higher MRZ related TEAEs occurred in 37 subjects (59%) with the majority of events occurring in the SOCs of general disorders and administration site conditions, nervous system disorders, gastrointestinal disorders and psychiatric disorders. Twenty-four of the subjects experienced an SAE and there was one TEAE of sudden death where relationship to MRZ could not be excluded.

As of 10 Jul 2019, 286 subjects have been enrolled in the study with 144 of these subjects enrolled in the MRZ treatment arm. As the study is on-going and is a non-company sponsored study, only SAE data are available.

In this study, 3 SAEs of encephalopathy have been reported, 2 on the MRZ arm and 1 on the standard TMZ-based radiochemotherapy arm. One case of encephalopathy on the MRZ arm was fatal with the final autopsy reported as leukoencephalopathy. This subject presented with ataxia and hallucinations but rapidly became unconscious 95 days after start of MRZ/TMZ treatment and 45 days after completing radiotherapy. The investigator considered this event to be related to MRZ. The 2 other cases of encephalopathy (1 related to para-influenza virus Type 3 and 1 related to radiation treatment) were recovered and resolving, respectively.

1.2 Assessment of Risks and Benefits

1.2.1 Review by the IDMC

The third IDMC review of the safety of the study and the first interim efficacy analysis (futility) took place in September 2020. Although the trial results did not cross the pre-specified futility boundary, the IDMC observed that there was as yet no evidence that this treatment provided a benefit in survival. The statistical data presented also suggested that it was extremely unlikely that a difference would emerge with additional patients or further follow-up. The IDMC observed that marizomib in this combination induced severe neurological and neuropsychiatric disorders, as well as other treatment-related grade 3-4 side effects, in a substantial proportion of the patients. The IDMC therefore recommended that the study be discontinued from further recruitment and that results be disclosed to medical community as soon as possible. However, if patients still on treatment were tolerating marizomib, they might be allowed to continue if so wished by the patient and treating physician

1.2.2 COVID-19

The risk/benefit assessment of COVID-19 is included in Appendix L: Specific guidelines during COVID-19 pandemic.

1.3 Rationale for pharmacodynamics

Population PD and exposure-response analyses for efficacy and safety are a fundamental component of the benefit/risk information.

Pharmacodynamics (PD) analysis will be performed on the blood of patients. This information will be used to conduct population PD and exposure-response analyses for efficacy and safety.

Central nervous system adverse events have been observed with marizomib treatment in previous trials. The PD data could be used to assess whether there is an exposure-response relationship for this toxicity.

2 Objectives of the trial

To compare the overall survival (OS) of glioblastoma patients treated with standard TMZ-based chemoradiotherapy alone or TMZ-based chemoradiotherapy in combination with marizomib.

2.1 General objectives

The primary objective of this study is to compare overall survival in patients receiving Marizomib in combination with standard treatment (TMZ with concomitant RT, followed by TMZ maintenance therapy: TMZ/RT→TMZ) with patients receiving standard treatment only (TMZ/RT→TMZ). The testing strategy is defined to assess this objective in both the whole population and the subgroup of unmethylated MGMT patients with adequate statistical power.

Secondary objective is to compare PFS in the two treatment arms in the whole population.

Further secondary objectives are:

To assess tumor response in the two treatment arms in the whole population

- To assess the safety and tolerability of marizomib combined with TMZ/RT→TMZ.
- To assess objective and self-perceived neurocognitive function and quality of life of patients treated with this approach.
- Descriptive and correlative translational research
- To evaluate Pharmacodynamics (PD) of MRZ in newly diagnosed GBM

2.2 End-points

Primary endpoint is OS.

Secondary endpoints are:

- PFS
- Quality of Life (modified EORTC QLQ C30/BN20)
- Mini Mental State Examination (MMSE)
- Best overall response, objective response, complete response, duration of response
- Frequencies and percentages of worst Adverse Events (AEs) or Laboratory Event grades

The following are exploratory endpoints:

- Activity of the proteasome in the tumor tissue prior to treatment start and correlation with patient's outcome.

3 Patient Selection criteria

Patients must fulfill all the following criteria to be eligible for the study.

3.1 Inclusion Criteria

- Histologically confirmed newly diagnosed glioblastoma (WHO grade IV)
- Tumor resection (gross total or partial), or open biopsy only (stereotactic biopsy not allowed)
- Availability of FFPE tumor block or 24 unstained slides for MGMT analysis
- Patient must be eligible for standard TMZ/RT→TMZ
- Karnofsky performance score (KPS) ≥ 70 (Appendix E)
- Recovered from effects of surgery, postoperative infection and other complications of surgery (if any)
- The patient is at least 18 years of age on day of signing informed consent
- Stable or decreasing dose of steroids for at least 1 week prior to inclusion
- The patient has a life expectancy of at least 3 months
- Patient has undergone a brain MRI within 14 days of randomization but after intervention (resection or biopsy)
- The patient shows adequate organ functions as assessed by the specified laboratory values within 2 weeks prior to randomization defined as adequate bone marrow, renal and hepatic function within the following ranges:
  - WBC ≥ 3×10^9/L
  - ANC ≥ 1.5×10^9/L
  - Platelet count of ≥ 100×10^9/L independent of transfusion
  - Hemoglobin ≥ 10 g/dl
  - Total Bilirubin ≤ 1.5 ULN
  - ALT, AST, alkaline phosphatase (ALP) ≤ 2.5 × ULN

  - Serum creatinine < 1.5 x ULN or creatinine clearance (CrCl) > 30 mL/min (using the Cockcroft-Gault formula)

- Women of child bearing potential (WOCBP - refer to Appendix H for definition) must have a negative urine or serum pregnancy test within 7 days prior to randomization
- Patients of childbearing / reproductive potential must agree to use adequate birth control measures, as defined by the investigator, during the study treatment period and for at least 6 months after the last study treatment. A highly effective method of birth control is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly (see Appendix H). Patients must also agree not to donate sperm during the study and for 6 months after receiving the last dose of study treatment.
- Women who are breast feeding must agree to discontinue nursing prior to the first dose of study treatment and until 6 months after the last study treatment.
- Ability to take oral medication
- Ability to understand the requirements of the study, ability to provide written informed consent and authorization of use and disclosure of protected health information, and agree to abide by the study restrictions and return for the required assessments.

- Before patient registration/randomization, written informed consent must be given according to ICH/GCP, and national/local regulations.

3.2 Exclusion Criteria

- Patients with known IDH mutation. IDH mutation testing should be conducted for younger patients (< 55years old0, patients with tumors with atypical features, or with history or present concurrent lower grade gliomas
- Prior treatment for glioblastoma other than surgery; prior RT to brain and/or prior chemotherapy for lower grade glioma. Placement of BCNU wafer during surgery is not allowed Planned additional treatment with Tumor-Treating Fields
- Known hypersensitivity to the active substance or any of the excipients in the IV formulation
- History of thrombotic or hemorrhagic stroke or myocardial infarction in past 6 months
- Congestive heart failure (New York Heart Association Class III to IV, see Appendix C), symptomatic ischemia, conduction abnormalities uncontrolled by conventional intervention, and myocardial infarction within 6 months prior to first dose
- Concurrent severe or uncontrolled medical disease (e.g., active systemic infection, diabetes, hypertension, coronary artery disease, psychiatric disorder) that, in the opinion of the investigator, would compromise the safety of the patient or compromise the ability of the patient to complete the study
- Known history or current evidence of active Hepatitis B (e.g., positive HBV surface antigen) or C (e.g., HCV RNA [qualitative] is detected) Known or current evidence of Human Immunodeficiency Virus (HIV) infection (positive HIV-1/2 antibodies)
- Prior or second invasive malignancy, except non-melanoma skin cancer, completely resected cervical carcinoma in situ, low risk prostate cancer (cT1-2a N0 and Gleason score ≤ 6 and PSA < 10 ng/mL), either totally resected or irradiated with curative intent (with PSA of less than or equal to 0.1 ng/mL) or under active surveillance as per ESMO guidelines. Other cancers for which the subject has completed potentially curative treatment more than 3 years prior to study entry are allowed.
- Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial

Important note: All eligibility criteria must be adhered to, in case of deviation discussion with Headquarters and study coordinator is mandatory.

4 Trial Design

This is a multicenter, randomized, controlled, open label phase III superiority trial with an early stopping rule for futility.

After signing the informed consent form and upon confirmation of the patient eligibility, patients will be randomized 1:1 to the experimental arm (addition of marizomib to the standard treatment) or the standard arm.

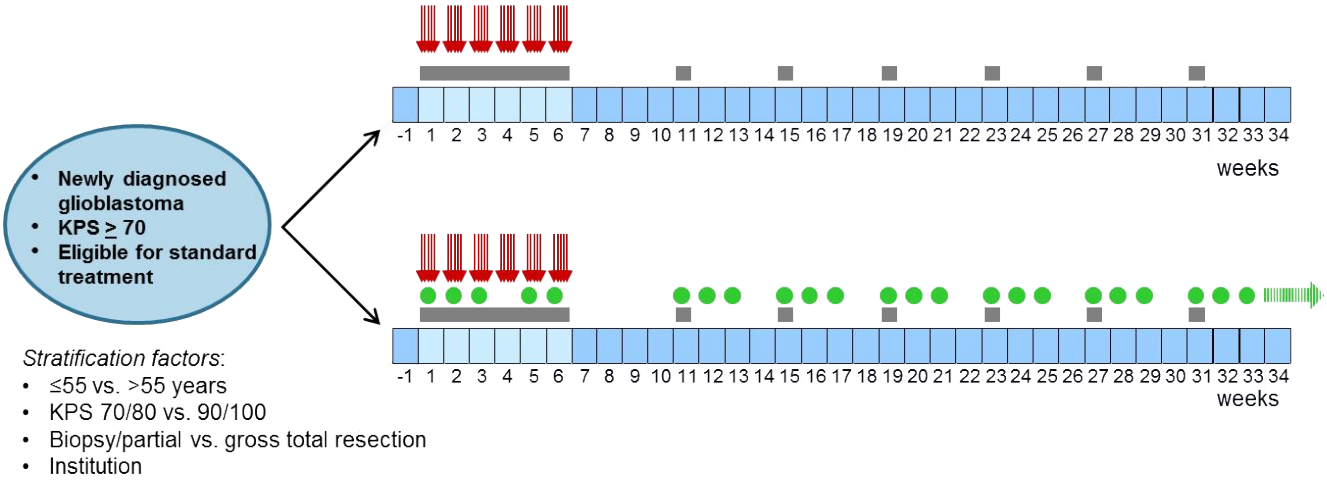
Experimental arm: Standard radiotherapy (60 Gy in 30 fractions over 6 weeks) + TMZ 75 mg/m^2 p.o. daily for 6 weeks (during radiotherapy) and marizomib (MRZ) dose 0.8 mg/m^2 IV at days 1, 8, 15, 29 and 36.

This is followed, after 4-week break, by up to 6 cycles of maintenance TMZ 150-200 mg/m^2 p.o. on days 1-5 of a 28-day cycle and up to 18 cycles of maintenance MRZ treatment (0.8 mg/m^2 IV) at days 1, 8, 15 of a 28-day cycle until disease progression, unacceptable toxicity or withdrawal of consent (see section 5.4).

Continuation of maintenance temozolomide beyond 6 cycles is not encouraged, but will not constitute a protocol violation as long as it does not exceed 12 cycles in total.

Standard arm: Standard radiotherapy (60 Gy in 30 fractions over 6 weeks) + TMZ 75 mg/m^2 p.o. daily for 6 weeks (during radiotherapy) then (after 4-week break) up to 6 cycles of maintenance TMZ 150-200 mg/m^2 p.o. on days 1-5 of a 28-day cycle.

Continuation of maintenance TMZ beyond 6 cycles is not encouraged, but will not constitute a protocol violation as long as it does not exceed 12 cycles in total.



Stratification factors:
- ≤55 vs. >55 years
- KPS 70/80 vs. 90/100
- Biopsy/partial vs. gross total resection
- Institution

Radiotherapy 5x per week (total dose of 60 Gy in 30 fractions)

Temozolomide 75 mg/m^2 p.o. for 6 weeks (during radiotherapy), followed (after a 4-week interval) by up to 6 cycles of maintenance TMZ chemotherapy 150-200 mg/m^2 p.o., days 1-5 of a 28-day cycle

Marizomib 0.8 mg/m^2 i.v. at days 1, 8, 15, 29 and 36 during radiotherapy, followed (after a 4-week interval) by adjuvant treatment at days 1, 8, and 15 of a 28-day cycle until disease progression, unacceptable toxicity, withdrawal of consent or up to 18 cycles post radiotherapy

All patients will have regular follow-up by MRI, 4 weeks after end of radiotherapy then every 8 weeks thereafter.

5 Therapeutic regimens, expected toxicity, dose modifications

5.1 Drug information

5.1.1 Marizomib

5.1.1.1 General information

Chemical name:	**(1*R*,4*R*,5*S*)-4-(2-chloroethyl)-1-((1*S*)-cyclohex-2-enyl(hydroxyl)methyl)-5-methyl-6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione**
Other chemical identifier:	Salinosporamide A
Molecular formula:	$C_{15}H_{20}ClNO_4$
Molecular weight:	313.78
Physical description:	White crystalline solid
Pharmacological class:	Proteasome inhibitor
Abbreviated names	NPI-0052, MRZ

5.1.1.2 Drug supply

Marizomib supplies and re-supplies will be provided by Celgene as long as patients are on protocol treatment. Guidelines for drug resupply will be provided in a separate document (see IMP Management Guidelines).

5.1.1.3 Packaging, dispensing and storage

The intravenous (IV) formulation consists of a kit containing 1 vial of marizomib lyophile (2 mg marizomib in 60 mg sucrose) presenting as white to light pink powder or cake and 1 vial of marizomib diluent.

The lyophilized drug product contains 2 mg API and 60 mg sucrose bulk excipient. Cartons contain one vial of lyophile together with a Diluent vial containing 55% propylene glycol, 5% ethanol, and 40% citrate buffer pH 5 (20 mL fill; 10 mL intended for use). The lyophile drug product reconstituted with 10 mL diluent results in a dosing solution comprised of 55% propylene glycol, 40% citrate buffer and 5% ethanol, with 6 mg/mL sucrose as a pharmaceutical excipient. The drug is delivered at 0.2 mg/mL at a final dosing solution of pH ~6.

Kits containing one vial each of marizomib lyophile and marizomib diluent should be stored at 2°C to 8°C in a secured area to prevent unauthorized access. A temperature log must be maintained and temperature excursion monitored during the study course. Please refer to the Pharmacy Manual and local product label, as applicable, for detailed handling instruction for the reconstituted solution.

5.1.1.4 Drug reconciliation procedures

Accountability of the investigational study drug is under the responsibility of the investigator and can be delegated to an appropriately qualified person.

Study drug accountability should be maintained by each site. Accountability records should include receipt date, batch numbers, expiry dates, patient SeqID, use by subject, dispensing dates, quantities (lowest unit) and stock balance.

In addition to internal accountability documentation on site, EORTC study-specific accountability and drug destruction forms will be supplied for this purpose, if site-specific forms are deemed not sufficiently detailed or do not provide enough information, according to EORTC Quality Assurance criteria.

The drug accountability and destruction forms will be verified during monitoring visits.

At the end of study, when all patients have stopped protocol treatment, complete drug reconciliation per batch should be available at the site for verification by EORTC in order to allow drug destruction or return procedure.

Both the unused and expired study medication must be destroyed, upon authorization of the sponsor, according to local regulations and procedures, and a copy of the destruction form must be returned to the EORTC Headquarters.

The medication provided for this trial is to be used only as indicated in this protocol and only for the patients entered in this study.

5.1.2 Temozolomide

Temozolomide (TMZ) is an approved drug for the treatment of patients with newly diagnosed glioblastoma. TMZ is available commercially and will therefore be taken off the shelf.

During radiotherapy, TMZ is administered at a dose of 75 mg/m^2 daily, starting at the first day of radiotherapy, typically for 42 days and for a maximum of 49 days. Four weeks after the last day of radiotherapy, treatment with TMZ is resumed at a dose of 150 mg/m^2 (cycle 1) and 200 mg/m^2 (subsequent cycles) daily for 5 days every 28 days (corresponding to a cycle) for up to 6 cycles. TMZ will be administered and prescribed according to the official label and the standard of care which has been defined in a previous EORTC/NCIC trial (Ref. 42).

5.2 Initial dose and schedule

MRZ will be administered IV over 10 minutes. Volume of administration will vary based on dose (0.8 mg/m^2) and patient body surface area (BSA). Capping is not allowed, because of potential underdosing. MRZ can be administered either through peripheral, PIC-line, central line or port-a-cath at investigator discretion. However, infusion site reactions are observed with peripheral administration; infusing by central line reduces the frequency and severity of these events (refer to Pharmacy Manual).

Patients should maintain good oral hydration during the study (e.g., 2 L/day). The volume and duration of hydration may be reduced at the discretion of the Investigator, especially for patients with low body weight or with conditions sensitive to fluid overload.

Patients should not drive a vehicle or operate heavy machinery while on this study.

MRZ will be administered as a 10-minute IV infusion on Days 1, 8, 15, 29 and 36 during the concomitant treatment (with TMZ+RT), and on Days 1, 8, and 15 of each 28-day cycle in adjuvant treatment (with TMZ) for a total of 6 cycles. After 6 cycles of TMZ have been completed, marizomib is administered on Days 1, 8, and 15 of each 28-day cycle for another 12 cycles.

Minimum re-treatment criterion prior to the beginning of each new cycle in the adjuvant treatment: creatinine ≤ 1.5 x ULN, Hgb ≥ 8 g/dL, platelets ≥ 75 x 10^9/L.

5.3 Treatment duration

In the standard arm, patients will receive up to 6 cycles of TMZ as maintenance at a dose of 150-200 mg/m^2 daily for 5 days every 28 days, unless treatment is discontinued for disease progression, unacceptable toxicity, or withdrawal of consent.

Continuation of maintenance temozolomide beyond 6 cycles (e.g., for a maximum of 12 cycles) is not encouraged but is left to the discretion of the Investigator and the interest of the patient.

In the experimental arm, patients will receive up to 6 cycles of MRZ+TMZ in the maintenance setting, followed by another 12 cycles of MRZ alone, unless treatment is discontinued for disease progression, unacceptable toxicity, withdrawal of consent, or the patient has completed the 18 cycles of MRZ as planned. In the event that one drug (TMZ or MRZ) is discontinued for reasons other than disease progression, the other will then continue as a single agent.

At study closure, all study participants may continue to receive study treatment as planned in the protocol (see chapter 4) provided that they benefit from it and all protocol-specified criteria for continuing study treatment are met. For all patients who discontinue treatment for reasons other than disease progression, whenever possible, tumor assessment will continue as per protocol until disease progression, or start of a new treatment regimen.

After disease progression, treatment will be left to the discretion of the treating physician. Any further anti-cancer therapy will not be considered as part of the protocol treatment. However, patients will be followed for survival and the start of first new anti-GBM therapy and its outcome.

5.4 Withdrawal criteria

The principal investigator should discontinue study treatment for a patient in the event of:

- Progressive disease
- Unacceptable overall toxicity for all drugs.
- Protocol violation
- Loss to follow-up

- Patient significant non-compliance
- Pregnancy
- Physician/Patient decision
- Death

An end of treatment visit should be performed, and follow-up for survival, subsequent therapy and date of progressive disease (PD) collected, whenever feasible.

Patients have the right to withdraw from the study at any time for any reason.

In the case that the patient decides to prematurely discontinue study treatment, the patient must be followed for disease assessments and survival follow-up, unless the patient decides to withdraw consent for the collection of these data. In the case that the patient withdraws consent, the patient must be asked if can still be contacted for survival follow-up only. The outcome of these discussions should be documented in both the medical records and in the eCRF.

5.5 Dose and schedule modifications

Treatment (MRZ +TMZ) may be administered -1 / +3 days of a scheduled dose for reasons other than toxicity.

5.5.1 MRZ

Acceptable MRZ dose reductions are as follows:

Dose Level	Weekly dose	Concomitant Treatment Schedule	Adjuvant Treatment Schedule
Starting dose	0.8 mg/m^2	Days 1, 8, 15, 29, 36	Days 1, 8 and 15 (28-day cycle)
Dose level -1	0.7 mg/m^2	Days 1, 8, 15, 29, 36	Days 1, 8 and 15 (28-day cycle)
Dose level - 2	0.55 mg/m^2	Days 1, 8, 15, 29, 36	Days 1, 8 and 15 (28-day cycle)
Dose level - 3	0.4 mg/m^2	Days 1, 8, 15, 29, 36	Days 1, 8 and 15 (28-day cycle)

The minimum permitted dose level for MRZ is 0.4 mg/m^2. If toxicity recurs at the minimum permitted dose of MRZ, MRZ treatment should be discontinued. Dose re-escalation is not permitted for MRZ.

Minimum re-treatment criterion prior to the beginning of each new cycle in the adjuvant treatment: creatinine ≤ 1.5 x ULN, Hgb ≥ 8 g/dL, platelets ≥ 75 x 10^9/L.

During adjuvant phase: Marizomib treatment may be held (skipped) a maximum of 3 consecutive doses for related toxicity.

If the 3 consecutive skipped doses are in the same cycle, and the subject is able/unable to resume marizomib on the scheduled Day 1 of the subsequent cycle, the Medical Monitor should be contacted to discuss continuation or permanent withdrawal of marizomib.

If the 3 consecutive skipped dose are in 2 consecutive cycles, and the patient is able/not able to resume treatment at the next planned visit, the Medical Monitor should be contacted to discuss continuation of marizomib or permanent withdrawal.

MRZ delays: -1day to +3 days: MRZ can be administered 1 day before and up to 3 days after the planned administration. The next dose will be administered at the next initially planned visit.

Detailed instructions for MRZ dose modifications and actions are provided in the Table below:

Marizomib-Related Adverse Event	Severity	Recommended action regarding MRZ administration
Central Nervous System		
Common CNS AEs include: Hallucinations, ataxia, dizziness, gait disturbance, balance disorder, fall, dysarthria, confusion	Grade 2	Consider other supportive treatment; generally no dose-reductions are recommended. Dose-reduction is recommended if intolerable by patient due to interference with daily routine and/or if duration of event lasts longer than 3 days.
	Grade 3	At the next scheduled MRZ dose administration, dose-reduce one dose level. During concomitant treatment, if AE has not resolved to ≤ Grade 1 (or baseline) by the next scheduled dose of MRZ, skip MRZ and administer TMZ/RT without delay; consider dose reduction with the next scheduled dose. During adjuvant treatment, if AE has not resolved to ≤ Grade 1 (or baseline) by Day 1 of next cycle, administer Day 1 TMZ and skip the Day 1 MRZ dose. Resume MRZ with the next scheduled dose at reduced level. If AE has not resolved to ≤ Grade 1 (or baseline) by Day 1 of next cycle, administer Day 1 TMZ and skip the Day 1 MRZ dose. Resume MRZ with the next scheduled dose at reduced level. If AE has not resolved to ≤ Grade 1 (or baseline) on Days 8 or 15, skip the MRZ dose and resume with the next scheduled dose at reduced level. If AE has not resolved to ≤ Grade 1 (or baseline) during adjuvant MRZ post-completion of TMZ, delay and reduce the MRZ dose. In addition, consider other supportive treatment.
	Grade 4	Stop MRZ until resolution to ≤ Grade 1 (or baseline). Discuss with Medical Monitor. If re-challenge is an option, reduce MRZ dose level (see MRZ dose reduction table) in agreement with Medical Monitor.

Marizomib-Related Adverse Event	Severity	Recommended action regarding MRZ administration
Gastrointestinal		
Nausea, Vomiting	Grade 1 or 2	Implement prophylactic anti-emetic regimen according to local guidelines. Maintain current MRZ dose schedule without dose modification. If (re)occurrence despite appropriate prophylaxis, dose-reduce one dose level (see MRZ dose reduction table) at the next scheduled MRZ dose administration.
	Grade 3 or 4	Implement prophylactic anti-emetic regimen according to local guidelines. If (re)occurrence despite appropriate prophylaxis, dose-reduce one dose level (see MRZ dose reduction table) at the next scheduled MRZ dose administration. In addition, consider other supportive treatment per local guidelines.
Other Adverse Events		
	Grade 2	Maintain current MRZ dose schedule without dose modification. Consider dose-reduction if intolerable by patient due to interference with daily routine and/or not resolved to ≤ Grade 1 (or baseline) at the next scheduled MRZ dose administration.
	Grade 3	At the next scheduled MRZ dose administration, dose-reduce one dose level (see MRZ dose reduction table). During concomitant treatment, if AE has not resolved to ≤ Grade 1 (or baseline) by the next scheduled dose of MRZ, skip MRZ and administer TMZ/RT without delay; consider dose reduction with the next scheduled dose. During adjuvant treatment, if AE has not resolved to ≤ Grade 1 (or baseline) by Day 1 of next cycle, administer Day 1 TMZ and skip the Day 1 MRZ dose. Resume MRZ with the next scheduled dose at reduced level. If AE has not resolved to ≤ Grade 1 (or baseline) by Day 1 of next cycle, administer Day 1 TMZ and skip the Day 1 MRZ dose. Resume MRZ with the next scheduled dose at reduced level.

Marizomib-Related Adverse Event	Severity	Recommended action regarding MRZ administration
		If AE has not resolved to ≤ Grade 1 (or baseline) on Days 8 or 15, skip the MRZ dose and resume with the next scheduled dose at reduced level. If AE has not resolved to ≤ Grade 1 (or baseline) during adjuvant MRZ post-completion of TMZ, delay and reduce the MRZ dose.
	Grade 4	Stop MRZ until resolution to ≤ Grade 1 (or baseline). Discuss with Medical Monitor. If re-challenge is an option, reduce MRZ dose level (see MRZ dose reduction table) in agreement with Medical Monitor.
When marizomib is administered as single agent (after completion of adjuvant temozolomide treatment)		
Any MRZ-related AE	Any grade	If patient is slow to recover from MRZ toxicity, a treatment delay can occur for each of the scheduled marizomib doses as needed.

5.5.2 RT Delays

RT-related toxicities should be managed as per local practice. RT dose modifications are not allowed per se, but information on managing delays is given in the radiotherapy section (see section 5.7.8). In case of any AEs leading to RT interruption or delays not considered related to either TMZ or MRZ, both drugs should continue as scheduled if medical condition allows it.

5.5.3 TMZ

During concomitant treatment part of the study, TMZ-related toxicities should be managed as per local practice. During adjuvant treatment, if the start of treatment cycle needs to be delayed due to TMZ toxicity (not related to MRZ), the planned cycle (TMZ + MRZ) may be delayed for a maximum of up to 14 days. If toxicity persists beyond 14 days, the TMZ treatment will be skipped during this cycle (The start of the cycle begins with the first dose of MRZ treatment and will be administered as scheduled) and TMZ treatment will be resumed with the following cycle.

Dose modifications for TMZ are allowed and should follow the standard of care at the institution. In case of any AEs leading to TMZ interruption (need to skip a treatment dose) and not considered related to MRZ, MRZ should continue as scheduled if medical condition allows it.

The combined TMZ + RT treatment increases incidence of phototoxicity. Patients should be advised to minimize UV light exposure for the duration of the combined treatment and for 1 month after the last RT treatment.

Prior to start of TMZ treatment, patients should be advised on the risk of potential irreversible infertility and/or testicular damage from TMZ and the possibility of sperm conservation.

5.6 Concomitant treatments

5.6.1 General

Concomitant medications to treat comorbid conditions and AEs are permitted. Enzyme-inducing anti-epileptic drugs (EIAEDs) are allowed. Steroids are allowed and dosing is at the discretion of the Investigator, with their use recorded in the case report form (CRF).

MRZ appears to have a very low potential for drug-drug interactions as it is neither an inhibitor nor an inducer of hepatic cytochrome P450s (CYPs) from different species, it is not influenced by multiple drug resistant/adenosine triphosphate (ATP)-binding cassette transporters and is inactive in a broad array of enzyme, ion channel, second messenger, and receptor assays.

Hydrolysis in the systemic circulation and tissues or gastrointestinal (GI) tract appears to be the major metabolic route for MRZ and the known metabolites are inactive both as proteasome inhibitors and cytotoxic agents.

The use of TMZ can reactivate opportunistic infections including CMV, HSV, HZV and PJP. However, PJP prophylaxis is not recommended as a standard treatment according to current guidelines (Ref. 52). Therefore, treatment will be prescribed as per local standards. If part of local standard of care, prophylaxis against *Pneumocystis jirovecii* can be initiated for patients receiving combined TMZ and RT for the 42-day (maximum 49 days) regimen regardless of lymphocyte count. If lymphopenia occurs, they are to continue the prophylaxis until recovery of lymphopenia to grade ≤ 1.

5.6.2 Supportive care in case of toxicity

In Phase 1 studies to date, MRZ has caused clinically significant nausea and vomiting requiring the use of anti-emetics as therapy and also as prophylaxis. In addition, nausea and vomiting are also very commonly associated with TMZ. Therefore, both the therapeutic and prophylactic use of anti-emetics is allowed in this study at the discretion of the Investigator as necessary (may not be needed at the first dose).

To date, MRZ has also caused some hallucinations, therefore both the therapeutic and prophylactic use of anti-psychotics is allowed in this study at the discretion of the Investigator as necessary.

5.6.3 Prohibited therapies

The following treatments are NOT permitted during the study treatment:

- Treatment with other systemic anti-cancer agents before disease progression (chemotherapy, immunotherapy, anti-tumor vaccines, targeted agents, or other treatments not part of protocol-specified anti-cancer therapy)
- Concurrent investigational agents of any type before disease progression
- Craniotomy, intra-tumoral interstitial therapy, any surgical procedures under investigation or any form of radiosurgery

Any of the above will lead to patient's discontinuation from study treatment.

Additional treatment with tumor treating fields in the adjuvant setting is discouraged but will not constitute a protocol violation.

Alternative therapies are discouraged and must be discussed with the local investigator.

5.6.4 ECG with use of Marizomib

To date, there has been no signal of a safety issue with ECG abnormalities including prolonged QTc with marizomib. There has been no signal of ECG abnormalities in patient treated with marizomib. However, a thorough

analysis of the QT/QTc data has not yet been submitted to the US FDA. Thus additional ECGs will be collected in the marizomib arm of the study.

12-lead ECGs will be collected for all subjects on marizomib at specified timepoints: baseline, Day 1 of concomitant treatment, Cycle 2 Day 1 of adjuvant treatment, and as clinically indicated and will be assessed locally.

ECGs on Day 1 of concomitant treatment and Cycle 2 Day 1 of adjuvant treatment will be collected within 15 minutes after end of MRZ infusion. The standard 12-lead ECGs (including heart rate, PR-interval, QRS, QT interval, and QTc interval) will be performed and recorded.

For subjects enrolled into the marizomib arm prior to the implementation of protocol version 5, 12-lead ECG on Day 1 of the subsequent two cycles of adjuvant treatment within 15 minutes after end of MRZ infusion.

5.6.5 Covid-19 vaccines

As per the European Medicines Agency (EMA):

If physicians decide to administer SARS-CoV-2 vaccines in patients enrolled in the study, decisions should be individualized based on the risk of SARS-CoV-2 complications and potential benefit from the vaccine, general condition of the patient and the severity of COVID-19 outbreak in a given area or region and in accordance with the vaccine label. Furthermore, the national guidelines and/or institutional guidelines must be followed.

The available SARS-CoV-2 vaccines, that are not live attenuated vaccines, are not contra-indicated in patients on anticancer treatment.

Treatment schedule should not be altered because of the COVID-19 vaccination.

The administration of a SARS-CoV-2 vaccine (including brand name) shall be added in the concomitant medication form in the eCRF and noted in the patient's medical file. Any possible vaccine related AE should be captured in the AE forms in the eCRFs, specifying the potential relationship to the vaccine.

5.7 Radiotherapy

RT will consist of a conventionally fractionated regimen delivering a total dose of 60 Gy in 30 fractions in 6 weeks, a fraction of 2 Gy once daily, 5 days per week. Participating investigators will find the provisions on this chapter summarized in the RTQA Guidelines.

5.7.1 Facility and Equipment

Institutions must comply with the Quality Assurance of Radiotherapy requirements and procedures described in detail in the Quality Assurance in Radiotherapy section 17.4.1.

Patients will be treated on megavoltage equipment, i.e. linear accelerator beams with a minimum nominal energy of 6 MV. SAD should be at least 100 cm. Electrons, particles and implants are not permitted. The use of Cobalt units is not allowed in this trial.

The volume should be treated by a multiple field technique, with all fields treated at each fraction

Treatment with a single beam and parallel pair alone are not acceptable.

Treatment with intensity modulated radiotherapy (IMRT) is recommended. It can be used provided it is i) *without simultaneous integrated boost*, ii) conventional fractionation, and iii) the dose prescription and homogeneity criteria are in accordance with ICRU 83 (2010).

3D treatment planning computers and BEV planning should be used. The use of DVH for planning is mandatory. Images, as digital reconstructed radiograph (DRR), should be available for assessment of setup accuracy.

5.7.2 Patient position and data acquisition

Patients can be planned and treated supine in a custom made immobilization shell (any fixation system with relocation accuracy ≤ 3 mm).

A single phase treatment volume will be used throughout treatment. A cone-down volume or boost volume is not allowed. All margins should be added using a 3D growth algorithm where possible.

The images of the pre-RT MRI, performed with the subject placed in the treatment position (supine), should be used to aid definition of the gross tumor volume (GTV) and the clinical target volume (CTV) on the planning CT without contrast (≤ 3 mm slice thickness). Wherever possible, an image co-registration should be done. Preferably the pre RT MRI should be within 2 weeks of the planning CT otherwise the planning CT should be done with contrast.

5.7.3 Volume definition

The definition of volumes will be in accordance with ICRU Reports #50, #62 and #83 [ICRU 1993; ICRU 1999; ICRU 2010].

5.7.3.1 Gross Target Volume (GTV)

For subjects whose tumor has been biopsied (open biopsy only; stereotactic biopsy not allowed): the region of enhancement (without edema) on planning CT plus pre-RT MRI.

For subjects whose tumor has been resected: The GTV is the surgical tumor bed plus any residual enhancing tumor as seen on the planning scan. Co-registration of planning CT and pre RT MRI should be performed.

5.7.3.2 Clinical Target Volume (CTV)

The GTV plus a margin to account for microscopic spread. This margin will usually be 1.5-2 cm maximum, but can be reduced in anatomical regions where spread is unlikely (e.g. bony structures). The exact GTV-CTV margin is left to the best estimate of each individual investigator; it may depend on various factors such as the tumor location, the previous use of steroids, etc.

In case of complete or subtotal removal, the position of the tumor bed may have shifted, and the CTV should take into account the new position of the abnormality on the planning CT scan and any post-operative imaging.

5.7.3.3 Planning Target Volume (PTV)

The PTV (PTV_6000) will take into account uncertainties of planning and setup. The margin between CTV and PTV should be based on known departmental values, but will usually be 0.5-0.7 cm.

5.7.3.4 Organs at Risk

The following Organs at risk (OARs) will be delineated (Ref. 38). Naming of the structures will follow Santanam *et al.* (Ref. 37):

OAR	Description
Eye balls	The whole of the outside of the globe should be contoured to include sclera and cornea. The macula lies opposite the lens.
Lenses	Seen at the anterior part of the globe.
Optic Nerves (if visible)	From the back of the globe to the optic chiasm passing through the optic canal to enter the skull anterior and inferior to the anterior clinoid. Should be delineated in continuity with the optic chiasm.

OAR	Description
Optic Chiasm	Sits above and behind the anterior clinoids and runs backwards above the sella turcica. The anterior and posterior 'limbs' should extend 5 mm to include the start of the optic nerves anteriorly and optic tracts posteriorly. The chiasm can sometimes only be seen on a single slice as it is about 3 mm thick in craniocaudal direction.
Lacrimal Glands	Situated in the upper lateral region, above the lateral rectus muscle, partly on top of the eyeball.
Internal ear	Sit just anterior to the lateral aspect of the internal auditory canal.
Brain Stem	The foramen magnum to the point where the optic tract passes lateral to the midbrain
Brain**	Whole brain parenchyma includes all intracranial contents, inclusive of target volumes.
Whole Brain minus PTV	For ease of DVH calculation.
Contralateral normal brain	To be delineated for tumors not crossing the midline.
Optic Nerve Planning Risk Volume (PRV)	Optic Nerves expanded by volumetric 3 mm
Optic Chiasm PRV	Optic Chiasm expanded by volumetric 3 mm

** Please do not include the brainstem in the contour of the contralateral brain, brain and brain –PTV contours

5.7.4 Dose

Dose prescription and recording should be according to ICRU 83 criteria. This also applies if the treatment is delivered by 3D-CRT.

The PTV should be encompassed by the 95% isodose. However, if the PTV is in close proximity to an OAR the 90% isodose is acceptable provided 98% of the PTV receives at least 90% of the prescribed dose.

The regimen consists of a total dose of 60 Gy in 30 daily fractions, for a total overall time of 6 weeks. The time interval between fractions should be at a minimum of 18 hours, with an acceptable variation of ±2 hours on weekdays, and a maximum interruption of 72 hours (±2 hours) for weekends or public holidays. The time of day of the RT should, if possible, be kept the same each day. This will also facilitate the delivery of TMZ and MRZ.

5.7.5 Treatment planning

The following are mandatory:

- Planning CT scan and pre-RT MRI is required for simulation and planning.
- Three-dimensional treatment planning computers and BEV planning.
- A dose calculation grid of 3 mm or less should be used.
- The use of DVH for planning.

5.7.5.1 Dose Limitations to Critical Structures

Whenever possible, attempts should be made to limit the maximum dose for the OARs as follows:

- Optic Chiasm: ≤55 Gy. to 0.03cc

- Optic Chiasm PRV ≤55Gy to 0.03cc
- Brainstem: ≤56 Gy. to 0.03cc
- Optic Nerves ≤ 56 Gy to 0.03cc
- Optic Nerves PRV: ≤56 Gy. to 0.03cc
- Eye balls, retina: ≤40 G to Dmax
- Lens: 10 Gy to 0.03cc
- Lacrimal glands: <40 Gy to 0.03cc
- Cochlea: ≤45 Gy if both sides are involved; otherwise ≤60 Gy. (Low priority OaR)to 0.03cc
- The dose to the normal brain minus the PTV should be kept as low as possible. The Dmean is to be ≤ 30 Gy

Dose to the contra-lateral normal brain should be Dmean ≤ 30Gy, except where the tumor or the PTV margin cross midline If required, supplementary shielding of OAR is allowed, even if it lowers the dose to a part of the PTV.

5.7.6 Treatment verification and accuracy

Treatment verification shall be performed at least weekly, preferably using an electronic portal imaging device (EPID), according to the standard correction protocol of the participating institute.

Copies of portal imaging used for verification should be available upon request.

5.7.7 Complications

Expected acute toxicity of conventional RT include headache, fatigue, hair loss, skin reaction, occasionally nausea, mucositis (if nasopharynx included), temporary reduced hearing (if ear canal included), and temporary loss of taste (if nasopharynx included).

Depending on the tumor location and the region to be irradiated, several tissues or organs are potentially at risk for late damage, such as cortical brain, brain stem, chiasm, ear (mid or internal), lachrymal gland and pituitary gland. All efforts should be made during planning to minimize the dose to critical structures.

Late complications will be recorded according to CTC version 5.0.

5.7.8 Treatment interruptions/modifications

No RT dose adjustments are recommended for treatment interruptions. Maximum overall treatment time should be ≤ 49 days. If radiotherapy is delayed, MRZ and/or TMZ should be held until radiotherapy treatment resumes. Should radiotherapy be held for longer and if it is believed to be of clinical benefit for the patient to restart RT + TMZ ± MRZ, sites should contact the medical monitor.

Reasons for treatment interruption include major worsening of neurological or mental status or any other medical condition that would preclude the continuation of RT. The decision for interruption and resumption of RT after interruption will be taken on an individual basis by the local investigator.

Dose adjustments or transient discontinuations of RT should be avoided as much as possible. In individual cases the treating radiation oncologist will discuss with the study coordinator whether lowering of the total tumor dose is necessary.

6 Clinical evaluation, laboratory tests and follow-up

6.1 Before treatment start

The following assessments should be done within 28 days of randomization:

- Signature of informed consent

- demographics, medical (and cancer) history
- tumor pathology report available
- Availability of FFPE tissue (1 paraffin block or 24 unstained slides minimum)
- fresh frozen tissue from participating centers

Within 14 days of randomization:

- HBV, HCV and HIV (if allowed by local legislation) serology
- laboratory tests including:
    - hematology - Hemoglobin (Hgb), hematocrit (Hct), red blood cell (RBC) count, white blood cell (WBC) count, ANC, platelet
    - Coagulation:
        - Prothrombin time (PT) or International Normalized Ratio (INR) and
        - partial thromboplastin time (PTT) or activated PTT (aPTT)
    - biochemistry - Sodium, potassium, chloride, calcium, magnesium, glucose, Urea or BUN, serum creatinine, uric acid, ALT, AST, alkaline phosphatase, total protein, albumin, and total bilirubin
    - urinalysis - protein, blood, glucose, pH; microscopic (RBC, WBC, casts) if abnormal urinalysis
- brain MRI scan with contrast after surgical resection or biopsy. The results of tumor assessments done as part of standard of care that are within the 14-day screening period do not have to be repeated if they were done at the participating site. All scans are to be uploaded on the EORTC imaging platform. For detailed acquisition parameters, see the study specific imaging guidelines.
- MMSE and Quality of life assessment (modified EORTC QLQ C30/BN20) (Appendix E and Appendix H)
- G8 geriatric screening tool (for patients aged 70 years and above)
- For participating centers, tests of objective neurocognitive function: HVLT-R, Trail Making Tests Part A & B and COWA and the MOS questionnaire on self-perceived neurocognitive function (Appendix J)

Within 7 days of randomization:

- physical examination including height, weight
- vital signs (heart rate, temperature, blood pressure)
- Karnofsky Performance Status (KPS) scale (Appendix E)
- 12-lead ECG
- baseline adverse event assessment
- ongoing medications
- For WOCBP, urine or serum pregnancy tests
- translational research:
    - Mandatory: 10 mL blood draw for plasma and 10 mL blood draw for serum
    - Optional: 10 mL blood draw for extracellular vesicles and 20 mL for PBMC; if available, fresh-frozen tissue

6.2 During treatment

Treatment should start within 1 week of randomization. (Delays of 48h due to drug delivery issues will not be considered a protocol deviation.)

6.2.1 During the 6 weeks of RT and TMZ ± MRZ

For WOCBP a pregnancy test (serum or urine) within 72 hours before start treatment.

The following assessments should be done on a weekly basis. If baseline assessments have been done within 14 days of start of treatment, they do not have to be repeated for cycle 1 week 1.

- concomitant medications and procedures
- adverse events
- hematology as in section 6.1
- Vital signs (heart rate, temperature, blood pressure)

At D1 marizomib arm only

- 12 -lead ECG within 15 minutes after end of MRZ infusion.

at 4 weeks (+ 5 days)

- biochemistry and coagulation parameters as in section 6.1

On the last day of RT (but before start of maintenance treatment):

- Karnofsky Performance Status (KPS) scale
- For WOCBP, urine or serum pregnancy tests
- MMSE and Quality of life assessment (modified EORTC QLQ C30/BN20)
- For participating centers, tests of objective neurocognitive function: HVLT-R, Trail Making Tests Part A & B and COWA and the MOS questionnaire on self-perceived neurocognitive function (Appendix J)
- translational research:
    - Mandatory: 10 mL blood draw for plasma and 10 mL blood draw for serum
    - Optional: 10 mL blood draw for extracellular vesicles and 20 mL for PBMC

6.2.2 During TMZ maintenance ± MRZ

The following assessment should be done before every cycle start (within 3 days before)

- physical examination (including weight)
- Karnofsky Performance Status (KPS) scale (Appendix E)
- vital signs (heart rate, temperature, blood pressure)
- concomitant medications and procedures
- adverse events
- hematology as in section 6.1
- biochemistry as in section 6.1
- For WOCBP, urine or serum pregnancy tests

At Cycle 1 marizomib arm only, pharmacokinetics.

* At Cycle 1 D 1 (first day of the first adjuvant cycle): first blood sample for pharmacokinetics immediately after end of MRZ infusion and second sample within 45 minutes after end of MRZ infusion.

* At Cycle 1 D 8: sample within 45 minutes after end of MRZ infusion.

At Cycle 2 Day 1 marizomib arm only

- a 12-lead ECG within 15 minutes after end of MRZ infusion.

Every 8 weeks (± 7 days)

- Brain MRI scans. The first scan should occur 4 weeks post end of RT. The 8-week imaging schedule will start after this scan.
  All scans are to be uploaded on the EORTC imaging platform. For detailed acquisition parameters, see the study specific imaging guidelines.

Every 12 weeks (± 7 days) after start of maintenance phase

- translational research:
  - Mandatory: 10 mL blood draw for plasma and 10 mL blood draw for serum
  - Optional: 10 mL blood draw for extracellular vesicles and 20 mL for PBMC

Every 16 weeks (± 7 days)

- MMSE and Quality of life assessment (modified EORTC QLQ C30/BN20)

Every 24 weeks (± 7 days)

- For participating centers, tests of objective neurocognitive function: HVLT-R, Trail Making Tests Part A & B and COWA and the MOS questionnaire on self-perceived neurocognitive function (Appendix J)

6.2.3 During Marizomib maintenance (experimental arm, after stopping TMZ maintenance)

The following assessment should be done before every cycle start (within 3 days):

- physical examination (weight)
- Karnofsky Performance Status (KPS) scale (Appendix E)
- vital signs (heart rate, temperature, blood pressure)
- concomitant medications and procedures
- adverse events
- hematology as in section 6.1
- biochemistry as in section 6.1
- For WOCBP, urine or serum pregnancy tests

Every 8 weeks (± 7 days), following the imaging schedule defined in section 6.2.2

- Brain MRI scans
  All scans are to be uploaded on the EORTC imaging platform. For detailed acquisition parameters, see the study specific imaging guidelines.

Every 12 weeks (± 7 days)

- translational research:
  - Mandatory: 10 mL blood draw for plasma and 10 mL blood draw for serum
  - Optional: 10 mL blood draw for extracellular vesicles and 20 mL for PBMC

Every 16 weeks (± 7 days)

- MMSE and Quality of life assessment (modified EORTC QLQ C30/BN20)

Every 24 weeks (± 7 days)

- For participating centers, tests of objective neurocognitive function: HVLT-R, Trail Making Tests Part A & B and COWA and the MOS questionnaire on self-perceived neurocognitive function (Appendix J)

6.3 After the end of treatment (Follow-up)

6.3.1 End-of-Treatment Visit

The following assessment should be done (28 ±7 days) after the last marizomib or temozolomide dosing (whether the patient has progressed or completed the full duration of planned treatment

- physical examination (weight)
- Karnofsky Performance Status (KPS) scale (Appendix E)
- vital signs (heart rate, temperature, blood pressure)
- concomitant medications and procedures
- adverse events
- hematology as in section 6.1
- biochemistry as in section 6.1
- urinalysis as in section 6.1
- For WOCBP, urine or serum pregnancy tests
- brain MRI scan if one has not been done in the previous 4 weeks and no progression as yet been recorded

If patient has stopped treatment due to progression:

- MMSE
- For participating centers, tests of objective neurocognitive function: HVLT-R, Trail Making Tests Part A & B and COWA and the MOS questionnaire on self-perceived neurocognitive function (Appendix J)
- translational research:
    - Mandatory: 10 mL blood draw for plasma and 10 mL blood draw for serum
    - Optional: 10 mL blood draw for extracellular vesicles and 20 mL for PBMC

6.3.2 Post Treatment Follow-up (every 12 weeks ± 7 days)

6.3.2.1 Patient has not progressed

- results of MRI scans done as part of standard of care will be collected, or done as per the study schedule of every 8 weeks (continuing on initial schedule) until disease progression.
- MMSE, Quality of life assessment (modified EORTC QLQ C30/BN20) every 16 weeks ± 2 weeks
- For participating centers, tests of objective neurocognitive function: HVLT-R, Trail Making Tests Part A & B and COWA and the MOS questionnaire on self-perceived neurocognitive function (Appendix J) every 12 weeks (± 7 days)
- survival status
- subsequent anti-GBM regimens, and treatment outcomes

6.3.2.2 Patient has progressed

To be collected until death.

- survival status
- subsequent anti-GBM regimens, and treatment outcomes
- Quality of life assessment (modified EORTC QLQ C30/BN20) every 16 weeks ± 2 weeks

At disease progression:

- MMSE

- For participating centers, tests of objective neurocognitive function: HVLT-R, Trail Making Tests Part A & B and COWA and the MOS questionnaire on self-perceived neurocognitive function (Appendix J)
- translational research:
    - Mandatory: 10 mL blood draw for plasma and 10 mL blood draw for serum;
    - Optional: 10 mL blood draw for extracellular vesicles and 20 mL for PBMC
- optional frozen tissue sample if patient undergoes salvage surgery

6.4 Summary table

	Before randomization			Within 72h of treatment start	Randomization	TMZ/RT (± MRZ)						TMZ ± MRZ MRZ maintenance							Follow-up (every 12 weeks ± 7 days)		
Day	-28 to -1	-14 to -1	-7 to -1			Day 1[k]	Day 1 MRZ only	weekly	At 4 weeks (+5d)	End of RT period	before cycle start	Cycle 1 day 1/8	Cycle 2 day 1 MRZ	Every 8 weeks	Every 8 weeks MRZ	Every 3 cycles	Every 16 wks (± 7d)	Every 24 wks	EOT (28d after last	FU without	FU after
Description																					
Signed informed consent	X																				
Demographics	X																				
Medical and cancer history	X																				
Tumor pathology assessment from archival FFPE	X																				
baseline adverse event assessment			X																		
Ongoing			X																		

	Before randomization			Within 72h of treatment start	**Randomization**	TMZ/RT (± MRZ)						TMZ ± MRZ MRZ maintenance							Follow-up (every 12 weeks ± 7 days)		
Day	-28 to -1	-14 to -1	-7 to -1			Day 1[k]	Day 1 MRZ only	weekly	At 4 weeks (+5d)	End of RT period	before cycle start	Cycle 1 day 1/8	Cycle 2 day 1 MRZ	Every 8 weeks	Every 8 weeks MRZ	Every 3 cycles	Every 16 wks (± 7d)	Every 24 wks	EOT (28d after last	FU without	FU after
medications																					
Brain MRI scans		X[a]												X[l]					X[m]	X[p]	
Mini Mental State Examination		X								X							X		X[n]	X[q]	
Quality of Life questionnaire (modified EORTC QLQ C30/BN20)		X								X							X			X[r]	X[r]
G8 geriatric screening tool[s]		X																			
Neurocognitive assessments[b]		X								X								X	X[n]	X[q]	
Physical examin			X								X								X		

	Before randomization			Within 72h of treatment start	Randomization	TMZ/RT (± MRZ)						TMZ ± MRZ MRZ maintenance							Follow-up (every 12 weeks ± 7 days)		
Day	-28 to -1	-14 to -1	-7 to -1			Day 1[k]	Day 1 MRZ only	weekly	At 4 weeks (+5d)	End of RT period	before cycle start	Cycle 1 day 1/8	Cycle 2 day 1 MRZ	Every 8 weeks	Every 8 weeks MRZ	Every 3 cycles	Every 16 wks (± 7d)	Every 24 wks	EOT (28d after last	FU without	FU after
ation including height[c], weight																					
Heart rate, temperature, blood pressure			X			X		X	X		X								X		
Karnofsky Performance Status			X							X	X								X		
12-lead ECG[t]			X				X						X								
Hematology[d]		X				X		X	X		X								X		
Coagulation[e]		X							X												
Biochemistry[f]		X							X		X								X		
Urinalysis[g]		X																	X		
FFPE tissue (1 paraffin block	X																				

	Before randomization			Within 72h of treatment start	Randomization	TMZ/RT (± MRZ)						TMZ ± MRZ MRZ maintenance							Follow-up (every 12 weeks ± 7 days)		
Day	-28 to -1	-14 to -1	-7 to -1			Day 1[k]	Day 1 MRZ only	weekly	At 4 weeks (+5d)	End of RT period	before cycle start	Cycle 1 day 1/8	Cycle 2 day 1 MRZ	Every 8 weeks	Every 8 weeks MRZ	Every 3 cycles	Every 16 wks (± 7d)	Every 24 wks	EOT (28d after last	FU without	FU after
or 24 unstained slides minimum)																					
Mandatory: 20 mL blood draw Optional: 30 mL blood draw[h]			X							X						X			X[n]		X[n]
Optional: fresh-frozen tissue[i]	X																				X[o]
Serum pregnancy test[j]				X						X	X								X		
Randomization					X																
Concomitant medications &						X		X	X		X								X		

	Before randomization			Within 72h of treatment start	**Randomization**	TMZ/RT (± MRZ)						TMZ ± MRZ MRZ maintenance							Follow-up (every 12 weeks ± 7 days)		
Day	-28 to -1	-14 to -1	-7 to -1			Day 1[k]	Day 1 MRZ only	weekly	At 4 weeks (+5d)	End of RT period	before cycle start	Cycle 1 day 1/8	Cycle 2 day 1 MRZ	Every 8 weeks	Every 8 weeks MRZ	Every 3 cycles	Every 16 wks (± 7d)	Every 24 wks	EOT (28d after last	FU without	FU after
procedures																					
Adverse events						X		X	X		X								X		
Survival status																				X	X
subsequent anti-GBM regimens, and treatment outcomes																				X	X

[a] Brain MRI scan with contrast after surgical resection or biopsy. The results of tumor assessments done as part of standard of care that are within the 14-day screening period do not have to be repeated if they were done at the participating site. All scans are to be uploaded on the EORTC imaging platform.

[b] For participating centers, tests of objective neurocognitive function: HVLT-R, Trail Making Tests Part A & B and COWA and the MOS questionnaire on self-perceived neurocognitive function (Appendix J)

[c] Height is only to be collected at baseline

[d] Hematology consists of hemoglobin (Hgb), hematocrit (Hct), red blood cell (RBC) count, white blood cell (WBC) count, ANC, platelet

[e] Coagulation consists of prothrombin time (PT) or International Normalized Ratio (INR) and partial thromboplastin time (PTT) or activated PTT (aPTT)

[f] Biochemistry consists of sodium, potassium, chloride, bicarbonate, calcium, magnesium, glucose, urea or BUN, serum creatinine, uric acid, ALT, AST, alkaline phosphatase, total protein, albumin, and total bilirubin

[g] Urinalysis consists of protein, blood, glucose, pH; microscopic (RBC, WBC, casts) analysis should be done if urinalysis is abnormal

[h] For translational research: Mandatory 10 mL blood draw for plasma and 10 mL blood draw for serum; Optional 10 mL blood draw for extracellular vesicles and 20 mL for PBMC

[i] If site collects fresh frozen tumor tissue, optional collection

[j] For WOCBP, urine or serum pregnancy tests are to be done within 7 days of randomization and within 72 hours of treatment start

[k] If baseline assessments have been done within 14 days of start of treatment, they do not have to be repeated for cycle 1 day 1

[l] The first MRI scan should occur 4 weeks post end of RT; the 8-week imaging schedule will start after this scan

[m] Brain MRI scan if one has not been done in the previous 4 weeks and no progression as yet been recorded

[n] At disease progression

[o] Frozen tissue sample will be collected at progression if the patient undergoes salvage surgery

[p] Results of MRI scans done as part of standard of care will be collected, or done as per the study schedule of every 8 weeks (continuing on initial schedule) until disease progression

[q] For all centers, MMSE every 16 weeks ± 1 week until disease progression;
For participating centers, tests of objective neurocognitive function: HVLT-R, Trail Making Tests Part A & B and COWA and the MOS questionnaire on self-perceived neurocognitive function every 12 weeks ± 2 weeks, until disease progression

[r] Quality of life assessment (modified EORTC QLQ C30/BN20) every 16 weeks ± 1 week until death or lost to follow up

[s] G8 will be measured in all patients aged 70 years and above at baseline[t].

[t].For subjects on the marizomib arm, 12-lead ECG to be collected on following days and timepoints ONLY: at baseline within 7 days of randomization: on D1 of concomitant treatment within 15 minutes after end of MRZ infusion; on Cycle 2 Day 1 of adjuvant treatment after end of MRZ infusion; and as clinically indicated.

For subjects enrolled prior to the implementation of protocol version 5., 12-lead ECG on Day 1 on the subsequent two cycles of afjuvant treatment within 15 minutes after end of MRZ infusion.

7 Criteria of evaluation

7.1 Evaluation of efficacy

We will use the following criteria to determine the efficacy of Marizomib.

7.1.1 General method of response assessment

Response to treatment is assessed on the basis of a set of target lesion(s) chosen before the first treatment administration (the complete list of target lesions must be reported on the initial measurement form before the start of treatment). These lesions must initially be measured in their two perpendicular dimensions, and these measurements must be repeated at each evaluation of the disease by the same method. Response evaluation is based on neuro-radiological imaging (MRI). For this protocol objective response (complete, partial response) and progression will be assessed by MRI (see section 7.1.1.4). Objective response will only be assessed in patients with measurable disease defined as a clearly enhancing tumor with two perpendicular diameters at entry equal or superior to 1 cm.

The contrast enhancing area will be considered as the basis for the tumor size assessment. Tumor size is defined as the product of the two largest perpendicular diameters. For evaluating partial and complete response, the baseline scan must be used for initial comparison. In initially responding (≥ 50% reductions in cross-sectional areas) or stabilized (< 50% reduction and < 25% increase in cross-sectional areas) patients, new scans must be compared to the nadir, this is the scan showing the maximum response (i.e. minimum tumor size) during or after treatment. In assessing response, changes on T2 weighted images must be taken into consideration.

7.1.1.1 Definition of target lesions

Only the following lesions are eligible as target lesions:

- MRI contrast enhancing lesions with two perpendicular diameters of 10 mm or more visible on 2 or more axial slices which are 5 mm apart.
- Target lesion(s) must be measurable in two perpendicular diameters

In most patients, only one lesion will be present. In case of multifocal disease, a minimum of 2 lesions and maximum of 3 largest enlarging lesions will be chosen as target lesions and the sum of the products of the perpendicular diameters will be determined. All other lesions than target lesions, if applicable, are assessed according to the same schedule. They are only taken into account in two situations:

- if one of them clearly progresses, the overall response to therapy will be evaluated as "progression", independent of the response of target lesions
- all lesions must have completely disappeared to report a "complete response".

Adequate investigations must be carried out at each evaluation of the disease to detect eventual new lesions. If any new lesion is found, the response will be evaluated as "progression". Regardless of the status of enhancing lesions, if progressive lesions are observed on T2 weighted images or FLAIR images, the patient will be considered radiologically progressive, but treatment may continue if this is considered to be in the best interest of the patient and there are no signs or symptoms of clinical progression.

By definition, non-target lesions are those that do not meet the criteria for target lesion.

7.1.1.2 Evaluation of patient treated after re-operation

Postoperative changes on contrast enhanced neuro-imaging may interfere with disease evaluation. Within the first three days after surgery on MR imaging a thin linear enhancement may develop around the resection cavity, thereafter this enhancement may become thick and nodular. Enhancement of dura and meninges may be more pronounced, even within the first days. The postoperative linear enhancement may persist for up to 3-6 months, dural and meningeal enhancement may last much longer. If MRI made within 48 hours after surgery shows enhancing lesions with a nodular or mass like appearance in areas showing tumor on the pre-operative scans this is highly suggestive of residual tumor. The use of diffusion-weighted MR imaging in the immediate postoperative MRI may help with the identification of ischemic areas around the surgical cavity that may show enhancement with further follow-up.

7.1.1.3 Schedule of disease evaluation

The initial assessment of disease (including measurement of all target lesions) must be performed in the two weeks preceding randomization. Follow-up assessments will be performed every 8 weeks (or earlier if clinically indicated) until disease progression.

7.1.1.4 Definition of response

The primary measure of response and progression will be determined by the local investigator according to the RANO criteria. All treatment decisions should be based on the RANO criteria as assessed by the local investigator.

Target lesions are measured in their two largest perpendicular diameters. Their area is conventionally calculated as the product of these diameters. In case of multifocal disease with more than one target lesion, the total tumor size is calculated as the sum of the area of all target lesions.

Response is defined as follows according to the RANO criteria, which also consider T2 weighted and FLAIR images:

- Complete response (CR) requires all of the following: 1) Complete disappearance of all enhancing measurable and non-measurable disease; 2) No new lesions; 3) Stable or improved non-enhancing abnormalities on FLAIR/T2 images as compared to baseline; 4) Patients must be off corticosteroids (or on physiologic replacement doses only) and stable or improved clinically.
- Partial response (PR) requires all of the following: 1) Only reductions of cross-sectional areas of 50% or more in the sum of product of perpendicular diameters of target lesions will be considered a response; when calculating the response, the baseline MRI must be used for comparison ; 2) No progression of non-target lesions; 3) No new lesions; 4) Stable or improved non-enhancing abnormalities on FLAIR/T2 images as compared to baseline; 5) Patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan, and should be stable or improved clinically.
- Progressive disease (PD):
    - Progression is defined by any of the following: 1) 25% increase in sum of the products of perpendicular diameters of enhancing lesions (compared with baseline if no decrease) on stable or increasing doses of corticosteroids; 2) a significant increase in T2/FLAIR non-enhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not due to comorbid events; 3) the appearance of any new lesions; 4) clear progression of non-measurable lesions; or 5) definite clinical deterioration not attributable to other causes apart from the tumor, or to decrease in corticosteroid dose. Failure to return for evaluation as a result of death or deteriorating condition should also be considered as progression.
    - If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if PD is confirmed at the next follow-up, the earlier date must be used as the date of progression
    - For patients operated at recurrence and without measurable or non-measurable disease after surgery, any new appearance of tumor will qualify for PD. In case non measurable tumor is left after surgery i.e. tumor less than 10 mm, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment. Modest increase in the size of a non-target lesion is not considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used as the date of progression. This implies that in case of gross total resection of the enhancing lesion, if at follow up minimal enhancement of unclear significance arises, treatment may continue until further follow-up gives unequivocal evidence of tumor progression.
- Stable Disease: This occurs if the patients did not qualify for complete response, partial response, or progression (see below) and requires: 1) No meaningful change in the appearance of the FLAIR/T2 images compared to baseline or to the nadir (point with the smallest FLAIR/T2 abnormalities) if a decrease occurred. 2) The patient should be stable clinically. In the event the steroid dosage has been increased for new signs and symptoms without confirmation of disease progression on imaging, and further follow-up imaging shows that with hindsight this increase in steroids was indeed unequivocally needed due to disease progression, the date of progression will be the date steroids were increased.
- In this protocol, although the primary endpoint is OS, in view of the relevance of objective responses, PR, CR, and equivocal PD need to be confirmed with an extra MRI made 4 weeks later.

Criterion	CR	PR	SD	PD
T1 gadolinium enhancing disease	None	≥ 50% ↓	<50% ↓ but <25% ↑	≥ 25% ↑
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑
New lesion	None	None	None	Present
Corticosteroids	None	Stable or ↓	Stable or ↓	Not applicable*
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓
Requirements for response	All	All	All	Any

*increase in steroids alone does not qualify for PD

7.1.2 Overall Survival

Overall Survival (OS): OS is defined as the number of days from date of randomization to the date of death due to any cause. If a patient has not died, the data will be censored at the last date documented to be alive.

7.1.3 Progression Free Survival

Progression Free Survival (PFS): PFS is defined as the number of days from date of randomization to the date of earliest disease progression based on Response Assessment in Neuro Oncology (RANO) criteria (as determined by the Investigator) or to the date of death due to any cause, if disease progression does not occur. Patients for whom neither death nor progression have been documented will be censored on the date of the last radiological assessment that the patient was progression-free. If a patient with no post-baseline radiological assessment then the data will be censored at the date of randomization. Patients with two or more missing response assessments prior to a visit with documented disease progression (or death) will be censored at the last visit where the patient was documented to be progression free. Patients who received new anti-cancer therapy or cancer-related surgery prior to progression or death will not be censored at the last assessment where the patient was documented as progression free prior to the new anti-cancer therapy or cancer-related surgery. Detailed censoring rules will be documented in the SAP.

7.1.4 Overall Response

The overall response is evaluated at each assessment of the disease according to RANO criteria.

7.1.4.1 Best overall response

Best overall response is the best response designation recorded from the date of randomization until disease progression.

7.1.4.2 Objective/complete response

Objective/complete response includes best overall responses CR and PR/ CR only. All responses must be confirmed by repeat MRI 4 weeks later.

7.1.4.3 Response duration

For responders, duration of objective response (CR/PR) and complete response (CR) will be measured similarly to PFS (see section 7.1.3) but starting from the time measurement criteria for CR/PR or CR (whichever is recorded first) is met

7.1.5 Mini Mental State Examination

The Mini Mental State Examination (MMSE): is a brief, standardized tool to grade patients' neurocognitive function. It is an 11-question measure that tests five areas of neurocognitive function: orientation, registration, attention and calculation, recall, and language. The maximum score is 30 which corresponds to the best neurocognitive function. Following Brown *et al.* (Ref. 6), the patient's neurocognitive function will be considered 'impaired' if the MMSE score is 26 or less and 'normal' if it is 27 or more. Since its creation in 1975 by Folstein *et al.* (Ref. 14), the MMSE has been validated and extensively used in both clinical practice and research. Following Tangalos *et al.* (Ref. 45) and as previously used by Brown *et al.*, a decline of more than 3 points in the MMSE score will be considered to represent clinically significant deterioration. See Appendix I. In this study, MMSE will be collected up to progression.

7.2 Evaluation of safety

7.2.1 Adverse events

All adverse events will be recorded; the investigator will assess whether those events are treatment-related (reasonable possibility, no reasonable possibility) and this assessment will be recorded in the database for all adverse events. A change in grading will be collected by giving an outcome date to the initial AE. A new adverse event needs to be reported to reflect the change in severity.

The collection period will start at baseline i.e. as from 2 weeks before randomization.

All adverse events will be followed until resolution while the patient remains on study treatment. When the patient discontinues study treatment, suspected adverse reactions (AEs for which there is a reasonable possibility that the treatment caused the AE) that started while on study treatment should be followed for 30 days from the date of the last dose of study treatment or until considered chronic/ stable (as judged by the Investigator), whichever comes first.

New SAEs and serious suspected adverse reactions that occur during the 30-day period from the date of the last dose of study treatment administered should be reported and followed until resolved or considered stable / chronic (as judged by the Investigator).

7.2.2 General evaluation of adverse events

This study will use the International Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, for adverse event reporting. A copy of the CTCAE can be accessed from the EORTC home page https://www.eortc.be/services/doc/ctc/.

Hematological and biochemistry adverse events will be assessed on the basis of at least monthly *blood counts*.

The highest CTCAE grading per cycle and per patient will be computed at the EORTC HQ for analysis.

Planned safety analysis and tabulations are described in the statistics section.

7.2.3 Serious adverse events

Serious adverse events are defined by the Good Clinical Practice Guideline.

Serious adverse events should be immediately reported according to the procedure detailed in this protocol (see chapter 16 on Reporting Serious Adverse Events)

7.2.4 Toxic deaths

Toxic death is defined as death due to toxicity (defined as adverse events that are not confirmed as unrelated). The cause of death must be reported as "toxicity".

The evaluation of toxic deaths is independent of the evaluation of response (patients can die from toxicity after a complete assessment of the response to therapy).

7.2.5 Evaluability for safety

All patients who have started study treatment will be included in overall safety analyses.

For hematological events, the medical review team may decide that blood counts have not been performed and/or reported according to the protocol and are therefore inadequate for the evaluation of one/several hematological parameters in some patients.

Patients who have discontinued treatment because of toxicity will always be included in the safety analyses.

7.3 Evaluation of MGMT status

Evaluation of MGMT is an integral part of the study design. MGMT status is divided into unmethylated (uMGMT) and methylated (mMGMT). Details of the evaluation can be found in chapter 11.

7.4 Evaluation of frailty using the G8 geriatric screening tool

7.4.1 Background

Older cancer patients have a much more heterogeneous general health status compared to young cancer patients. Some older patients are in perfect general health, while others are vulnerable or frail. Frailty is a well-known concept in geriatric medicine (Ref. 9). It is defined as a multi-factorial syndrome, resulting in a reduction of the physiological reserve and of the capability to resist stressful events (homeostatic capacity). Frailty is associated with an increased risk of unfavorable clinical events: disability, hospitalization, institutionalization, death. In oncology, the construct of frailty is as well used to describe patients with increased risk of treatment-associated morbidity and mortality. Presence of frailty can be detected by a so-called (Comprehensive) Geriatric Assessment (GA). Performance of GA is advised in older cancer patients by the International Society of Geriatric Oncology, SIOG (Ref. 55). GA is time consuming (takes about 30 minutes). Therefore, short geriatric screening tools such as the G8 have been developed as a short and easy to use measurement of general health status. The G8 score has been specifically developed in oncology, includes 8 items, takes a few minutes to complete, and can be completed by any health care worker (Ref. 2). The score ranges from 1 to 17. A score greater than 14 indicates that there is little risk that further GA reveals significant problems in the further assessed GA domains. The G8 was shown to strongly predict functional decline and overall survival (Ref. 26). G8 is by far the best studied geriatric screening tool in oncological patients, and also has better performance for detection of geriatric problems than other geriatric screening tools such as VES-13 (Ref. 11).

7.4.2 Assessments

G8 will be measured in all patients aged 70 years and above at baseline. G8 has to be completed by the clinician, the nurse or the trained coder. This screening tool includes 7 items of the Mini Nutritional Assessment and the age of the patient. The English version of G8 is included as a protocol appendix.

7.4.3 Objective

The inclusion of the G8 screening tool in EORTC trials will allow a uniform, easy and established approach of frailty at baseline. The G8 tool itself has been developed as a screening tool, and not a tool for follow-up.

The treating physician may decide which actions are needed based on the G8 result (e.g. further geriatric assessment in case of a G8 score of less or equal to 14; geriatric interventions if specific problems are detected within specific geriatric domains).

The assessment of frailty as defined by G8 in all patients aged 70 years and above entered in EORTC trials will allow interpretation of whether new treatment strategies have been tested in both fit and less fit patients which has importance for the generalizability of the study results.

8 Statistical considerations

8.1 Statistical design

8.1.1 Sample size

For this study, we assumed that in the whole trial population the standard treatment plus marizomib presents with a superior OS efficacy compared to the standard treatment alone estimated by a hazard ratio (HR) equal to 0.74 (26% reduction of the hazard of death). This corresponds to a median OS of 16 months in the standard treatment alone compared to 21.6 months for standard treatment plus marizomib (Ref. 8; Ref. 17). We also assume that at the time of final analysis, the MGMT methylation status will be distributed 60% unmethylated, 30% methylated and 10% undetermined. We also hypothesized that the marizomib effect would be mainly present in the unmethylated MGMT subgroup where it would display a HR=0.70 (median OS of 13 months in the control arm and compared to 18.6 months for marizomib). The effect in the methylated MGMT subgroup would be HR>0.80 and in the undetermined cases which are assumed to be a balanced mixture of unmethylated and methylated MGMT cases the effect would be in the line with the overall population, i.e. HR=0.74.

Based on the network of institution, it should be possible to recruit 400 patients/year (150 patients in the first year, and then 400 patients per year).

For the primary endpoint OS, the formal statistical testing is based on comparisons between two treatment groups in both ITT population and unmethylated subgroup. We will use a graphical method (Ref. 5) to control overall Type 1 error at one-sided 2.5%. We have to recruit 750 patients to show the OS difference with 86% power (taking into account the interim analysis for futility) and overall one-sided 1.5% significance in the whole population and with 80.7% power and one sided 1% significance in the unmethylated MGMT subgroup (uMGMT). We will recruit these patients in about 30 months and will follow them up for about 19 months, the time necessary to observe the required 488 deaths (320 in uMGMT). We will perform the test in the ITT population and in the uMGMT subgroup simultaneously. If one of them is significant, we will attribute the assigned alpha to the other. At the final analysis, we will provide treatment effect estimates in the uMGMT and in the methylated MGMT (mMGMT) subgroups.

In order to avoid exposing too many patients to a possibly ineffective and/or toxic treatment, a non-binding futility analysis will be conducted on the whole population when about 88 deaths occur (18% information time). The interim analysis will be evaluated by an Independent Data Monitoring Committee (IDMC). The IDMC will recommend continuing the study or stopping the study for futility. If the observed hazard ratio (HR) is >1.12, the study may be considered to be futile.

We will analyze other endpoints at exploratory two-sided 5% significance.

8.1.2 Randomization and stratifications

Patients will be centrally randomized (for practical details, see section on registration / randomization procedure). A minimization technique will be used for random treatment allocation. Pocock & Simon, 1975; Freedman & White, 1976). The minimization algorithm will be detailed in the SAP.

Stratification factors are:

- Institution,
- Age (≤55, >55 years),

- Karnofsky performance status (70/80, 90/100),
- Extent of surgery (partial/biopsy, gross total).

8.2 Statistical analysis plan

8.2.1 Analysis populations

- Intention-to-treat population (ITT): All randomized patients will be analyzed in the arm they were allocated by randomization.
- Per protocol population (PP): All randomized patients who are eligible and have started their randomized treatment arm. Patients with major protocol deviations as defined in the medical review plan are also excluded from the PP population.
- Safety population (SP): All randomized patients who have started any treatment arm i.e. if a patient received treatment arm other than the patient's randomized treatment arm, then the patient will be assigned to the treatment arm that the patient actually received during the study in the analysis.
- Patients who did not start any treatment arm are excluded from PP and SP.
- Patients excluded from PP or SP will be reported in separate tables with the reason(s) of exclusion.
- Subgroups: The following subgroups will be defined: MGMT methylation status (uMGMT, mMGMT, unknown/missing), age (≤55, >55 years), gender (male, female), Karnofsky performance status (70/80, 90/100), baseline steroid use (yes, no), extent of surgery (partial/biopsy, gross total).

A patient will be considered to be eligible if he/she did not have any deviation from the patient entry criteria listed in chapter 3 of the protocol. Potential eligibility problems will be assessed by the Clinical Research Physician at time of medical review.

8.2.2 Primary and secondary endpoints

8.2.2.1 Primary endpoints

The primary endpoint is OS.

8.2.2.2 Secondary endpoints

Secondary endpoints are:

PFS based on investigator assessment according to RANO 2010 criteria (Ref. 53).

ORR based on investigator assessment

CR/PR rate based on investigator assessment

DoR based on investigator assessment

Quality of Life according to the methodology described in chapter 10.

Mini Mental State Examination (MMSE).

Incidence of Adverse Event (AEs) in MedDRA terms graded according to NCI CTCAE Version 5.0; Laboratory results as measured by CTCAEs Version 5.0 criteria.

8.2.2.3 Exploratory endpoints

Activity of the proteasome in the tumor tissue prior to treatment start and correlation with patient's outcome to assess prognostic and/or predictive value.

8.2.3 Statistical methods

8.2.3.1 Efficacy analyses

We will conduct all primary efficacy analyses in the intent-to-treat population.

In the primary analyses, differences between the treatment groups in OS will be assessed by a stratified LogRank test adjusted for the stratification factors assessed at randomization (except institution), testing the null hypothesis (H0):

- H0: $HR_{MRZ\ arm/control} = 1$

Versus the alternative hypothesis (H1)

- H1: $HR_{MRZ\ arm/control} < 1$

We consider this test as confirmatory and will perform it at a 1-sided significance level α=0.015 in the ITT population and α=0.01 in the uMGMT subgroup. If one of them is significant, the assigned alpha will be transferred to the other and the overall Type 1 error will be controlled at one-sided 2.5% by graphical method.

Kaplan-Meier survival curves (product-limit estimates) will be presented by treatment group, in the ITT population and by MGMT subgroup, together with a summary of associated statistics (median survival time, 6-, 12-, 18-, 24-month OS rate estimates and estimates for every 6 months thereafter as applicable) including the corresponding two-sided 95% confidence intervals (calculated by Greenwood formula's estimation of the standard deviation for rates and by Brookmeyer and Crowley technique for the median).

The hazard ratio (HR) (including two sided 97% and 95 % confidence interval in the ITT population and two sided 98% and 95 % confidence interval in the uMGMT subgroup) of the Marizomib group over the control group will be calculated by Cox's proportional hazards model stratified by the stratification factors assessed at randomization (except institution).

The primary analysis will take place after 488 deaths (320 uMGMT) deaths have occurred.

A re-randomization-test analysis will be performed to support the primary analysis in the ITT population and in uMGMT.

The re-randomization test will be performed as follows:

- The procedure will use 50,000 replications.
- Based on the value of their randomization stratification factors, for each replicate, subjects will be (virtually) re-assigned to treatments using the Medidata BALANCE minimization randomization algorithm in the order in which they were randomized into the trial.
- For each replicate the stratified log-rank test statistic adjusted by randomization stratification factors comparing the duration of overall survival will be computed.
- The re-randomization test p-values will be the fraction of replications where the log-rank p-values from the replicates are less than or equal to the corresponding p-values from the original analysis.

Robustness of the results will be established if the re-randomization test p-values are then found to be comparable to the corresponding p-values from the original analysis.

Secondary analyses of efficacy are supportive and will be analyzed in a non-confirmatory sense. Therefore no adjustments for multiplicity will be done. The following analyses will be performed:

The stratified LogRank test will be applied on the PFS time to test for differences between the 2 treatment groups. The Cox's proportional hazards model stratified by the stratification factors assessed at randomization (except

institution) will provide the hazard ratio (including 95 % confidence interval). Summary of associated statistics for each treatment arm (median PFS time, 6-, 12-, 18-, 24-month PFS rate estimates and estimates for every 6 months thereafter as applicable) will be displayed with 95 % confidence interval computed using the same methods as for OS, and the Kaplan-Meier curve for PFS will be presented.

For PFS and OS, Kaplan-Meier estimates will be calculated and unstratified Cox's proportional hazards model will be fit for each subgroup as defined in Section 8.2.1, in the ITT population only. Forest Plot will be displayed with a subgroup by treatment interaction test.

The best overall response will be presented in contingency table with frequencies and percentages. The objective response (ORR: CR/PR) and complete response rates will be reported with exact (binomial) two-sided 95% CI. The medians of objective (PR/CR) and complete (CR) response duration will be estimated from the Kaplan-Meier curves. The Brookmeyer and Crowley technique will provide two-sided 95% CI.

The evolution of MMSE over time will be interpreted taking into account the attrition as a result of patients assessed only until progression. All MMSE results will thus be conditional on the patients being otherwise free of progression. The distribution of the MMSE at each time point of evaluation will be described on the two treatment arms separately using means and their associated standard error (a graphical display will be considered). Median and range will also be provided. The proportion of patients with 'normal' and 'impaired' MMSE score at baseline and at key timepoints of evaluation (e.g. Baseline, at end of radiation therapy and then every 16 weeks, see table 6.4) will also be displayed. Longitudinal analysis might also be performed and detailed in the SAP.

All secondary analyses will be performed at 2-sided significance level α=0.05 for exploratory purpose.

8.2.3.2 Safety analysis

All analyses will be performed in the safety population:

The safety and tolerability will be followed from study treatment initiation through up to 30 days after the last administration of study treatment.

The safety analyses will be reported for the whole study time and by treatment period as defined below:

The chemoradiation period (TMZ/RT or TMZ/RT+MRZ) will start on the day of the first administration of radiation therapy and end 27 days after the day of the last administration of radiation therapy.

The adjuvant TMZ period (adjuvant TMZ +/- MRZ) will start on the day of the first dose of adjuvant TMZ and end-up 27 days after the first day of administration of the last cycle of adjuvant TMZ.

The maintenance marizomib period (MRZ) will start 28 days after the first day of administration of the last cycle of adjuvant TMZ and end-up 27 days after the first day of administration of the last cycle of maintenance marizomib.

The follow-up period (FUP) will start 28 days after the first day of administration of the last cycle of maintenance marizomib up to 30 days after the last administration of marizomib

Baseline value will be defined as the last value on or before the first dose of study treatment is administered; if multiple values are present for the same date, the average of these values will be used as the baseline. For patients who were not treated, the value on or prior to randomization date will be used. Baseline laboratory and AE grades will be presented together with other baseline data in the ITT population.

Hematological and biochemistry parameters

All laboratory values will be graded. The worst grade of each hematological and biochemistry parameter will be calculated for each patient. Frequencies and percentages of grade 1, 2, 3, 4 in each category will be tabulated. A column with pooled grade 3/4 frequencies and percentages will also be displayed.

In a separate table, the frequencies and percentages of patients with at least one grade (≥1) or one grade 3/4 hematological or biochemistry toxicity will be presented.

All adverse events (AE)

The worst grade of each AE item will be calculated for each patient. Tables with all grades, grades 3/4 and grade 5 frequencies and percentages will be displayed.

In a separate table, the frequencies and percentages of patients with at least one grade (≥1) or one grade 3/4 or one grade 5 AE of any event will be presented.

Related AEs

The worst grade of each likely related AE item will be calculated for each patient. Tables with all grades, grades 3/4 and grades 5 frequencies and percentages in each AE term will be displayed.

In a separate table, the frequencies and percentages of patients with at least one grade (≥1) or one grade 3/4 or one grade 5 related AE of any event will be presented.

SAEs and Related SAEs

After reconciliation with the SAEs listing extracted from the EORTC pharmacovigilance database, the worst grade of each (related) serious AE category will be calculated for each patient. Tables with all grades, grades 3/4 and grades 5 frequencies and percentages in each (related) SAE term will be displayed.

In a separate table, the frequencies and percentages of patients with at least one grade (≥1) or one grade 3/ 4 or one grade 5 (related) SAE of any event will be presented.

All deaths, as well as deaths within 30 days after last dose of study treatment, will be tabulated.

8.2.3.3 Pharmacokinetics analysis

Pharmacokinetics analysis will be detailed in the statistical analysis plan.

8.2.4 Pre-planned sensitivity or exploratory analyses

If the percentage of patients excluded from PP is superior to 10% in at least one treatment arm, all efficacy analyses will be repeated in the PP population.

For both PFS and OS, the stratified LogRank test and the Cox's proportional hazards model will also be computed stratified by the stratification factors assessed at randomization (except institution) and MGMT methylation status.

Other exploratory analyses may be performed on the basis of subgroups of patients (see section 8.2.1), but results of these exploratory analyses may not serve as a basis for drawing conclusions concerning protocol efficacy.

8.2.5 Prognostic factor analyses

Data of this trial will be included into the EORTC newly diagnosed GBM data warehouse for further pooled analyses of prognostic factors and exploration of other research questions.

8.2.6 Data recording and display

Frequency tables will be tabulated (by treatment group or otherwise) for all categorical variables by the levels of the variables as they appear on the CRF (with %). Categories with a text field specification will be tabulated as categories and then supplemented by a listing with the following information for the patients fulfilling the condition for the specification (patient id, institution, treatment group, value of the item and text field contents).

Dates relating to events prior to entry will be presented as the delay in days (or weeks, months, or years) between the past event and the date of entry (date of randomization – date of past event + 1) and presented using the median and range as well as mean and standard deviation. For example, on the randomization checklist, the date of last administration of prior treatment (or the date of first diagnosis of the cancer) will be presented as the time elapsed (in days, weeks, months or years, as appropriate) since the day of the last administration and the date of entry on study (date of randomization – last administration/diagnosis +1).

Other delays (e.g. re-treatment delays) are presented as continuous variables using the median and range as well as mean and standard deviation.

Continuous variables for which a coding system exists (such as for laboratory data) will be recoded into categories (for adverse events, the grading scale specified in the protocol will be used). Whenever no specific scale exists, lab data will be categorized based on the normal range: for example, below the lower normal limit (when appropriate), within the normal range, above the upper normal limit (ULN) and the degree to which it is above the ULN (for example > 2.5 x ULN, > 5 x ULN, > 10 x ULN). For laboratory data, the nadir is generally displayed. The nadir in a given cycle is the lowest laboratory value in that cycle; the overall nadir for a patient is the lowest laboratory value among all cycles.

Other continuous variables (for example age, dose …) are presented using the median range (minimum, maximum), mean and standard deviation.

If appropriate, continuous data may also be presented in categories (for example, age may also be grouped in decades).

8.3 Interim analyses

The IDMC will review safety and efficacy data for the study after the randomization of 100 patients with a minimum of 3 months of follow-up. The interim review is aimed to assess the study safety and is not designed to stop the study early for lack or outstanding efficacy. Nevertheless efficacy data will be reviewed by the IDMC to evaluate the risk/benefit profile of each treatment arm.

One non-binding futility interim analysis will be performed in the ITT population and reviewed by the IDMC when about 406 patients are recruited i.e. approximatively 20 months after start of accrual. At that time, 88 deaths (information fraction=18%) should already have been observed in the ITT population. The futility boundary is 1.12. It was chosen because the probability to stop for futility in absence of effect was about 30%. A percentage which was considered appropriate. If the observed HR is larger than (>) 1.12 than futility may be declared. The probability to stop for futility in case the targeted effect is true (HR=0.74) is only equal to 2.6%. We will not perform an interim analysis in the uMGMT subgroup. Nevertheless, the IDMC might recommend to continue the trial even if futility is demonstrated (HR>1.12) for the whole group but an effect in the uMGMT subgroup is suggested. By design, this decision will not have an impact on the power of the trial. Further to company's discussions with FDA the following change to the initial interim analysis plan was strongly suggested: “A small alpha penalty should be paid for the futility analysis, as it will entail a review of the efficacy data.” A small alpha penalty was therefore implemented although data was initially planned for futility purpose only.

A small alpha spending of 0.00001 will be allocated to this interim analysis. The primary efficacy endpoint (OS) will be tested at a nominal 1-sided alpha level of 0.01499 in the overall population on the ITT set and unchanged level of 0.01 in the uMGMT group as no interim analysis will be performed in this subgroup.

The alpha spending function used is of the Rho family. The Rho spending function was first published by Kim and DeMets (1987) and was generalized by Jennison and Turnbull (2000). It has following functional form: $\alpha(t) = \alpha t^{\rho}$, $\rho > 0$. When $\rho = 1$, the corresponding stopping boundaries resemble the Pocock stopping boundaries. When $\rho = 3$, the boundaries resemble the O’Brien-Fleming boundaries. Larger value of ρ yield increasingly conservative

boundaries. In this study, the small alpha spending of 0.00001 corresponds to rho = 4.26. The associated treatment effect boundary is HR=0.40. If a smaller HR would be observed the IDMC could decide to stop the trial for efficacy.

At the clinical cutoff date (28/04/2020) for the futility analysis presented at the IDMC meeting on 14/09/2020, 106 death events were observed out of 616 randomized patients (716 registered).

Although the trial results did not cross the pre-specified futility boundary the IDMC observed that there was as yet no evidence that this treatment provided a benefit in survival. The statistical data presented also suggested that it was extremely unlikely that a difference would emerge with additional patients or further follow-up. The IDMC observed that marizomib in this combination induced severe neurological and neuropsychiatric disorders, as well as other treatment-related grade 3-4 side effects, in a substantial proportion of the patients. These observed effects were within the known safety profile. As per the previous IDMC reviews for safety, the IDMC recommendations allowed the trial to continue under close follow up of the aforementioned side effects.

Based on the results of the Interim Analysis, the IDMC recommended, that the study be discontinued from further recruitment and that results be disclosed to the medical community as soon as possible. Patients still on treatment who are tolerating marizomib, may be allowed to continue if so wished by the patient and treating physician.

8.4 Follow-up analysis

Further to the recommendations of the IDMC, the patient recruitment had to be prematurely closed. The final number of randomized patients was 749 (750 planned). The results of this study had also to be prematurely disclosed. The interim analysis was considered as the final analysis of this study.

All randomized patients will be followed till the total number of OS events for the initially planned final analysis was observed (488 deaths). At that date, a follow-up analysis will be performed in accordance to the updated Statistical Analysis Plan for descriptive purpose only, with more mature data for all endpoints.

8.5 End of study

End of study occurs when all of the following criteria have been satisfied:

- 1. Thirty days after all patients have stopped protocol treatment
- 2. The trial is mature for the primary and follow-up analyses as defined in the protocol
- 3. The database has been fully cleaned and frozen for this analysis

EORTC reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (e.g., IRB/EC, regulatory authorities, etc.).

9 Trial Governance and Data Monitoring

9.1 Study committees

9.1.1 Study Management Group (SMG)

The Study Management Group is set up for this study. It consists of the EORTC Headquarters team in charge of running the study (clinical research physician, statistician, clinical scientist, clinical operations manager and data managers) and the principal study coordinator.

The EORTC Headquarter team is responsible for the day -to-day conduct of the trial. The Study Coordinator will assist the team in case of problems with patient evaluation (eligibility, treatment compliance, safety).

The Study management Group also performs the medical review as indicated below.

9.1.2 Study Steering committee (SSC)

The Study Steering Committee for this study is composed of the study coordinators, the representatives of Academic Groups collaborating to the study, at least one representative of the EORTC Headquarters (Study Clinical Research Physician or Clinical Scientist).

This committee provides the general oversight of the study and has the executive power. The SSC monitors study progress and conduct and advises on its scientific credibility. The SSC will consider and act, as appropriate, upon the recommendations of the independent data monitoring committee.

9.1.3 Independent data monitoring committee (IDMC)

The independent data monitoring committee for EORTC studies (IDMC) is in charge of the independent oversight of this study. The composition of the IDMC is described in EORTC Policy "Independent Data Monitoring Committees for EORTC studies" (ref. EORTC POL004) and its functioning is ruled by the charter annexed to the Policy.

The study-specific experts on the IDMC performing this review will be selected for their relevant expertise with the disease and/or treatments assessed in the study.

The IDMC reports its recommendations in writing to the Study Management Group through the clinical operations manager to the Study Steering Committee and other relevant parties (supporting bodies, collaborative groups…).

9.2 Data Monitoring

9.2.1 Monitoring during medical review meetings

The medical review will be performed on a regular basis by the clinical research physician assisted as needed by the study management group. The main study coordinator will, in particular, support the Study Clinical Research Physician during the medical review process and will assist the team in case of problems with patient evaluation (safety, eligibility, treatment compliance). The main study coordinator is also responsible for the review and approval of the medical review plan and medical review reports.

For blinded trials, the medical review is conducted blinded to treatment allocation.

If at any time during the course of the study, the medical review identifies safety signals or other elements that could affect the potential risks and benefits to the study participants. These will be reported to the Study Steering Committee and may trigger a review by the EORTC Independent Data Monitoring Committee (IDMC).

9.2.2 Monitoring by the IDMC

The IDMC will be asked to give advice on whether the accumulating data from the trial justifies continuing recruitment of further patients or further follow-up.

The IDMC will review the trial whenever safety problems or other elements are identified during the medical review or by the SMG and/or SSC that could affect the potential risks and benefits for study participants.

The IDMC will also review the intermediate reports of accumulating data according to the study interim monitoring plan described in the statistical section of this protocol (see section 8.3). If a decision is made to continue without change, the IDMC may advise on the frequency of future reviews of the data on the basis of accrual and event rates.

While the trial is ongoing the accumulating data will generally remain confidential, unless the SSC and IDMC agree that the data should be made public.

10 Quality of life assessment

10.1 Rationale

Health related quality of life (HRQoL) is a multidimensional construct, which can be defined as a state of general well-being reflecting physical, psychological, and social well-being and the impact of the disease and/or treatment related symptoms on daily-life functioning. The patient's subjective perspective is an inherent component of HRQoL and is therefore best assessed via self-administration.

Reducing mortality and morbidity is still the most important factor in cancer clinical research. Nevertheless, issues such as reducing side effects, symptom relief and improving patients' satisfaction have also become relevant parameters in the evaluation of medical strategies. Cancer treatments may produce adverse effects and diminish a patient's quality of life even when survival is extended. Progress in the acceptance of new cancer therapies is sometimes critically dependent on their HRQoL consequences.

Particularly in GBM patients, who suffer from an incurable disease with a median overall survival of slightly more than a year despite intensive treatment, the balance between quantity and quality of survival gain due to (experimental) treatment is pivotal. If treatment-related side effects influence the QOL of these patients in a negative way, possible gains in terms of progression-free or overall survival will have to be balanced against the burden of treatment. It is for this reason that QOL is included as a secondary endpoint in the current study of newly-diagnosed GBM patients.

10.2 Objective

The main objective of QOL assessment within this trial is to determine the impact of addition of marizomib to temozolomide and radiation therapy on five chosen domains being primarily global QOL, with fatigue, physical function, neurocognitive function, communication and motor dysfunction as secondary QOL outcomes. It is expected that these are likely to be most affected in patients, based on the toxicity profiles and information of previous studies.

The Ho hypothesis will be tested that there is no difference between patients in both arms during and after treatment regarding global QOL. A secondary objective is to evaluate the effect of the treatment on the remaining symptoms and functioning scales as treatment-related side effects may have a (temporary) negative influence on the health-related domains of QOL of these patients.

10.3 HRQoL instrument

Quality of life will be assessed with the EORTC Quality of Life Questionnaire (QLQ-C30) version 3. This instrument is composed of multi-item and single-item scales. These include five functional scales (physical, role, emotional, social, and neurocognitive), three symptom (fatigue, nausea and vomiting and pain) and a global health status/QoL scale and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). All scales and single items meet the standards for reliability. The reliability and validity of the questionnaire is highly consistent across different language-cultural groups (Ref. 1). The average time to complete the questionnaire is approximately 10 minutes.

While this standard is used in EORTC studies, it lacks some dimensions that pertain to the QL issues in certain brain cancer. Therefore, we will also use the EORTC Brain Cancer module (QLQ-BN20), designed for use in brain tumor patients undergoing protocol treatment or radiotherapy. It includes 20 items assessing visual disorders, motor dysfunction, communication deficit, future uncertainty, as well as other specific symptoms, such as headaches, seizures or drowsiness. A retrospective validation study has been performed confirming the psychometric validity of this questionnaire.

10.4 Study design

Patients are eligible for the QOL assessment in this study if they fulfill the eligibility criteria (see chapter 3). Should the patient refuse to fill out the form, then this should exclude the patient from further participation in the study. Patients will be informed in the patient informed consent form that they will have their QOL assessed regularly while involved in this trial. In this phase 3 study, OOL will be evaluated in a longitudinal design in all patients entered in both arms of the study.

The QOL questionnaires must be filled out at the hospital when patients come for a scheduled visit according to the EORTC "Guidelines for administration of questionnaires" (see Appendix F). The pre-treatment questionnaires must be filled within 2 weeks before start of treatment. Subsequent questionnaires are administered after the end of combined chemo- and radiotherapy, and subsequently coinciding with the MRI visits and MMSE schedule in both treatment arms, also after tumor progression.

Master copies of the QOL questionnaires will be sent to the participating institutions. The clinical report forms will include a question whether the QOL forms have been filled in, and if not, the reason why. The questionnaire will be handed out to the patients by the investigator or a study nurse prior to seeing the doctor for clinical evaluations. The patient should complete the questionnaires by her/himself in her/his own language during the visit as completely and accurately as possible. It is recommended that a key person (e.g. research nurse) at each center should be responsible for questionnaire data collection in order to optimize the compliance of the patient and to ensure the completeness of the data.

10.4.1 HRQoL schedule

The time windows for eligible HRQoL assessments will be as follows:

Assessment	Time window
Baseline	No earlier than 14 days before randomization and no later than the day of randomization itself.
At the end of radiation therapy	No earlier than day of last radiation therapy treatment and no later than the first day of TMZ maintenance administration
During TMZ maintenance: every 16 weeks	Every 16 weeks during TMZ maintenance ± 7 days (at MRI scan visit).
After TMZ maintenance: every 16 weeks until death	Every 16 weeks ± 7 days. (at MRI scan visit)

10.5 Statistical considerations

The primary QOL endpoint that is considered relevant for this study is the Global health/QOL status scale of the QLQ-C30 instrument. The secondary QOL endpoints will be the fatigue, physical function, neurocognitive function, communication and motor dysfunction scales. Other scales will be analyzed on an exploratory basis. The "financial difficulties" scale of the QLQ-C30 will not be analyzed at all.

The sample size calculation has been performed based on overall survival data. This is the primary endpoint and therefore no calculation has been performed based on changes in QOL. The primary QOL endpoints that are considered relevant to this trial are detailed above. The QOL data will give information to support or reject the null hypothesis that there is no difference between patients in both arms during and after treatment.

Data will be scored according to the algorithm described in the EORTC scoring manual (Ref. 13). All scales and single items are scored on categorical scales and linearly converted to 0-100 scales. Reporting of data will be mainly descriptive, as this is an exploratory analysis.

10.5.1 Primary analysis

The following statistical tests will be done corresponding to the objective listed in section 10.2.

The following two summary scores will be calculated per subject for each selected scale:

- the average change during treatment (AC-DT) = the average of all post-baseline scale scores up to and including the end-of-treatment visit (section 6.3.1) minus the score at baseline. Only scores from valid HRQOL forms will be included.
- the average change after treatment (AC-AT): = the average of all post-baseline scale scores during follow-up (i.e. after the end-of-treatment visit (section 6.3.1)) minus the score at baseline. Only scores from valid HRQOL forms will be included.

Description of the AC-DT and AC-AT will be presented (mean, standard deviation, median, first and third quartiles, minimum, maximum) by treatment group together with mean difference, 95% CI and the non-parametric test p-value (Wilcoxon).

10.5.2 Sensitivity analysis

The primary analysis will be repeated in the per protocol population.

The primary analysis will also be repeated taking all received HRQoL forms into account (i.e. including invalid/unassigned forms).

In addition, two new summary statistics will be created:

- Deterioration during treatment (D10-DT) = A binary variable indicating whether the patient experienced a 10 point decrease from baseline at any post-baseline visit up to and including the end of study treatment visit.
- Deterioration after treatment (D10-AT) = A binary variable indicating whether the patient experienced a 10 point decrease from baseline at any follow-up visit (i.e. after the end of study treatment visit).

Description of the D10-DT and D10-AT will be presented (mean, standard deviation, median, first and third quartiles, minimum, maximum) by treatment group together with mean difference, 95% CI and the non-parametric test p-value (Wilcoxon) to supplement the main analysis.

10.5.3 Missing data

Missing data is a potential major source of bias in HRQoL assessment.

In order to check the potential impact in the study, the compliance mechanism will be investigated prior to initiating the HRQoL analysis. Characteristics of patients with and without valid HRQoL data will be compared and trends over time per dropout pattern will be investigated. Model building will be used in order to investigate whether the compliance mechanism is linked to selected prognostic variables.

Once the main analysis is completed, sensitivity analyses will be undertaken to verify the robustness of the results vis-à-vis the missing data.

In case overall compliance is deemed too low (<50%), only an exploratory analysis will be performed in lieu of the main analysis.

11 Translational research

11.1 Objective and projects description

Marizomib is a pan-proteasome inhibitor described in Section 1.1. Prior evidence is showing a trend regarding Marizomib therapeutic efficacy and baseline proteasomal activity in tumor cells (see section 1.1). Therefore, in this study, we plan to investigate the proteasomal activity in patients with sufficient amount of tissue available for these analyses. We have 2 objectives: firstly, we would like to confirm baseline proteasome activity and clinical response (PFS and OS), and secondly, we want to see if the proteasome activity is modulated by Marizomib in patients with tissue at baseline and at salvage surgery.

To perform proteasome activity measurement, frozen tumor tissue, at study entry and after salvage surgery should it occur, will be collected. Moreover, proteasomal activity will also be measured in the collected buffy coat and PBMC samples. The assessment of the proteasomal activity will be done by Eurofins (Breda, The Netherlands).

Proteasomal activity will be calculated based on the catalytic activity of the proteasome's three subunits and will be determined using a spectrofluorometric assay at a laboratory specified at a later date. However, at this stage, the exact substrates and precise mechanisms that govern marizomib activity in human tumors is not fully understood. So we plan to collect sufficient samples to facilitate exploratory research as our understanding improves. These analyses are of exploratory nature. Since the number of samples that are available for analysis cannot be predicted exactly, no statistics are provided.

Extracellular vesicles will be isolated from EDTA blood and stored at IBBL (Luxembourg, LU) for biomarker discovery.

FFPE Tumor tissue will be prospectively collected at IBBL (Integrated BioBank Luxembourg, LU) and send to HistoGeneX (Antwerp, BE) for central testing of the MGMT status. Since MGMT status will be used in the primary OS analysis to determine if there is a difference in treatment effect which is dependent on this variable, this initial tumor tissue is a MANDATORY requirement within this protocol. Subsequently, tissue samples will be stored at an EORTC central biobank (IBBL, Luxembourg; Rotterdam, NL or Zurich, CH). To allow for comprehensive immunohistochemical assessments of tumor tissue specimens, tissue microarrays (TMA) will be generated.

Future research might include isolation of ctDNA and gDNA from plasma. Depending on the study results, we may look for soluble factors in the serum which may be of interest as potential biomarkers. There is some preliminary data to suggest that these methods could give insights into the perturbations taking part at the tumor site without need for serial tissue examination (which is almost impossible in CNS tumors in routine practice). The ultimate goal of such work would be to define a tumor specific signature in the peripheral blood which could be used to monitor and predict response to therapy.

Exploratory research on tumor tissue or blood may also include evaluation of a multigene or DNA-methylation signature to predict benefit from marizomib. We may also investigate other molecular pathways related to the development of these specific tumors from a biological point of view; such pathways include, but are not limited to, tumor cell proliferation, growth, invasion and metastasis, metabolism, angiogenesis, apoptosis, immune response, inflammation, and genomic instability. Multiple molecular and cellular techniques might be used to assess those exploratory biomarkers and will be performed by expert laboratories.

MGMT testing facility:

HistoGeneX N.V.
Sample Reception Team
Sint-Bavostraat 78-80
2610 Wilrijk

Belgium
Email: info@histogenex.com
Phone: +32 3 50 20 500

Storage facility FFPE tissue:

EORTC Brain Tumor Group Tissue Repository
Erasmus MC Hospital
Erasmus MC Josephine Nefkens Institute - Dept of Pathology
Doctor Molewaterplein 50-60,
3000DR Rotterdam,
The Netherlands
Email: j.m.kros@erasmusmc.nl
Phone: +31 104087905

Storage facility blood derivates: Integrated BioBank of Luxembourg (IBBL) Biorepository, Floor 1

1, Rue Louis Rech, entrée B
L-3555 Dudelange
Luxembourg
Email: eortc@ibbl.lu
Phone + 352 26 970 520

Proteasome assessment facility

Eurofins Central Laboratory, B.V.
Bergschot 71
4817 PA
Breda
The Netherlands
Email: MarjoleinKuypers@eurofins.com
Phone: +31 (0)76 573 73 63

11.2 Sample Collection

For more details in collection and shipment of samples, refer to the HBM guidelines, provided as a separate document.

11.2.1 Tumor samples

FFPE samples are mandatory for this study. If the patient consents to the TR and frozen tissue is available, collection will take place at baseline and at salvage surgery.

11.2.2 Blood samples

Plasma and serum samples will be collected at study entry, after completion of radiotherapy and every 3 cycles until progression. Samples will also be collected at the time of tumor progression. All samples will be collected and processed as described in the HBM guidelines and stored centrally at IBBL Luxembourg for future research.

PBMC and extracellular vesicles will also be collected as described in the HBM guidelines.

All blood derivatives will be centrally collected and stored at IBBL Luxembourg. The collected buffy coat and PBMC samples will be shipped to Eurofins (Breda, NL) for the assessment of the proteasome activity.

11.2.3 Sample overview

Specimen type(s)	Specimen amount	Collection time point(s)
Mandatory		
Tumor tissue	1 paraffin block or 24 unstained slides minimum	Study entry
Plasma and buffy coat	10mL + buffy coat	Study entry After completion of RT Every 3 cycles At progression
Serum	10mL	Study entry After completion of RT Every 3 cycles At progression
Optional		
Fresh frozen	1 cc	Study entry After salvage surgery should it occur
plasma samples (vesicles)	10 mL	Study entry After completion of RT Every 3 cycles At progression
PBMCs	20 mL	Study entry After completion of RT Every 3 cycles At progression

From the central biobank, HBM and relevant data may be transferred to other research laboratories performing molecular analyses or involved in downstream projects, including the incidence of certain molecular markers in a given patient population or biomarker discovery. All leftover material remaining after the pre-defined translational studies are performed, must always be returned to IBBL or another EORTC central biobank.

HBM and relevant data can be further used by EORTC alone, in collaboration with other partners or transferred to other researchers, including commercial partners, possibly outside of Europe.

11.3 Data storage, transfer and development of analysis plans

The translational projects will be the result of the work of collaborating institutions and EORTC HQ. No hypothesis was provided for any project therefore no statistical design or power calculations could be performed. The translational projects will be exploratory and descriptive. Project set-up, bio-informatics and statistical analysis plan will be jointly developed for each project. These documents will be reviewed and approved by EORTC trial statistician, TR scientist, and bioinformatics expert before starting any analysis. They will specify analytical and methodological details. Clinical and patient-reported outcome data will be stored in the EORTC clinical database and genomic data will be stored at the European Genomic Archive (EGA). Transfer of data will be performed according to applicable policies (e.g. EORTC POL008) or according to jointly approved data transfer charters.

11.4 General principles for human biological material (HBM) collection

Human biological material (HBM) collection involves the collection and storage of biological material, residual biological material or derivatives in compliance with ethical and technical requirements.

Biobanking refers to the chain of procedures that encompass the life cycle of the biological material, e.g. from collection, shipping to long term storage and use, and may also be subject to local regulation and/or national/international legislation.

In this study, biological material will be centralized and stored at EORTC Brain Tumor Group Tissue Repository at Erasmus MC Hospital, Rotterdam, The Netherlands (FFPE tissue) and Integrated BioBank Luxembourg, Luxembourg (blood derivates). From there, the biological material will be used or distributed to the other research laboratories involved in the translational research (TR) projects specified in this protocol or defined in the future.

The following principles apply to storage of HBM:

- The biobank will have a designated manager responsible for collection and will act as a communication point with the EORTC.
- The collected HBM should be documented, i.e. the amount remaining and its location.
- The Study Steering Committee (SSC)/Group committee will be responsible for all TR project review and prioritization, including the consideration of newly proposed TR projects not specified in the protocol. In the absence of a SSC, responsibilities of the SSC are transferred to the Group and/ or EORTC HQ as applicable.
- Final decisions on the use of HBM will be determined by a majority vote of *the* SSC/Group committee. Additional expertise may be sought through advisory non-SSC/Group committee members.

Access to HBM (see EORTC Biobanking Policy POL020): HBM may be used for another purpose for which it was originally collected, subject to meeting ethical principles/and is covered by informed consent/ethics approval. In the case of secondary use of HBM, (i.e. for new TR projects that are not specified in the clinical study protocol and that were not foreseen at the time of protocol writing) interested parties may apply for the use of HBM and will follow the next steps:

- A short description of the new TR projects will be written and submitted to EORTC HQ for coordination with the appropriate SSC/Group committee.
- The SSC/Group committee will prioritize the TR projects. Access procedures defined by the SSC/Group committee will build on the following key points:
    - Project prioritization
        - should be strongly based on scientific merit,
        - should consider the contribution of the different investigators to the trial and TR project,

- will take into consideration if the applicant is an EORTC member or not (whilst maintaining the principle of access to the wider scientific community and commitments owed to study participants and ethical committees).

- Protection of confidentiality must be respected.

- An EORTC HQ feasibility check, including recommendations for regulatory and ethical matters and other restrictions on the use of the HBM, will take place. If in the event the HBM collections are still retained at individual clinical sites, the TR project leader and the involved EORTC Group are responsible for collecting and providing information on availability of HBM for the feasibility assessment.
- Prioritized TR projects will then be reviewed by the Translational Research Advisory Committee (TRAC).
- Once SSC/Group committee prioritization, the EORTC HQ feasibility assessment, and TRAC review are complete and when all applicable competent Ethics Committees approvals are in place and ethical principles are met, the TR project can be activated and HBM release and analysis can commence.
- The EORTC Board will mediate any disagreements of opinion between TRAC, the EORTC HQ feasibility assessment, the SSC/Group committee and the TR project leader(s), as needed.

11.5 Ancillary Radiotherapy related research projects

11.5.1 Artificial Intelligence for Automated QUality Assurance in RadioTherapy for glioblastoma target volume and organs at risk delineation - AQUA RT

11.5.1.1 Background

This trial has mandatory RTQA procedures that include the collection and central review of all patients' radiotherapy treatment plans, the individual case review (ICR) (as in Section 17.4.1). This peer review process requires considerable effort by physicians and physicists and entails considerable costs. Parts of the process could be automated or semi-automated, making it easier and cheaper to run trials with radiotherapy as part of the treatment. This ancillary project stems from these observations. The project name is "Artificial Intelligence for Automated QUality Assurance in RadioTherapy for glioblastoma target volume and organs at risk delineation - AQUA RT".

11.5.1.2 Description of the project

The aim of the project is to use autosegmentation algorithms to create alternative segmentations for tumor volume and organs at risk, and to use these segmentations as a surrogate for peer review in evaluating protocol compliance of the contours submitted by investigators. The final goal is to validate an automated peer review procedure for future use in clinical trials.

11.5.1.3 Data needed

The treatment plans submitted and reviewed as part of the RTQA procedures, as well as the review results themselves, will be used in the research project. This includes:

- Complete RT dataset
    - DICOM-IMAGES
        - Planning CT

        - Pre-RT MRI –transaxial images, co-registered with planning CT
    - DICOM-RTSTRUCT (delineations)
    - DICOM-RTDOSE (3D dose matrix for the entire plan)
    - DICOM-RTPLAN
- Complete Individual Case Review dataset (the outcome of the external RTQA review)

11.5.1.4 Involved institutions

- ***Scientific leader of the project, supervision of autosegmentation and automatic delineation review***
  Mauricio Reyes, Prof. Dr.
  ARTORG Center for Biomedical Engineering Research
  Center for AI in Medicine
  University of Bern
  Murtenstrasse 50
  3007 Bern
  Switzerland
  Email: mauricio.reyes@med.unibe.ch
- ***Medical leader of the project, supervision of data curation and storage***
  Nicolaus Andratschke, Prof. Dr.
  Department for Radiation Oncology
  University Hospital Zurich
  University of Zurich
  Rämistrasse 100
  8091 Zurich
  Switzerland
  Email: nicolaus.andratschke@usz.ch
- ***Data curation and storage, medical co-leader***
  Jonas Willmann, Dr.
  Department for Radiation Oncology
  University Hospital Zurich
  University of Zurich
  Rämistrasse 100
  8091 Zurich
  Switzerland
  Email: jonas.willmann@usz.ch
- ***Deep learning autosegmentation of targets and organs at risk, development of automatic delineation review tool***
  Amith Kamath, PhD candidate
  ARTORG Center for Biomedical Engineering Research
  Center for AI in Medicine
  University of Bern
  Murtenstrasse 50
  3007 Bern
  Switzerland
  Email: amith.kamath@unibe.ch

The project is led by Prof. Mauricio Reyes, Dr. Jonas Willmann, Prof. Nicolaus Andratschke and Mr. Amith Kamath.

11.5.1.5 Publication of results

First and last authorships in all publications stemming from this project will be held by Prof. Mauricio Reyes, Dr. Jonas Willmann, Prof. Nicolaus Andratschke and Mr. Amith Kamath. Additional co-authors include the PIs of the trial, the RTQA HQ staff, the RTQA Physics Chair, the RTQA reviewers, and one investigator from each of the 5 participating centres that provided most datasets.

11.5.2 Optimizing CTV margins for Radiotherapy in GBM by Machine Learning

11.5.2.1 Background

Recurrences in GBM patients after postoperative chemoradiotherapy mostly occur within or at the margin of the treatment volume. The standard clinical target volume (CTV) is typically defined as an isotropic 2 cm expansion around the surgical cavity and the area of contrast enhancement. This isotropic margin is not patient specific and does not take into account the preferential tumor growth along the white matter tracts of the brain. This project aims at optimizing the CTV margins using Machine Leaning.

11.5.2.2 Description of the project

The project has 4 exploratory objectives:

- Comparison and validation of manual vs automated tumor/target definition.
- Analysis of the pattern of recurrences using deep learning methods.
- Generate anisotropic, personalized CTV margins based on patient, treatment, and imaging parameters via deep learning methods.
- Mathematical modeling of tumor growth and assessment of tumor proliferation.

11.5.2.3 Methods/analysis plan

The longitudinal imaging data for each patient will be automatically co-registered. The recurrence volume will be automatically segmented. For the first three objectives, the GTV (manual and automated) and recurrence volumes will be geometrically analyzed to identify recurrence or growth patterns. The influence of patient and treatment parameters (for example age, MGMT-status, type of resection, treatment arm, radiation dose distribution) on the recurrence/growth patterns will be investigated. All parameters found to be relevant will be used to generate optimized, personalized, probability-based anisotropic CTV margins. The Fisher-Kolmogorov growth model assuming uniform proliferation rate and difference in white and grey matter diffusion will be used to assess tumour proliferation.

11.5.2.4 Data needed

- All pre and post op imaging dataset (according to Imaging guidelines; including 3D T1w pre- contrast, DWI, 2D FLAIR, GE-EPI perfusion if available, T2w-TSE, 3D T1w post-contrast)
- Complete RT dataset
    - DICOM-IMAGES
        - Planning CT
        - Pre-RT MRI –transaxial images, co-registered with planning CT

- DICOM-RTSTRUCT (delineations)
- DICOM-RTDOSE (3D dose matrix for the entire plan)
- DICOM-RTPLAN

- Clinical dataset:

Patient and treatment characteristics: date of birth (alternatively age at diagnosis), sex, performance status before surgery/at diagnosis, performance status before radiotherapy, date of surgery, extent of surgery, date of diagnostic MRI, date of postoperative MRI, date of planning-CT and planning-MRI, start/end date of RT, total dose and fraction dose, start/end date of concomitant anticancer drugs (for each compound), start/end date of adjuvant anticancer drugs (for each compound), pathology incl. MGMT and IDH, date of radiological/clinical progression, survival.

11.5.2.5 Involved institutions

Scientific leader of the project

Slavka Lukacova, MD, PHD

Aarhus University Hospital/Arhus University

Dept. of Oncology/Institute of Clinical Medicine

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Denmark

Email: slavka.lukacova@auh.rm.dk, Tel: 0045 40465210

Machine Learning segmentation of targets using RT and MRI datasets &

Pattern analysis/statistical analysis of treatment parameters vs recurrence

Anouk Trip, MD, PhD

Aarhus University Hospital

Danish Center for Particle Therapy

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Mathematical modelling of tumor growth

Jesper F. Kallehauge, Assoc. prof., Medical Physicist

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11.5.2.6 Publication of results

Results (planned publications: Recurrence pattern analysis, Individualizing CTV, Growth modelling) will be shared on a peer reviewed scientific radio-oncology journal within 2 years of the data release. Anouk Trip, Jesper F. Kallehauge, Slavka Lukacova will be first or last authors. The trial PIs will be co-authors. Other co-authors may be included from the top recruiting institutions.

12 Results dissemination policy

12.1 Study disclosure

12.1.1 Trial Registration

This trial will be registered in a public database (https://www.clinicaltrialsregister.eu). As the clinical trial (CT) regulation 536/2014 of the European Union (EU) becomes applicable, more information about this trial will be uploaded in this public database in compliance with European requirements on transparency. Information posted, among others, will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

In accordance with applicable EU regulations, a summary of the trial results will be made publicly available within one year of the end of study declaration.

EORTC as Sponsor of this trial will submit the summary of the results based on the final analysis report in compliance with the regulations.

12.1.2 Final Analysis Report

A Final Analysis Report that reports summary statistics of all the data collected for the study and presents an interpretation of the study results will be issued by the EORTC Headquarters. It will form the basis for the manuscript intended for publication. The Final Analysis Report or a summary thereof will be distributed to all participating groups, the supporting companies and ethics committees and the results will be posted in relevant public databases (as in section 12.1.1).

12.2 Publication policy

All publications must comply with the terms specified in the EORTC Policy 009 “Release of Results and Publication Policy” version 4.2 dated March 2015 or later.

In accordance with the Policy 009, results of the present study will be made public once the study data are mature for the final analysis of the primary study endpoint (as described in the section “statistics” of the present protocol),

irrespective of the findings (positive or negative). Deviations from the results disclosure rules specified in the Policy require authorization by the Independent Data Monitoring Committee (IDMC).

The primary trial publication will be written on the basis of the final analysis report and shall be published in a peer-reviewed scientific journal within 1 year of the date of the database lock.

Prior to submission, all publications (papers, abstracts, presentations…) will be submitted for review to the EORTC Headquarters statistician and clinical research physician, to all co-authors and to the designated representative of Celgene, if any as per contractual agreement. Approval of the manuscript by EORTC Headquarter representatives is required before submission of the manuscript reporting on an EORTC study for publication.

The authorship rules conform to the recommendations of the International Committee of Medical Journal Editors defining the roles of authors and contributors (http://icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html).

All other investigators and scientific contributors to the study who do not qualify for authorship will be acknowledged in the publication.

Sources of funding or support to the study will be disclosed and acknowledged in the publication.

The name “EORTC” and of any collaborative Group must be visible in the publication's header of all publications.

12.3 Data sharing

EORTC is committed to ensuring that the data generated from its studies be put to good use by the cancer research community and, whenever possible, are translated to deliver patient benefit.

It is therefore EORTC's policy to consider for sharing upon request from qualified scientific and medical researchers all data generated from its research whilst safeguarding intellectual property, the privacy of patients and confidentiality.

Considering that ongoing research contributing to the completion of datasets must not be compromised by premature or opportunistic sharing and analysis of data, the EORTC will not release the data of its study until the primary study results have been published; unless authorization for release has been granted according to the terms of EORTC Policy 009.

Requests for accessing the data of published trials should be filed through the data sharing tab on the EORTC website (www.eortc.org).

13 Investigator authorization procedure

Investigators will be authorized to register and/or randomize patients in this trial only once they have returned the following documents to their Data Center (for the EORTC investigators see chapter 19: Administrative responsibilities, for non-EORTC investigators: see your group specific appendix):

- The updated signed and dated Curriculum Vitae of the Principal Investigator in English with a GCP training proof.
- The (updated) list of the normal ranges, for their own institution signed and dated by the head of the laboratory. Please make sure normal ranges are provided also for those tests required by the protocol but not routinely done at the investigator’s institution.
- The Confirmation of interest by Principal Investigator Form (CIF), stating that the investigator will fully comply with the protocol. This must include an estimate of yearly accrual and a statement on any conflict of interest that may arise due to trial participation.

NB: A signed conflict of interest disclosure form will be required only if a possible conflict is declared on the CIF.

- The Study Agreement between EORTC and investigator's institution.
- A copy of the favorable opinion of the local or national (whichever is applicable) ethics committee mentioning the documents that were reviewed (including the version numbers and version dates of all documents). A list of all members of the ethics committee is also requested.
- A copy of the translated and adapted (according to all national requirements) Patient Information / Informed Consent sheet. Version numbers and dates must be clearly stated on each page.
- The signature log-list of the staff members with a sample of each authorized signature and the indication of the level of delegations.
- The full name, address, phone numbers and e-mail address of the local pharmacist who will be responsible for the trial medication (for any trial where the drug will be provided).
- An accreditation, a certification, an established quality control / external quality assessment or another validation should be provided for the own laboratory.

The center specific applicable list of required documents will be included in the protocol activation package, with proper instructions as required by this protocol, your group and / or the applicable national law

The new investigator will be added to the “authorization list”, and will be allowed to register/randomize patients in the trial as soon as

- All the above mentioned documents are available at their Data Center.
- All applicable national legal and regulatory requirements are fulfilled.

Patient registration/randomization from centers not (yet) included on the authorization list will not be accepted.

14 Patient registration & randomization procedure

14.1 General procedure

Patient registration will only be accepted from authorized investigators (see chapter 13 on “Investigator authorization procedure").

Patients should be registered directly on the Medidata Rave EDC system, accessible 24 hours a day, 7 days a week (please consult CRF guidelines for further information). To access Medidata Rave EDC system, the investigator needs a username and a password which will be provided by the EORTC Headquarters.

In case of problems investigators can contact the EORTC Clinical Data Manager (during Brussels business hours).

As soon as the registration process is started, a Subject ID is allocated to the patient. This number allows the identification of the patients in Medidata Rave EDC.

14.2 Randomization

Eligibility criteria will be checked at time of randomization. Once eligibility has been verified, treatment will be randomly allocated to the patient, together with a sequential patient identification number. This number will allow the identification of the patients in the Medidata Rave EDC system that will be used to complete the Case Report Forms.

14.3 Stock management process

An IVRS system will be used for the drug supply. For more details in, refer to the IMP management guidelines, provided as a separate document.

15 Forms and procedures for collecting data

15.1 Case report forms and schedule for completion

Data will be reported on the electronic CRFs specifically designed by the EORTC Headquarters for this study.

Data should be electronically sent to the EORTC Headquarters through the Medidata Rave EDC system (https://imedidata.com), with the exception of the HRQoL forms, which are paper case report forms (CRFs).

The paper CRF(s) will be made available to the institution at the time the institution is authorized.

SERIOUS ADVERSE EVENTS SHOULD BE IMMEDIATELY REPORTED ACCORDING TO THE PROCEDURE DETAILED IN THIS PROTOCOL (see chapter 16 on Reporting Serious Adverse Events).

The electronic CRFs to be completed for a patient and their submission schedule are available on the Medidata Rave EDC website immediately after the registration and are also described in the "guidelines for completion of case report forms" that are provided to each participating investigator.

All data must be electronically approved and sent by the responsible investigator or one of his/her authorized staff members.

15.2 Data flow

The forms must be completed according to the schedule defined in the guidelines for completion of Case Report Forms.

The list of staff members authorized to enter data must be identified on the signature log and sent to the EORTC Headquarters by the responsible investigator before the start of the study.

In all cases, it remains the responsibility of the principal investigator to check that data are entered in the database as soon as possible and that the electronic forms are filled out completely and correctly.

The EORTC Headquarters will perform extensive consistency checks on the received data. Queries will be issued in order to resolve other inconsistent data. The queries for the electronic forms will appear in the Rave EDC system and must be answered there directly.

A copy of the questionnaires should be sent to EORTC Headquarters as soon as possible, while the original source document should be kept on site.

When satellite institutions are involved, all contact is made exclusively with the primary institution, for purposes of data collection and all other study related issues.

If an investigator (or an authorized staff member) needs to modify a CRF after the form has been electronically sent to the EORTC Headquarters, he/she should edit the concerned data point in the Rave EDC system. The data should then be signed again.

For more information on the data flow, please refer to the study specific guidelines.

15.3 HBM* sample registration and tracking

Once the patient is registered, the investigator or his/her authorized staff must register the patient’s samples on the EORTC tracking tool. This tool is designed to register, manage and track Human Biological Materials collected in the frame of EORTC clinical trials.

Details about access the tracking tool, register samples and tracking shipments are described on the guidelines of HBM* management.

(*) Human Biological Material

16 Reporting of Serious Adverse Events

ICH GCP and EU Directive 2001/20/EC require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.

16.1 Definitions

These definitions reflect the minimal regulatory obligations; specific protocol requirements might apply in addition.

AE: An Adverse Event is defined as “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 can therefore be any unfavorable and unintended signs (such as rash or enlarged liver), symptoms (such as nausea or chest pain), an abnormal laboratory finding (including results of blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment, whether or not considered related to the investigational medicinal product.

AR: An Adverse reaction of an investigational medicinal product is defined as “any noxious and unintended response to a medicinal product related to any dose administered”.

All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

UAR: An Unexpected Adverse Reaction is “any adverse reaction, 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 summary of product characteristics (SmPC) for a marketed product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

Severity: The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe, or as described in CTC grades); the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as “serious,” which is based on patient/event outcome or action criteria usually associated with events that pose a threat to patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

SAE: A Serious Adverse Event is defined as any untoward medical occurrence or effect in a patient, whether or not considered related to the protocol treatment, that at any dose:

- results in death
- is life-threatening (i.e. an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- requires inpatient hospitalization or prolongation of existing patient hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is a medically important event or reaction.
  Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency

room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

SAR: A Serious Adverse Reaction is defined as any SAE which is considered related to the protocol treatment.

SUSAR: Suspected Unexpected Serious Adverse Reaction.

SUSARs occurring in clinical investigations qualify for expedited reporting to the appropriate Regulatory Authorities within the following timeframes:

- Fatal or life-threatening SUSARs within 7 calendar days
- Non-fatal or non-life-threatening SUSARs within 15 calendar days

Inpatient hospitalization: a hospital stay equal to, or greater than, 24 hours.

Second primary malignancy is one unrelated to the treatment of a previous malignancy (and is NOT a metastasis from the previous malignancy).

Secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the previous malignancy.

16.2 Exceptions

The following situations do not need to be reported as SAEs:

- Elective hospitalization for pre-existing conditions that have not been exacerbated by trial treatment.
- A hospitalization which was planned before the patient consented for study participation and where admission did not take longer than anticipated.
- A hospitalization planned for protocol related treatment or protocol related procedure as per institutional standard timelines.
- Social and/or convenience admission to a hospital.
- Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an (S)AE.
- Situations where an untoward medical occurrence did not occur (palliative care, rehabilitation, overdose without occurrence of an adverse event).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

16.3 Severity assessment

The severity of all AEs (serious and non-serious) in this trial should be graded using CTCAE v5.0 https://www.eortc.be/services/doc/ctc/

16.4 Causality assessment

The investigator is obligated to assess the relationship between protocol treatment and the occurrence of each SAE following the definitions in this table:

Relationship to the protocol treatment	Description
Reasonable possibility	There is a reasonable possibility that the protocol treatment caused the event

No reasonable possibility	There is no reasonable possibility that the protocol treatment caused the event

The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, medical history, concurrent conditions, concomitant therapy, other risk factors, and the temporal relationship of the event to the protocol treatment will be considered and investigated.

The decision will be recorded on the SAE form and, if necessary, the reason for the decision will also be recorded.

16.5 Expectedness assessment

The expectedness assessment is the responsibility of the *sponsor* of the study, unless otherwise specified in the Group specific appendix. The expectedness assessment will be performed against the following reference documents:

- *For Temozolomide*: Summary of Product Characteristics (SmPC), the RSI is section 4.8 in the SmPC
- *For Marizomib*: Investigator's Brochure. The RSI is the IB section entitled “Reference Safety Information”

16.6 Reporting procedure for investigators

This procedure applies to all Serious Adverse Events (SAEs) occurring from the time a subject is randomized until 30 days after last protocol treatment *administration* and to any SAE that occurs outside of the SAE detection period (after the 30-days period), if it is considered to have a reasonable possibility to be related to the protocol treatment or study participation.

Randomization till 30 days after last protocol treatment *administration*:	All SAEs
From day 31 after last protocol treatment *administration*:	Only related SAEs

Any secondary malignancy should also be reported in expedited way as an SAE with the appropriate seriousness criteria!

All reporting must be done by the principal investigator or authorized staff member (i.e. on the signature list) to confirm the accuracy of the report.

All SAEs must be reported immediately and no later than 24 hours from the time the investigator or staff became aware of the event.

All SAE-related information needs to be provided in English.

If any relevant additional document in local language is uploaded or forwarded to the Pharmacovigilance Unit relevant to an SAE (e.g. autopsy report), this must be accompanied by a translation in English, or the relevant information must be summarized in the electronic SAE-form.

Investigators participating through EORTC must report all SAE-related information to the Medidata Rave EDC system (www.imedidata.com).

If the iMedidata Rave EDC system is out of service, contact the Pharmacovigilance Unit for further instructions to report your SAE/Pregnancy:

EORTC Pharmacovigilance Unit:

Email: pharmacovigilance@eortc.org
Tel No. +32 2 774 1676
Fax No. +32 2 772 8027

Investigators participating through non-EORTC groups should consult their group specific appendix for further details on the reporting of Serious Adverse Events.

To enable the *sponsor* to comply with regulatory reporting requirements, all initial SAE reports should always include the following minimal information: an identifiable patient (SeqID), a suspect medicinal product if applicable, an identifiable reporting source, the description of the medical event and seriousness criteria, as well as the causality assessment by the investigator. Follow-up information of any reported serious adverse event must be completed within 7 calendar days of the initial report. If no SAE follow-up information is provided within this deadline, the *EORTC Pharmacovigilance Unit* will make a request to the investigator.

Queries sent out by the *EORTC Pharmacovigilance Unit* need to be answered within 7 calendar days.

16.7 Reporting responsibilities of the Sponsor

The EORTC Pharmacovigilance Unit will forward all SAE reports to the appropriate persons within the EORTC Headquarters *and to the pharmacovigilance contact at the pharmaceutical company*.

The EORTC Pharmacovigilance Unit will provide a six-monthly summary which will be added in the Trial Status Report and which will be accessible to all participating investigators.

The EORTC Pharmacovigilance Unit will take in charge the *reporting of SUSARs/unexpected events to the all Competent Authorities, Ethics committees (of EORTC centers), EudraVigilance Clinical Trial Module (EVCTM), all EORTC participating investigators and all central Data Managers of all Cooperating Groups, whenever applicable.*

16.8 Pregnancy reporting

Pregnancy occurring during a patient's participation in this trial, although not considered an SAE, must be notified to the EORTC Pharmacovigilance Unit within the same timelines as an SAE (within 24 hours) on an electronic Pregnancy Notification Form. The outcome of a pregnancy should be followed up carefully and any adverse outcome to the mother or the child should be reported. This also applies to pregnancies in female partners of a male patient participating in this trial.

- Any pregnancy in a female subject or in a female partner of a male subject diagnosed during the treatment period or within 6 months after last protocol treatment administration must be reported to the EORTC Pharmacovigilance Unit
- This must be reported within 24 hours of first becoming aware of the event to the Medidata Rave EDC system (www.imedidata.com) on an electronic pregnancy form.
- If an SAE occurs in conjunction with the pregnancy, please also report an SAE as explained in the SAE reporting section

17 Quality assurance

17.1 Control of data consistency

Data forms will be entered in the EORTC Headquarters database by using the Medidata Rave EDC system. Computerized and manual consistency checks will be performed on newly entered forms; queries will be issued in case of inconsistencies. Consistent forms will be validated.

17.2 On-site monitoring

The EORTC Headquarters will subcontract Premier Research to perform on-site monitoring visits according to the approved study-monitoring plan.

The first visit in a participating site will be performed within 3 months after the first patient's randomization at this site. Frequency and number of subsequent visits will depend on site's accrual and quality observed during the first visit.

The aim of these site visits will be:

- to check informed consent and patient eligibility
- to verify that the site facilities remain adequate for performing the trial
- to verify that the principal investigator and site staff involved in the trial are working in compliance with GCP and protocol requirements
- to assess the consistency of data reported on the case report forms with the source data
- to check that Serious Adverse Events have been properly reported and that follow-up information or queries are correctly fulfilled
- to check on any protocol deviations and retrain sites when necessary
- to assist the site in resolving any outstanding queries and potential temperature excursion
- to control the drug accountability process
- to check site and pharmacy files

17.3 Audits

The EORTC is responsible for the performance of the EORTC investigators.

The investigator, by accepting to participate in this protocol, agrees that EORTC, any third party (e.g. a CRO) acting on behalf of the EORTC, or any domestic or foreign regulatory agency, may come at any time to audit or inspect their site and all subsites, if applicable.

This audit consists of interviews with the principal investigator and study team, review of documentation and practices, review of facilities, equipment and source data verification.

The investigator will grant direct access to paper and/or electronic documentation pertaining to the clinical study (e.g. CRFs, source documents such as hospital patient charts and investigator study files) to these authorized individuals. All site facilities related to the study conduct could be visited during an audit (e.g. pharmacy, laboratory, archives …). The investigator agrees to co-operate and provide assistance at reasonable times and places with respect to any auditing activity.

If applicable, the company(ies) supplying the study drug(s) may have access to anonymized data but will not have access to source documents.

If a regulatory authority inspection is announced, the investigator must inform the EORTC Headquarters Compliance and Audits immediately (contact at: Complianceandaudits@eortc.org) In this way EORTC can provide support in preparing and/or facilitating the inspection. EORTC representatives/delegates may also attend the inspection.

17.4 Other central review procedures

17.4.1 Quality assurance in radiotherapy

All documents pertaining to RTQA requirements and procedures will be sent to the centers after receipt of the signed commitment form at the EORTC Headquarters.

The RTQA procedure consists of completing the following prior to institution authorization:

- Level I: Facility Questionnaire (FQ) and Beam Output Audit (BOA)
- Level II: Benchmark Case (BC)
- Level V: Credentialing for the use of IMRT

During the trial, the following RTQA patient-specific procedure must be performed:

- Level IV: Extensive Individual Case Review (E-ICR)

The RTQA procedures are summarized here and described in detail in the "RTQA Guidelines" document which will be supplied by RTQA team prior to institution authorization. In case of questions or difficulties, please contact the trial RTQA team at the following address: rtqa1709@eortc.org.

17.4.1.1 Prior to authorization

17.4.1.1.1 Facility questionnaire (FQ) and Beam Output Audit (BOA)

All EORTC centers at authorization must have a valid EORTC FQ and a valid BOA performed by an external auditor. Both must be not older than 2 years. This questionnaire must be filled in electronically and submitted on line. The web link is on the web page of EORTC under the Study Tools section.

All centers at authorization must have a valid BOA. Additional information can be found at the EORTC website under the Study Tools section.

To determine if a previously submitted FQ and or BOA is valid please contact rtqa1709@eortc.org and along with EORTC institution number.

17.4.1.1.2 Benchmark Case

All EORTC centers prior to authorization will perform a BC procedure if planning on treating patients with IMRT. Institutions planning on treating patients with 3D-CRT do not have to complete this procedure. This is a two-step procedure that contains a delineation and planning exercise according to the protocol in a provided patient case. The benchmark case will be centrally reviewed by the RTQA reviewers of the trial.

17.4.1.1.3 Complex Dosimetry check

All EORTC centers prior to authorization must be credentialed for the use of their IMRT technique via the Virtual Phantom Procedure (VPP). This procedure consists of irradiating the site's in-house phantom based on the RT plan created for the BC and further details can be found in the "RTQA Guidelines".

17.4.1.2 Patient-specific RTQA program

17.4.1.2.1 Extensive individual case review (E-ICR)

For all patients the following must be submitted for central review: all patient digital treatment data, including pre-operative imaging, and completed Radiotherapy planning eCRF must be submitted prior to the start of RT treatment and as soon as possible after randomization. The first 2 patients recruited per institution will be prospectively reviewed. All other patients will be reviewed retrospectively.

Should the review result in an “unacceptable protocol variation”, the institution might be withdrawn from the authorization list and no longer be in the position to enter patients in the trial, until a resubmission results in an “acceptable per protocol” or "acceptable variation" review. The same rule will apply if case plans are not submitted within the requested timelines.

All details about the submission procedure, timelines and supplementary forms are described in the RTQA Guidelines.

17.4.1.3 RTQA report

The primary RTQA-related research projects include analyses of the Benchmark Case (BC) procedure (site activation) and the Individual case review. The analysis of the BC will focus on target volume (TV) and organs at risk (OAR) delineation variability and the impact on dose parameters. In the ICR analysis, the variations of Target Volumes and OAR delineation will be determined in trial patients and compared with the results from the BC analysis.

The results of the BC and ICR analyses will be submitted for publication after the first main trial results publication or presentation. Submission will be to a peer-reviewed journal focusing on radiation oncology. First authorship will be held by the Emmanuel van der Schueren, a fellow who was involved in the analysis of the respective data, last authorship by the Clinical Chair of the RTQA group who supervised the work. Additional co-authors will include the EORTC HQ staff involved in the work, the RTQA Physics Chair, the RTQA reviewers, the PIs of the trial, and one investigator from each of the 5 participating centers that included and uploaded most cases.

17.4.2 Scan submission Quality Assurance and Quality Control in imaging

The EORTC HQ will track all scans of all patients received from the sites and will request/query missing/incomplete scans. Furthermore, if the scans arrive in unacceptable quality or in a non-acceptable format, the site will be informed to provide substitute scans.

Scans will be uploaded by the participating centers via the EORTC imaging platform. Please refer to the imaging guidelines for more details.

17.4.3 Imaging QA/QC level description

The QA procedure consists of completing the following:

- Prior to site authorization: Imaging Guidelines “read and understood” acknowledgment signature page.
- During the trial, the following imaging procedures will be performed: Prospective scans QC

17.4.3.1 Imaging guidelines “read and understood” acknowledgment page signature

Every site participating in an EORTC study with centralized imaging, must comply with the minimum requirements established as specified in the imaging guidelines. The first page of the imaging guidelines must be signed and returned to the EORTC HQ for every new version of the imaging guidelines. The page must be signed by the department head radiologist. This is mandatory from all institutions in this study before activation to participate in

17.4.3.2 Prospective scan quality control

QC will be performed prospectively, on an on-going basis. The EORTC Imaging Officer will be reviewing all scans for all patients to check for artifacts and to ensure compliance with the imaging guidelines and study protocol.
Every subsequent scan on the same patient must be done with the same scanner across all visits. In case of scanner breakdown or change of scanners in the department, you need to notify the EORTC HQ.

17.4.4 Scan submission

All scans acquired in the frame of this study should be uploaded to the EORTC imaging platform. Alternatively, scans can be sent on disc to the EORTC HQ. For more info, see Imaging guidelines for sites.

18 Ethical considerations

18.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at https://www.ema.europa.eu/documents/scientific-guideline/ich-e6-r1-guideline-good-clinical-practice_en.pdf).

The protocol must be approved by the competent ethics committee(s) as required by the applicable national legislation.

18.2 Subject identification

The name of the patient will neither be asked for nor recorded at the EORTC Headquarters. A sequential identification number will be automatically allocated to each patient registered in the trial. This number will identify the patient and will be included on all case report forms. In order to avoid identification errors, the patient's code (maximum of 4 alphanumerics) and date of birth or year of birth (as allowed per applicable legislation) will also be reported on the case report forms.

18.3 Informed consent

All patients will be informed about:

- the aims of the study
- the possible adverse events
- the procedures and possible hazards to which the patient will be exposed
- the mechanism of treatment allocation
- strict confidentiality of any patient data
- medical records possibly being reviewed for trial purposes by authorized individuals other than their treating physician

The template of the patient's informed consent statement is given as a separate document dated and version controlled to this protocol.

An adapted translation of the PIS/PIC will be provided by EORTC Headquarters and it is the responsibility of the Coordinating investigators for this trial (sometimes called National Coordinators) to adapt it to national/local requirements where necessary.

The translated informed consent documents are to be submitted to ethics committees for approval. The competent ethics committee for each institution must approve the informed consent documents before the center can join the study. It is the responsibility of the competent ethics committee to ensure that the translated informed documents comply with ICH-GCP guidelines and all applicable national legislation.

It is emphasized in the patient information sheet that participation is voluntary and that the patient is free to refuse further participation in the protocol whenever he/she wants to. This will not have any impact on the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered and/or randomized at the EORTC Headquarters. The written informed consent form must be signed and personally dated by the patient or by the patient's legally acceptable representative.

All of the above must be done in accordance with the applicable national legislation and local regulatory requirements.

Chapters 19 through 21 pertain specifically to the participation of EORTC investigators. Participants from other organizations should consult the appendix that is specific to their group to determine if the contents of these sections are superseded by procedures specific to their group.

19 Administrative responsibilities

19.1 The study coordinator

The Study Coordinator works closely with the study team to develop the outline and full protocol and discusses the contents of the reports with the study team. The Study coordinator is responsible for publishing the study results. He/she will assist the Clinical Research Physician for answering some clinical questions concerning eligibility, treatment, and contributes to the medical review of the patients.

Study coordinator:

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19.2 The EORTC Headquarters

The EORTC Headquarters will be responsible for writing the protocol and PIS/IC, reviewing the protocol, setting up the trial, collecting case report forms, controlling the quality of the reported data, organizing the medical review and generating reports and analyses in cooperation with the Study Coordinator. All methodological questions should be addressed to the EORTC Headquarters.

EORTC HEADQUARTERS

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19.3 The EORTC group

All questions concerning ongoing membership in the group should be addressed to the chairman and/or secretary of the group.

For new membership contact Membership Committee at membership@eortc.org.

Brain Tumor Group EORTC group

Chairperson:

Matthias Preusser
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20 Trial sponsorship and financing

EORTC is the legal Sponsor for all EORTC participants.

The contact details of the EORTC are:

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Financial support is provided by Celgene.

21 Trial insurance

A clinical trial insurance has been taken out according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

Clinical trial insurance is only valid in centers authorized by the EORTC Headquarters. For details please refer to the section on investigator authorization.

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Appendix B: Abbreviations

5-ALA	5-Aminolevulinic acid
AE	Adverse Events
AlkPhos	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated PTT
AR	Adverse reaction
AST	Aspartate Aminotransferase
ATP	Adenosine triphosphate
BBB	Blood brain barrier
BCNU	Bis-chloroethylnitrosourea
BEM	Beam's eye view
BOA	Beam Output Audit
BSA	Body surface area
C1D1	Cycle 1, Day 1
CIF	Principal Investigator Form
CMV	Cytomegalovirus
CNS	Central nervous system
COWA	Controlled Oral Word Association
CrCl	Creatinine clearance
CT	Computer Tomography
CTA	Clinical trial agreement
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical target volume
CYPs	Hepatic cytochrome P450s
d	Days
DVH	Dose volume histogram
DRR	Digital reconstructed radiograph
eCRF	Electronic case report form
EGA	European Genomic Archive
EGFR	Epidermal growth factor receptor
EIAED	Enzyme-inducing anti-epileptic drug
E-ICR	Extensive Individual Case Review
EOT	End of treatment
EORTC	European Organisation for Research and Treatment of Cancer
EPID	Electronic portal imaging device
EVCTM	EudraVigilance Clinical Trial Module
FFPE	Formalin Fixed Paraffin Embedded
FQ	Facility Questionnaire
GA	Geriatric Assessment
GI	Gastrointestinal
GTV	Gross tumor volume
H0	Null hypothesis

HBM	Human biological material
Hct	Hematocrit
Hgb	Hemoglobin
HQ	Headquarter
HRQoL	Health related quality of life
HSV	Herpes simplex virus
HVLT-R	Hopkins Verbal Learning Test – Revised
HZV	Herpes zoster virus
HR	Harzard ratio
IB	Investigator's Brochure
ICH/GCP	International Conference on Harmonisation /Good Clinical Practice
ICRU	International Commission on Radiation Units and Measurements
IDH	Isocitrate dehydrogenase
IDMC	Independent Data Monitoring Committee
IIT	Intention-to-treat
IMP	Investigational medicinal product
IMRT	Intensity modulated radiotherapy
INR	International Normalized Ratio
IV	Intravenous
IVRS	Interactive Voice Response System
KPS	Karnofsky performance score
LFT	Liver functions tests
MGMT	O-6-Methylguanine-DNA methyltransferase
mMGMT	Methylated MGMT
MMSE	Mini-Mental State Examination
MOS	Medical Outcomes Study
MRI	Magnetic resonance imaging
MRZ	Marizomib
NCIC	National Cancer Institute of Canada
NYHA	New York Heart Association
OAR	Organs at risk
ORR	Overall response rate
OS9	Overall survival at 9 months
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PFS6	Progression Free Survival Rate at 6 months
PIS/IC	Patient Information / Informed Consent sheet
PJP	*Pneumocystis jiroveci* pneumonia
PK	*Pharmacokinetics*
PO	per os
POL	Policy
PP	Protocol population
PSA	Prostate-Specific Antigen
PT	Prothrombin time
PTT	Partial thromboplastin time
PTV	Planning Target Volume

PWB	Packed whole blood
QA&C	Quality Assurance and Control
QLQ	Quality of Life Questionnaire
QoL	Quality of Life
RBC	Red blood cells
RP2D	Recommended phase II dose
RT	Radiotherapy
SAE	Serious Adverse Event
SAD	Source-to-axis distance
SAR	Serious Adverse Reaction
SMG	Study Management Group
SmPc	Summary of product characteristics
SOC	Standard of care
SS	Safety population
SSC	Study Steering committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TMT A & B	Trail Making Test Part A & Part B
TMZ	Temozolomide
TR	Translational research
TRAC	Translational Research Advisory Committee
TTFields	Tumor-Treating Fields
UAR	Unexpected Adverse Reaction
ULN	Upper normal limit
uMGMT	Unmethylated MGMT
VPP	Virtual Phantom Procedure
WBC	White blood cells
WHO	World Health Organisation
WOCBP	Women of child bearing potential

Appendix C: New York Heart Association (NYHA) classification of heart failure

Class I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

(The Criteria Committee of the New York Heart Association: Diseases of the Heart and Blood Vessels; Nomenclature and Criteria for Diagnosis, 6th ed Boston, Little, Brown 1964).

Appendix D: Common Terminology Criteria for Adverse Events

In the present study, adverse events and/or adverse drug reactions will be recorded according to the

Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.

The EORTC Headquarters web site https://www.eortc.be/services/doc/ctc/ provides a link to the appropriate CTC web site. This link will be updated if the CTC address is changed.

Appendix E: Karnofsky scale for performance status

Index	Performance scale
100	Normal; no complaints.
90	Able to carry on normal activities; minor signs or symptoms of disease.
80	Normal activity with effort.
70	Cares for one self. Unable to carry on normal activity or to do active work.
60	Ambulatory. Requires some assistance in activities of daily living and self-care.
50	Requires considerable assistance of frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospitalization indicated though death not imminent.
20	Very sick; hospitalization and active supportive treatment.
10	Moribund.
0	Dead.

Appendix F: EORTC Quality of Life evaluation: guidelines for administration of questionnaires

EORTC Quality of Life evaluation: guidelines for administration of questionnaires

The instructions given below are intended to provide some general guidelines for collecting quality of life (QOL) data in EORTC studies. These instructions apply for all types of questionnaires.

1. Who is the responsible person (RP) for QOL data collection?

In each institution, the principal investigator is the responsible for the local organization of QoL data collection. This can be delegated to a physician, data manager, (research) nurse or a psychologist. Such a person should have the full protocol at his/her disposal as well as the questionnaire(s). This person would also be the intermediate contact point in case of any necessary clarification asked by the EORTC Headquarters.

2. Who should fill out the questionnaire?

In principle it is the patient who has to complete the QOL forms and preferably without help from others. In the case where a patient is too sick to fill out the questionnaire by him/herself or if the patient is not able to complete the questionnaire for such reasons as forgetting his/her glasses, another person could read the questions without making any suggestions and report the answers on the forms. It is not allowed for another person to fill in the questionnaire as if (s)he was the patient (proxy assessment) unless specifically allowed by the protocol.

3. What instructions should be given to the patient?

At entry in a study, the RP should give the patient an explanation of the objective of the study and instructions for completing the questionnaires.

The patient should be informed that participation in the QOL protocol is voluntary and that the information provided is confidential (identification is only for administrative purposes and includes date of birth and today's date (completion date)).

The following issues should be explained to the patient:

- The schedule of assessments.
- The questionnaire is a self administered questionnaire that should be completed by the patient him(her)self. The patient can ask for aid in reading or writing but should not let another person provide the answers.
- The patient should circle the choice that best corresponds to his/her situation.
- There is no right or wrong answer to any of these questions. The answers will not influence any medical decision making.
- All questions should be answered.
- The patient will be given a questionnaire in the default language(s) of the hospital. If desired, the patient may request another language. The RP will then contact the EORTC Headquarters for the appropriate translation.

The RP should make sure that the patient understands the instructions.

At each subsequent assessment as defined by the protocol, the patient should receive the questionnaire from the RP or from other appropriate staff if the RP is unavailable.

4. Where should the patient complete the questionnaire?

The patient should complete the questionnaire at the clinic, and, ideally in a quiet, private room. If this is not possible, the waiting room is an acceptable alternative. In general it does not take long to complete the questionnaire, but patients should be given the time they need to answer all questions.

5. When should they complete the questionnaire?

The timing of the planned QoL assessments is detailed in the protocol. When a QOL assessment is planned, the questionnaire should be given to the patient preferably before the meeting with the physician, ensuring that the patient has enough time to complete the questionnaire. If the patient is to receive a therapy, the questionnaire should be filled out before administration of the treatment (unless indicated otherwise in the protocol). The questionnaire should not be taken home and/or mailed (unless indicated otherwise in the protocol).

6. Review of the completed questionnaire

After the patient has completed the questionnaire, the person handling the questionnaire should:

- Complete the “Hospital Staff” specific data box.
- Check that the completion date is correctly filled in by the patient.
- Screen the questionnaire for omissions.

If this is the case:

- Please ask the patient the reason for omissions. It may be that patient forgot to flip a page or did not understand a question. The patient should not be forced to provide an answer if (s)he does not wish to do so.
- Additional explanation may be provided, but the questions should not be rephrased.

7. Missing forms

If for some reason the patient is unable or does not wish to complete a quality of life questionnaire the reason and the date of visit should be documented on the corresponding CRF (case report form).

8. Mailing to EORTC Headquarters

A copy of the questionnaires should be sent to EORTC Headquarters as soon as possible, while the original source document should be kept on site. As it is impossible to retrospectively collect missing quality of life data, please make sure the patient completes the questionnaire at the time-point when he/she is supposed to complete it.

Thank you very much for your cooperation.

Appendix G: G8 geriatric screening tool (Version 1.0 - December 2010)

To be completed by: Clinician, nurse or trained coder.

Notes: This screening tool includes 7 items of the Mini Nutritional Assessment and the age of the patient.

Score: Total score by adding up coded answers.

G8 Screening tool			
	Items	**Possible answers**	**Score**
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	**0:** severe reduction in food intake **1:** moderate reduction in food intake **2:** normal food intake	……..
B	Weight loss during the last 3 months?	**0:** weight loss >3kg **1:** does not know **2:** weight loss between 1 and 3 kg **3:** no weight loss	……..
C	Mobility	**0:** bed or chair bound **1:** able to get out of bed/chair but does not go out **2:** goes out	……..
E	Neuropsychological problems	**0:** severe dementia or depression **1:** mild dementia or depression **2:** no psychological problems	……..
F	Body Mass Index (weight in kg/height in m^2)	**0:** BMI less than 19 **1:** BMI 19 to less than 21 **2:** BMI 21 to less than 23 **3:** BMI 23 or greater	……..
H	Takes more than 3 medications per day	**0:** yes **1:** no	……..
P	In comparison with other people of the same age, how does the patient consider his/her health status?	**0:** not as good **0,5:** does not know **1:** as good **2:** better	……..

	Age	**0:** >85 **1:** 80-85 **2:** <80	……..
	Total score (0-17)		…….

Appendix H: Acceptable birth control methods

Women of childbearing potential (WOCBP) are defined as premenopausal females capable of becoming pregnant (i.e. females who have had evidence of menses in the past 12 months, with the exception of those who had prior hysterectomy).

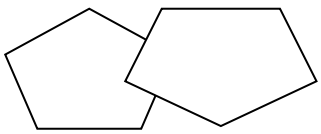
A highly effective method of birth control is defined as a method which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence (the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient)

Appendix I: Mini Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor."(The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

Appendix J: Neurocognitive test battery

Certification and Administration procedures for the Neurocognitive Test Battery and collection of Patient Reported Outcome (PRO) Questionnaires

1.1 General Procedures: Certification for Test Administration

The healthcare professional (e.g. nurse, psychologist) who is responsible for neurocognitive test administration in this study requires pre-certification by M. Klein in order to participate in this protocol. For this pre-certification, the test administrator who will be evaluating patients must first obtain, (print) and review the following documents; instructions, test scoring forms, a training video and a training video post test. These documents are available on a password-protected website at VU University Medical Center Amsterdam. To obtain website and password information contact M. Klein, EORTCsupport@vumc.nl.

The training video of neurocognitive test administration must be reviewed along with the scoring forms and the "Test Instructions for the Neurocognitive Test Battery" (see 1.3). The instructions and the training video should be retained for review and reference during this study. After viewing the training video, the trainee must complete a post test and a "practice" assessment on a non-patient volunteer (e.g. coworker, friend), including completion of scoring forms.

After meeting the requirements of certification for test administration, the Certification Worksheet for test administrator (see Appendix K hereunder) must be completed and signed. All materials (the training video post test, completed test forms of "practice" assessment and the signed Certification Worksheet) must be scanned and emailed to M. Klein, who will score it and review any procedural errors with the trainee. Email: EORTCsupport@vumc.nl

If the trainee demonstrates competency, he/she will be notified of the approval to administer the tests to study subjects as part of the EORTC 1709 study and study enrollment may commence. A notification of certification will be sent to both the site and to EORTC for their records and to ensure that only the EORTC 1709 study-approved examiners are testing subjects on the EORTC 1709 study.

M. Klein will be available by telephone and e-mail if questions arise about the testing procedures, phone: +31 20 4448432 / email: EORTCsupport@vumc.nl. If there are administration or procedural errors, M. Klein will discuss the test administration and scoring issues over the phone with the test administrator (5-10 min).

The test forms of each certified examiner will be reviewed by M. Klein for quality control purposes. Procedural deviations (if any) will be identified, and sites will be notified of the results of the review. If significant procedural variations are noted, re-training ('re-certification') of the test administrator will be requested.

1.2 General Procedures: Neurocognitive Assessment

The tests that constitute the neurocognitive function (NCF) battery were selected because they are widely used standardized psychometric instruments that have been shown to be sensitive to the neurotoxic effects of cancer treatment in other clinical trials. NCF has been demonstrated to predict tumor progression and independently predict survival for patients with CNS tumors. This battery has also been demonstrated to be practical in terms of cost and burden to the patient, with good compliance in multicenter trials. They are widely used, standardized psychometric instruments with published normative data that take into account age and, where appropriate, education, gender and handedness. The tests were also selected to minimize the effects of repeated administration.

In addition to objective assessments of neurocognitive functioning, patients' self-reported cognitive function will be assessed with a six-item scale developed for use in the Medical Outcomes Study (MOS scale). (Ref. 58) This scale assesses day-to-day problems with cognitive function, such as difficulty with reasoning and problem solving, slowed reaction time, forgetfulness, and problems with concentration. This questionnaire is included in the scoring forms.

Cognitive Domain	Test	Time to Administer (minutes)
Memory	Hopkins Verbal Learning Test – Revised (HVLT-R)	8
Visual-motor processing speed	Trail Making Test (TMT) Part A	3
Executive Function	Trail Making Test (TMT) Part B	5
Verbal fluency	Controlled Oral Word Association (COWA)	5
	Total	21

The tests are to be administered in one session by a certified examiner. Test instructions (see 1.3 Test instructions for the Neurocognitive Test Battery) must be followed verbatim with every patient at every study visit. Results of the HLVT-R, TMT and COWA should be recorded on the test forms with a black pen. All test forms must be clearly signed by the test administrator. Original patient test forms should be kept at site.

Administer the tests in the following order to every patient at every visit:

1) HVLT-R - Part A Free recall

2) TMT - Part A

3) TMT - Part B

4) COWA

5) HVLT-R - Part B Delayed recall

6) HVLT-R - Part C Delayed recognition

Sequencing of alternate forms

Neurocognitive test battery is to be administered at study registration and at various follow-up moments as indicated in the summary table of this protocol (section 6.4) and the neurocognitive guidelines. Two of the tests to be administered have alternate forms or versions in order to reduce the effects of practice. See the table below for the forms to be administered at study registration and subsequent sessions. The forms should continue to be alternated in this order for the duration of the study. The packets (version 1-6) available on the website will contain the correct alternate forms. Additionally, patients should not be given copies of their tests to avoid learning the material between test administrations.

Test	Study Registration	2nd visit	3rd visit	4th visit	5th visit	6th visit	7th visit > > >
HVLT-R	Form 1	Form 2	Form 3	Form 4	Form 5	Form 6	Form 1
COWA	Form 1	Form 2	Form 1	Form 2	Form 1	Form 2	Form 1
Dutch	'B-D-H'	'P-M-C'	'B-D-H'	'P-M-C'	'B-D-H'	'P-M-C'	'B-D-H'
English	'C-F-L'	'P-R-W'	'C-F-L'	'P-R-W'	'C-F-L'	'P-R-W'	'C-F-L'
French	'P-B-G'	'A-T-V'	'P-B-G'	'A-T-V'	'P-B-G'	'A-T-V'	'P-B-G'
German	'A-M-V'	'K-P-W'	'A-M-V'	'K-P-W'	'A-M-V'	'K-P-W'	'A-M-V'
Italian	'C-F-G'	'P-D-L'	'C-F-G'	'P-D-L'	'C-F-G'	'P-D-L'	'C-F-G'

1.3 Test instructions for the Neurocognitive Test Battery

1) HOPKINS VERBAL LEARNING TEST - REVISED (HVLT-R)

This test has three parts and six alternate forms. Complete the three learning trials, **Part A - Free Recall,** first. Complete **Part B - Delayed Recall** after a 20-minute delay that includes administration of TMT and COWA.

Complete **Part C - Delayed Recognition** immediately after Delayed Recall.

Part A – Free Recall: Trial 1

Examiner: "I am going to read a list of words to you. Listen carefully, because when I am through, I'd like you to tell me as many of the words as you can remember.

You can tell them to me in any order. Are you ready?"

Read the words at the rate of one word every 2 seconds.

Examiner: "OK. Now tell me as many of those words as you can remember."

Check off the words the patient recalls on the form.

If a word is said that is not in the list (for example, "intrusion"), do not write that word on the form and do not say anything to the patient about the word not being on the list.

There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.

If not, move on to trial 2. Later, you can record the number of correct words on the test form.

Part A – Free Recall: Trial 2

Examiner: "Now we are going to try it again. I am going to read the same list of words to you.

Listen carefully, and tell me as many of the words as you can remember, in any order, including the words you told me the first time."

Read the words at the rate of one word every 2 seconds.

Check off the words the patient recalls on the form. Incorrect/non-list words are not recorded on the test form.

There is no time limit and patients should be encouraged to do their best.

If he/she cannot think of any more words move on to trial 3. Later, record the number of correct words.

Part A – Free Recall: Trial 3

Examiner: "I am going to read the list one more time. As before, I'd like you to tell me as many of the words as you can remember, in any order, including all the words you've already told me."

Read the words at the rate of one word every 2 seconds.

Check off the words the patient recalls on the form. Incorrect/non-list words are not recorded on the test form.

There is no time limit and patients should be encouraged to do their best.

Do not tell the respondent that recall of the words will be tested later!

Record the time on the clock that you complete Part A – Free Recall (for example, 10:00 A.M.) on the designated space 'Part A Stop Time' on the HVLT-R form.

2) TRAIL MAKING TEST (TMT) * Timed Test *

This test has two parts (A and B), which both have a sample exercise and a test exercise.

Part A – Sample

The Sample for Part A must be completed/attempted by each patient at every assessment. Place the Sample A worksheet flat on the table, directly in front of the patient (the bottom of the worksheet should be approximately six inches from the edge of the table). Give the patient a black pen.

Examiner: "On this page are some numbers. Begin at number 1 (point to 1) and draw a line from 1 to 2 (point to 2), 2 to 3 (point to 3), 3 to 4 (point to 4), and so on, in order, until you reach the end (point to the circle marked END). Draw the lines as fast as you can. Ready, begin."

If the patient completes Sample A correctly and in a manner demonstrating that he/she understands what to do, proceed immediately to Test A. If the patient makes a mistake on Sample A, point out the error and explain it. The following explanations of mistakes serve as illustrations:

"This is where you start (point to number 1)."

"You skipped this circle (point to the circle omitted)."

"You should go from number 1 to 2 (point), 2 to 3 (point), and so on, until you reach the circle marked END."

If it is clear that the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient cannot complete Sample A, take his/her hand and guide him/her through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on the copy.

Examiner: "Remember, begin at number 1 (point to 1) and draw a line from 1 to 2 (point to 2), 2 to 3 (point to 3), 3 to 4 (point to 4) and so on, in order, until you reach the circle marked END (point to END). Do not skip around, but go from one number to the next in proper order. Remember to work as fast as you can. Ready, begin."

If the patient does not succeed, or it becomes evident that he/she cannot do the task, discontinue testing and indicate the corresponding reason on the TMT Recording Form. If the patient completes Sample A correctly and appears to understand what to do, proceed immediately to Test A.

Part A – Test

After the patient has completed Sample A, place the Test A worksheet directly in front of the patient.

Examiner: "Good! Let's try the next one. On this page are numbers from 1 to 25. Do this the same way. Begin at number 1 (point) and draw a line from 1 to 2 (point), 2 to 3 (point), 3 to 4 (point) and so on, in order, until you reach the circle marked END (point). Do not skip around, but go from one number to the next in proper order. Remember to work as fast as you can. Ready, begin."

Start timing as soon as the instruction is given to "begin".

Watch closely in order to catch any errors as soon as they are made. If the patient makes an error, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred.

The patient must complete the test in 3 minutes or less.

Do not stop timing until he/she reaches the circle marked "END".

If the patient does not complete the test within 3 minutes terminate the testing. The test can also be discontinued if the patient is extremely confused and is unable to perform the task. Collect the worksheet and complete the TMT Recording Form indicating the reason the test was terminated and the last correct number reached on the test.

If the patient successfully completes the test collect the worksheet and record the time to completion on the TMT Recording Form in minutes and seconds.

Examiner: **"That's fine. Now we'll try another one."**

Part B – Sample

The Sample for Part B must be completed/attempted by each patient at every assessment. Place the

Sample B worksheet flat on the table, directly in front of the patient.

Examiner: "On this page (point) are some numbers and letters. Begin at number 1 (point) and draw a line from 1 to A (point), A to 2 (point), 2 to B (point), B to 3 (point), 3 to C (point) and so on, in order, until you reach the end (point). Remember, first you have a number (point), then a letter (point), then a number (point), then a letter (point), and so on. Draw the lines as fast as you can. Ready, begin."

If the patient completes Sample B correctly proceed immediately to Test B. If the patient makes a mistake, point out the error and explain it. The following explanations of mistakes serve as illustrations:

"You started with the wrong circle. This is where you start (point to number 1)."

"You skipped this circle (point to the circle omitted)."

"You should go from number 1 (point) to A (point), A to 2 (point), 2 to B (point), B to 3 (point) and so on, until you reach the circle marked END (point)."

If it is clear the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient cannot complete Sample B, take their hand and guide them through the trail using the opposite end of the pen.

Examiner: "Now you try it. Remember, begin at number 1 (point) and draw a line from 1 to A (point), A to 2 (point), 2 to B (point), B to 3 (point) and so on, in order, until you reach the circle marked END (point). Ready, begin."

If the patient does not succeed or it becomes evident that s/he cannot do the task, discontinue testing and indicate the corresponding reason on the TMT Recording Form. If the patient completes Sample B correctly and appears to understand what to do, proceed immediately to Test B.

Part B – Test

After the patient has completed Sample B, place the Test B worksheet directly in front of the patient.

Examiner: "Good! Let's try the next one. On this page are both numbers and letters. Do this the same way. Begin at number 1 (point) and draw a line from 1 to A (point), A to 2 (point), 2 to B (point), B to 3 (point), 3 to C (point) and so on, in order, until you reach the circle marked END (point). Remember, first you have a number (point), then a letter (point), then a number (point), then a letter (point), and so on. Do not skip around, but go from one circle to the next in the proper order. Draw the lines as fast as you can. Ready, begin."

Start timing as soon as the instruction is given to "begin".

Watch closely in order to catch any errors as soon as they are made. If the patient makes an error, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred.

The patient must complete the test in 5 minutes or less.

Do not stop timing until he/she reaches the circle marked "END".

Collect the worksheet and record the time to completion on the scoring form in minutes and seconds.

If the patient does not complete the test within 5 minutes terminate the testing. The test can also be discontinued if the patient is extremely confused and is unable to perform the task. Collect the worksheet and complete the TMT Recording Form indicating the reason the test was terminated and the last correct number or letter reached on the test.

At the top of both Sample forms and Test forms please write: patient code, case number, date of evaluation, institution name, name of certified tester, and the certified tester's phone number.

3) CONTROLLED ORAL WORD ASSOCIATION TEST (COWA) * Timed Test *

This test has three parts (letters) and two alternate forms.

Examiner: "I am going to say a letter of the alphabet, and I want you to say as quickly as you can all of the words that you can think of that begin with that letter. You may say any words at all, except proper names such as the names of people or places. So you would not say 'Rochester' or 'Robert'. Also, do not use the same word again with a different ending, such as 'Eat,' and 'Eating.'

For example, if I say 'S,' you could say 'son', 'sit,' 'shoe,' or 'slow.'

Can you think of other words beginning with the letter 'S'?"

Wait for the patient to give a word. If it is a correct response, say "good", and ask for another word beginning with the letter "S". If the patient gives an inappropriate word on either occasion, correct the patient, and repeat the instructions. If the patient then succeeds, proceed to the test. If the patient fails to respond, repeat the instructions. If it becomes clear that the patient does not understand the instructions or cannot associate, stop the procedure, and indicate the reason(s) on the scoring form. If the patient has succeeded in giving two appropriate words beginning with the demonstration letter, proceed to the test.

Examiner: "That is fine. Now I am going to give you another letter and again you say all of the words beginning with that letter that you can think of. Remember, no names of people or places, just ordinary words. Also, if you should draw a blank, I want you to keep on trying until the time limit is up and I say STOP. You will have one minute for each letter.

The first letter is '__'. Begin".

Start timing immediately, see scoring form. Allow exactly one minute for each letter.

Record the patient's responses on the scoring form.

If the patient discontinues before the end of the time period, encourage him/her to try to think of more words. If he/she is silent for 15 seconds, repeat the basic instruction and the letter.

(e.g., "**Tell me all the words you can think of that begin with a 'C'**").

No extension on the time limit is made in the event that instructions are repeated.

Continue the evaluation with the remaining two letters, allowing one minute for each.

Add the total number of correct responses in each column on the COWA scoring form.

All incorrect and repeated responses must be crossed out with one single line, initialed and dated.

All duplicate entries that have been verified to have different meanings must be marked "OK", initialed and dated.

COWA - Recording and scoring

The scoring form provides lines on which the patient's responses can be entered (e.g. write in the word that is said by the patient). If his/her speed of word production is too fast to permit verbatim recording, a "+" should be entered to indicate a correct response. It can be helpful for the first several patients and for patients known to be fast with their word production to tape record the session for transcription at a later time.

Incorrect responses should be recorded and struck through with a single line followed by your initials and the date in the margin next to the error. If the patient provides more responses than there are lines on the scoring form, place check marks in the boxes to indicate correct responses only.

The instructions include a specific prohibition against giving proper names or different forms of the same word. Therefore, inflections of the same word (e.g. eat-eating; mouse-mice; loose-loosely; ran-run-runs) are not

considered correct responses. Patients often give both a verb and a word derived from the verb or adjective (e.g., fun-funny; sad-sadness). These are not considered correct responses.

On the other hand, if the word refers to a specific object (e.g., foot-footstool; hang-hanger), it would be counted as a correct answer. Many words have two or more meanings (e.g. foot; can; catch; hand). A repetition of the word is acceptable IF the patient definitely indicates the alternative meaning to you.

Foreign words (e.g. pasta, passé, lasagna) can be counted as correct if they can be considered part of the lexicon of the relevant language, the criterion being listed in a standard dictionary of that language. Slang terms are OK if they are in general use.

Count all the correct responses. The number of correct words should be indicated below each column on the scoring form that is sent to M. Klein. If the test is discontinued or omitted, please mark this on the bottom of the test form and indicate the reason.

4) HOPKINS VERBAL LEARNING TEST - REVISED (HVLT-R)

Part B – Delayed Recall

Do not read the list of words again!

Record the time on the clock that you start Part B – Delayed Recall (for example, 10:20 A.M.) on the designated space 'Part B Start Time' on the HVLT-R form.

Administer Part B – Delayed Recall after completing all Trail Making Tests and the COWA. There should be at least 20 minutes between Part A and Part B of the HVLT-R.

Examiner: "Do you remember that list of words you tried to learn before? Tell me as many of those words as you can remember."

Check the box on the corresponding line of the HVLT-R scoring form for each word the patient accurately recalls.

If a word is said that is not in the list (for example, "intrusion"), do not write that word on the form and don't say anything to the patient about the word not being on the list.

There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.

Record the number of words that were correctly recalled on the scoring form.

Part C – Delayed Recognition

Examiner: "Now I'm going to read a longer list of words to you. Some of them are words from the original list, and some are not. After I read each word, I'd like you to say "Yes" if it was on the original list or "No" if it was not. Was [word] on the list?"

Read the words from the top of the columns down.

Check either the "Y" (Yes) or "N" (No) box next to each word to indicate the patient's response.

Guessing is allowed.

If the test is discontinued or omitted, please mark this on the bottom of the test form and indicate the reason.

The score for this portion of the HVLT-R is the number of list words (i.e. words that in CAPS) correctly identified ("yes" response) minus the number of non-list words (i.e. words in lower case) incorrectly identified ("yes"

response). Therefore, the actual score can range from –12 (no list words identified and all non-list words identified) to +12 (all list words identified and no non-list words identified).

END NEUROCOGNITIVE TEST BATTERY

You have now completed the neurocognitive test battery.

Summary of Requirements for Examiner Approval for the EORTC 1709 study

Prior to testing a patient, potential examiners must:

Read "Certification & Administration procedures for the Neurocognitive Test Battery and PRO Questionnaires"

Contact Martin Klein (EORTCsupport@vumc.nl) to obtain website and password information to get access to a password-protected website with all the necessary information

Obtain instructions and copies of the neurocognitive tests from the password-protected website in Dutch, English, French, German or Italian

Watch the training video available at the password-protected website

Complete the training video post test available at the password-protected website

Complete a "practice" assessment (see 1.1)

Complete the Certification Worksheet (see Appendix K)

Send ALL completed documents (training video post test, test forms of "practice" assessment and signed Certification Worksheet) to the attention of M. Klein.

Scan documents and EMAIL: EORTCsupport@vumc.nl

Summary of Testing Patients for the EORTC 1709 study

Certified examiners must:

Inform the patient of the date for neurocognitive assessment.

On date of testing, neurocognitive testing should be completed in one session:

Test instructions (see 1.3) must be followed verbatim with every patient at every study visit.

All tests should be completed in black pen.

All test results are recorded on the test forms.

In the event that a patient cannot complete a test, specify the reason(s) on the test form.

All test forms must be signed clearly by test administrator with correct study identifiers.

Before dismissing the patient, thank the patient for cooperation.

Remind of next appointment and that these tests will be repeated.

Patients should not be given copies of their tests to avoid learning the material between test administrations.

Please keep original test forms at site. In the event of questions, contact M. Klein.

Send ALL completed documents (neurocognitive scoring forms) as soon as possible to the attention of M. Klein.

Scan documents and EMAIL: EORTCsupport@vumc.nl

Appendix K: Certification Worksheet for test administrator

EORTC 1709 study

This worksheet must be completed and signed by the person requesting certification and submitted to M. Klein prior to the registration of any patients to the EORTC 1709 study. Refer to "General Procedures: Certification for Test Administration" (Appendix J) for details.

_____(Y) 1. Have you reviewed the "Certification & Administration procedures for the Neurocognitive Test Battery (Appendix J)?

_____(Y) 2. Have you watched the training video of neurocognitive test administration and completed the post test?

_____(Y) 3. Have you completed a "practice" neurocognitive assessment?

_____ _____

Signature of test administrator Date

_____ _____

Printed name of test administrator Institution number/Name

_____ _____

Telephone number of test administrator Email of test administrator

If you have any questions regarding the certification and/or test administration, please contact M. Klein. Once you have completed this form, please attach both the "practice" neurocognitive assessment forms and the training video post test and submit to:

M. Klein

Phone: +31 20 4448432

Email: EORTCsupport@vumc.nl

For M. Klein's Use Only

_____ (Y/N) The above individual has been certified for administering the neurocognitive assessments for this study.

Signature _____ Date _____

Appendix L: Specific protocol instructions during the COVID-19 pandemic

Note: All instructions listed in this Appendix will be solely applicable during the COVID-19 crisis. Furthermore, please ensure that any protocol deviations resulting from COVID-19 are:

- Adequately documented in the eCRFs as well as the patient's medical records or in a NTF to be stored in your Study binder (ISF).
- Always begin deviation text with "COVID-19"

Introduction

Current information suggests that cancer patients have a higher risk of infection and serious complications from infections including COVID-19, than other patients.

It is strongly recommended that investigators exercise medical/clinical judgement, and decisions regarding each patient should be individualized after considering the overall goals of treatment, the patient's current oncologic status and treatment tolerance as well as their general medical condition.

In addition, investigators should adhere to local and institutional guidelines for SARS-CoV-2 infection and suspected COVID-19 infection.

Risk-benefit assessment

Introduction to trial

The EORTC trial 1709 is a randomized phase III trial in which the standard of care for patients with newly diagnosed glioblastoma, consisting of temozolomide-based chemoradiotherapy, is compared with the same treatment combined with marizomib, a novel proteosome inhibitor. Its purpose is to compare safety and efficacy of the experimental therapy with the current standard of care.

Benefits

In September 2020, the IDMC committee did recommend stopping the study 's recruitment by lack of evidence regarding the survival benefit (Refer to Section 1.2.1)

Risks related to the trial especially during the COVID-19 crisis

There are potential risks associated with the treatment administered in the trial, and during the COVID-19 crisis, these risks may be increased:

- The fact that included patients need to come for regular visits to the hospital, increases their exposure risk to persons who are contagious for SARS-CoV-2. General rules like social distancing (1.5 m) and avoidance of persons with possible signs or confirmed diagnosis can be applied. However, SARS-CoV-2 can also be contagious in persons who do not have symptoms, so every hospital visit increases the risk of attracting SARS-CoV-2 infection.
- The treatment regimes in both arms may impair the patients' immune system. This may lead to an increased risk of acquiring a SARS-CoV-2 infection with subsequent occurrence of COVID-19 including complications up to death.
- Deviations on the treatment regimen, e.g. delays and interruptions, related to the COVID-19 crisis, can negatively influence the efficacy of the drugs and thus the benefit for the patients on trial

COVID-19 vaccination:

As per the European Medicines Agency (EMA):

If physicians decide to administer SARS-CoV-2 vaccines in patients enrolled in the study, decisions should be individualised based on the risk of SARS-CoV-2 complications and potential benefit from the vaccine, general condition of the patient and the severity of COVID-19 outbreak in a given area or region and in accordance with the vaccine label. Furthermore, the Country guidelines and/or institutional guidelines must be followed.

Treatment schedule should not be altered because of the COVID-19 vaccination.

The administration of a SARS-CoV-2 vaccine stating the name of the vaccine used (e.g. Moderna, Pfizer BioNTech, AstraZeneca Oxford, …) shall be added in the concomitant medication form in the eCRF and noted in the patient's medical file. Any possible vaccine related AE should be captured in the AE forms in the eCRFs, specifying the potential relationship to the vaccine.

Proposed measures for patients already enrolled during the COVID-19 crisis and recruitment

The study coordinators in collaboration with EORTC, propose the following guidelines as long as the current COVID-19 crisis is ongoing.

Please ensure that any protocol deviations resulting from COVID-19 are:

Adequately documented in the eCRFs as well as the patient's medical records or in a Note to file (NTF) to be stored in your Study binder (ISF)

Always specify the reason of the deviation: "COVID-19"

All COVID-19 related deviations have to be reported to EORTC HQ via 1709@eortc.org

1. Recruitment of new patients

The trial is closed to recruitment.

2. Guidelines for study assessments

2.1 With respect to study imaging procedures:

For the baseline study imaging procedures, the protocol requirements have to be fully met.

For on-study imaging procedures, it is preferred that the patient have imaging performed at the investigative site as directed in the protocol.

If difficulties are encountered to perform the imaging as per the protocol, there are several possibilities, in order of preference:

Have the imaging performed offsite, locally according to the protocol-specified timing. Guidance should be given by the site to the local imaging facility about conducting scans according to all applicable requirements (modality etc. as per 1709 Imaging Guidelines).

Have the imaging performed at the site but delayed to a significant extend (a window of 2 weeks instead of 1 week will be allowed) due to travel restriction/safety of the participant.

Have the imaging performed offsite but delayed (a window of 2 weeks instead of 1 week will be allowed) due to travel restriction/safety of the participant.

Skip the imaging only if impossible to perform due to travel restriction/safety.

For all above situations, site needs to report this in the comment fields of the applicable CRFs as well as in the Source Data.

2.2 With respect to study treatments:

In general, patients with a deadly cancer such as glioblastoma should receive the best possible treatment, also during the ongoing pandemic. Withholding or interrupting tumour-specific treatment should therefore be avoided whenever possible. For the ongoing EORTC-1709 (MIRAGE) trial, the goal is therefore – taking in account directives of local and national authorities - to treat patients as closely to the protocol guidelines as possible, without endangering their safety and keeping the risk/benefit ratio for the patient acceptable.

Patients on treatment will be treated as per protocol, in both arms. Protocol assessments should be performed as per protocol as much as possible. Again, taking in account local and/or national directives.

Assessments should be done at the investigative site if possible.

In the event it is not possible or not in the best interest of a patient to travel to the treating site because of COVID-19, the following options are proposed (depending whether IMP administration is required during the visit):

If assessments are required prior to study treatment administration, as stated in the protocol (chapter 6, “Clinical evaluation, laboratory tests and follow-up”) and administration of study treatment cannot be postponed the following should be considered:

Arrange the exact date of the visit (and time) in the centre and perform the assessments in advance

Provide standard laboratory assessments (as described for the respective visit in chapter 6 “Clinical evaluation, laboratory tests and follow-up”) of the subject either by qualified staff of contracted laboratories or contractually secured healthcare providers whom employ appropriate safety measures and excludes patients whom are quarantined or living with or have been quarantined with a confirmed COVID-19 case

Treatment related laboratory exams can be done in certified offsite facilities.

Visits that do not involve administration of study treatment, and that cannot be met because of the COVID-19 crisis, can be replaced by a telephone consultation.

These deviations will not to be considered as protocol violations and must be documented clearly both in the eCRFs as well as in the patients' medical file on site as a COVID-19-related deviation (please specify every deviation in the eCRF with “COVID-19”). All other COVID-19-related deviations to the protocol will be documented equally. In case of doubt, the 1709 medical monitor can always be contacted to discuss (1709medmon@eortc.org). COVID-19-related deviations will not be considered protocol violations as long as they do not endanger the safety of the patient.

With respect to Marizomib (MRZ):

It is advised to follow protocol treatment as closely as possible under the present circumstances for both treatment arms, in the best interest of the patient. Skipping or interrupting treatment will also follow the protocol guidelines, the same as for toxicities or non-toxicities (see chapter 5 of the protocol “Therapeutic regimens, expected toxicity, dose modifications”). Interruptions exceeding the described period (e.g., 3 consecutive marizomib administrations or a full cycle in both arms) must be discussed with the medical monitor

(1709medmon@eortc.org) to decide if it is still in the best interest of the patient to restart the treatment or further delay.

Marizomib (MRZ), seen the parenteral administration (IV) and the tight timelines between start of reconstitution and start of administration, must be administered at your institution. Delays and skipping of administration are allowed as described in the protocol (chapter 5 “Therapeutic regimens, expected toxicity, dose modifications”).

With respect to Temozolomide (TMZ)

TMZ will continue to be distributed to the patient as per the sites local practice.

2.3 With respect to patient physical visits:

Patient physical visits which do not require study treatment administration or are not crucial for the safety of the patient can be changed in phone visits where needed.

2.4 With respect to patient reported data:

Quality of Life (QoL) questionnaires can be collected through phone or a video conference. Voice scripts are available on the study web documentation.

If phone assessment cannot be arranged, the QoL questionnaires can be collected by providing the questionnaires to the patients. Patients should be instructed to complete the questionnaires within the intended timepoint (according to protocol). Patients should also complete the date on the form with the date they completed the questionnaire. Sites are requested to make their own guidelines to patients in their own language.

MMSE and neurocognitive testings cannot be collected through phone or video conference. If impossible to perform due to travel restriction/safety, a protocol deviation should be documented as this is not according to protocol.

2.5 With respect to collection of biomaterial:

If the collection of a sample is part of the inclusion criteria (FFPE tumor tissue block or 24 unstained slides) and if impossible to collect the sample(s) due to travel restriction and/or safety concerns, the patient cannot be enrolled in the trial.

The collection of sample(s) can be skipped only if all following (2) criteria are met

- The HBM samples are not part of the inclusion criteria and
- The collection of the HBM samples is impossible to perform due to travel restrictions and/or safety concerns.

If these 2 criteria are fulfilled, the sample collection can be skipped and a deviation must be entered, as this was not according to the protocol.

2.6 With respect to collection of RTQA

Concerning the mandatory central review of the treatment plan for the first two patients per site, we acknowledge that timely submission of the data by investigators and review by our reviewers may not be feasible during this pandemic with reduced personnel. We ask that you continue to send the data for all patients (those for prospective or retrospective review) as soon as possible and we will continue to send the cases to our reviewers asking also for their evaluation as soon as possible. Despite this, as a temporary measure, please do not hold up a patient’s treatment waiting for review and proceed as planned. We will inform you when processes should be returned to timely reviewing.

2.7 With respect to on-site monitoring visits

All on-site monitoring visits are currently suspended. CRAs will contact your staff to schedule the next monitoring visit, when the situation will evolve positively and in compliance with the Governments and sites recommendations. In the meantime, EORTC 1709 study team will keep in touch with your staff to provide any support deemed necessary.

3. Serious adverse event reporting:

- Sites should follow the SAE reporting as described in the protocol e.g. the sites should continue to report SAEs immediately and no later than 24 hours from the time the investigator or site staff became aware of the event, as described in the protocol. There are no specific adaptations to the protocol defined SAE reporting procedure due to COVID-19.
- Should sites have any SAE reporting related questions, please contact us at pharmacovigilance@eortc.org
- Should there be a suspected or confirmed serious case of COVID-19 infection, report it as SAE:
    - Please remember to provide the mandatory SAE information as per protocol and as per the CRF completion guidelines.
    - Please indicate if the COVID-19 infection was confirmed by a test.
    - Please provide as much information as available.

4. Informed consent

In all participating countries, except Germany, if an amendment is currently ongoing requiring re-consent of already enrolled patients and/or additional consent is necessary for the implementation of new urgent changes in trial conduct (mainly expected for reasons related to COVID-19), alternative ways of obtaining such re-consents should be considered during the pandemic e.g. contacting the trial participants via phone or video-calls and obtaining oral consents supplemented with email confirmation. Any consent obtained this way should be documented and confirmed by way of normal consent procedures at the earliest opportunity when the trial participants will be back at the regular sites.