

Intergroup Study (EORTC 26053_22054)

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Phase III trial on Concurrent and Adjuvant Temozolomide chemotherapy in non-1p/19q deleted anaplastic glioma. The CATNON Intergroup trial.

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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 chapters or other collaborative group(s) specific appendix and unless otherwise specified).

The chapters 18 to 21 and the PIS/IC (Appendix F, Appendix G, Appendix H,) 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 18-21 (unless otherwise specified).

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Protocol summary

Title of the Study	Phase III trial on Concurrent and Adjuvant Temozolomide chemotherapy in non-1p/19q deleted anaplastic glioma. The CATNON Intergroup trial.
Objective(s)	This trial is a follow up study of EORTC 26981 and of EORTC 26951 addressing the overall strategy of optimizing the treatment in newly diagnosed anaplastic glioma patients without combined 1p/19q loss. Patients will be randomized immediately after surgery to one of the four following therapeutic options: Arm 1 : RT alone (and further treatment including chemotherapy at progression) Arm 2 : RT & concurrent CT Arm 3 : RT + adjuvant CT Arm 4 : RT & concurrent CT + adjuvant CT Twelve months of adjuvant treatment is foreseen. Patients will be included based on the 1p/19q status of the tumor. Centers with known expertise in 1p/19q testing will be allowed to include patients based on local testing, with central review for 1p/19q testing (and histology). For sites without access to 1p/19q testing a central facility will be created. Methylation status of the MGMT promoter gene will be a stratification factor. Primary objectives: To assess whether concurrent radiotherapy with daily temozolomide chemotherapy improves overall survival as compared to no daily temozolomide in non-1p/19q deleted anaplastic glioma. To assess whether adjuvant temozolomide chemotherapy improves survival as compared to no adjuvant temozolomide chemotherapy in non-1p/19q deleted anaplastic glioma
Methodology	Phase III – difference
Number of patients Number planed (Statistical design) Number analyzed	This is a 2 by 2 factorial design with Overall Survival as the primary endpoint when comparing: Patients receiving RT alone or RT + adjuvant TMZ to those receiving RT & concurrent TMZ or RT & concurrent TMZ + adjuvant TMZ. [<u>Comparison I</u>]: test for superiority of the concurrent TMZ chemotherapy] Patients receiving RT alone and RT & concurrent TMZ to those receiving RT + adjuvant TMZ or RT & concurrent TMZ + adjuvant TMZ. [<u>Comparison II</u>]: test for superiority of the adjuvant TMZ chemotherapy] For both comparisons, to detect a reduction of the risk of death of 22.5% based on a two-sided logrank test, at an overall significance level of 5% and a power of 83%, a total of 534 events are needed. With an estimated accrual rate of 150 patients per year, a total of 748 patients can be recruited in 5 years. A minimum follow-up of 2 ½ years will be needed to observe the events. One interim analysis for efficacy only is planned when 41% of the

	events have been observed (219). To perform this interim look 11 additional events were necessary to preserve the study power.
Diagnosis and main criteria for inclusion	Histologically confirmed newly diagnosed anaplastic oligodendroglioma, anaplastic oligoastrocytoma or anaplastic astrocytoma by local diagnosis and absence of combined 1p/19q loss Availability of tumor material for central 1p/19q assessment, central MGMT promoter methylation assessment and central pathology review Previous surgery for a low grade tumor is allowed, provided histological confirmation of an anaplastic tumor is present at the time of progression WHO performance status 0-2 Age $\geq$ 18 years Start of radiotherapy within 8 days from randomization Start of radiotherapy within 7 weeks (49 days) from surgery No prior chemotherapy No prior radiotherapy to the brain
Treatment Test product, dose and mode of administration	Radiotherapy (arms 1-4) Radiotherapy will consist of a conventionally fractionated regimen, delivering a total dose of 59.4 Gy in 6.5 weeks, in a once daily schedule of 1.8 Gy per fraction for a total of 33 fractions. Concomitant temozolomide (arms 2 & 4) Patients randomized to concomitant temozolomide will receive temozolomide continuously at a daily dose of 75 mg/m² during radiotherapy. The drug will be administered orally 1 hour before each session of radiotherapy during weekdays. During weekends without radiotherapy, the drug will be taken in the morning. The dose administered will be determined using the body surface area (BSA) calculated at the beginning of the concomitant treatment. The daily dose will be rounded to the nearest 5 mg. Adjuvant temozolomide (arms 3 & 4) Patients randomized to adjuvant temozolomide will start adjuvant temozolomide after a 4 week resting period after the end of radiotherapy. Temozolomide will then be administered orally once a day for 5 consecutive days (days 1-5). The starting dose for the first cycle will be 150 mg/m²/day with a single dose escalation to 200mg/m²/day in subsequent cycles if no significant toxicity is observed in the first cycle. The dose administered will be determined using the BSA calculated at the beginning of each treatment cycle. The dose will be rounded to the nearest 5 mg.

Duration of treatment	Concomitant temozolomide (arms 2 & 4) The concomitant temozolomide is scheduled to last for 6.5 weeks according to the radiotherapy schedule during which temozolomide will be administered on a daily basis for a maximum of 7 weeks in case of radiotherapy delays. Adjuvant temozolomide (arms 3 & 4) One cycle is defined as 28 days and a maximum of 12 cycles will be administered.
Reference therapy, dose and mode of administration	Radiotherapy (arm 1-4) Radiotherapy will consist of a conventionally fractionated regimen, delivering a total dose of 59.4 Gy in 6 weeks 3days, in a once daily schedule of 1.8 Gy per fraction for a total of 33 fractions.
Criteria for evaluation	
Efficacy	Overall survival (OS) All patients will be followed until death. The duration of survival is the time interval between randomisation and the date of death due to any cause. Patients not reported dead and lost of follow up will be censored on the date of their last visit. Progression-free survival (PFS) Disease progression is defined as radiological or neurological/clinical progression (which ever occurs first); progression free survival (PFS) is the time interval between the date of randomization and the date of disease progression or death which ever occurs first. If neither event has been observed, the patient is censored at the date of the last follow up examination Neurological deterioration free survival This study will assess neurological deterioration as a secondary endpoint to investigate if the prolongation of progression free survival translates into a better preservation of neurological function. Neurological deterioration is defined as a decrease in WHO performance status. Quality of Life analysis will also be used to assess neurological deterioration free progression.
Safety	This study will use the International Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, for toxicity and adverse event reporting.

Statistical methods	For the primary analysis of OS and PFS, two-sided superiority logrank tests will be computed at an overall significance level of 5%. The Kaplan-Meier technique will be used to obtain estimates of the OS and PFS. The Cox proportional hazard model will be fitted with the treatment and the following adjustment factors: WHO performance status (PS 0 vs >0), Age (≤ 50 vs > 50), Presence of 1p loss (Yes vs No), Presence of oligodendroglial elements (Yes vs No). The MGMT promoter methylation status will be used as a stratification factor. Changes in MMSE scores over time will be analyzed. The distributions in treatment arms will be compared at each evaluation point using a Chi-square test for trend. A Bonferroni adjustment of the type I error rate will be used to correct for multiple tests.
Central pathology Translational research	Central pathology review will be performed. Upfront assessment of 1p/19q LOH is mandatory Following registration of the patient as soon as possible after surgery the following material must be sent: A paraffin embedded tumor sample (preferably a tumor block, otherwise 30 unstained slides) 20 ml whole blood collected in an EDTA tube the pathology review and 1p/19q review reports Following central pathology review, central 1p/19q assessment, MGMT promoter methylation status determination and IDH mutation analysis, the H&E stained slides will be entered into the EORTC virtual tumor bank.
Quality of Life	The main objective of QoL assessment within this clinical trial is to determine the impact of no adjuvant chemotherapy versus adjuvant therapy until progression for anaplastic glioma on overall health/QoL. Based on the recent EORTC study 26981, the hypothesis is that we expect no differences between arms using the global QOL scale during treatment, but there may be a later benefit to the adjuvant therapy arm if disease progression is achieved, thereby leading to a better global QOL.

Trial organization

- ◆ This trial is an Intergroup Trial, jointly conducted by several national/international cancer clinical research groups in different countries of European Union and third countries.
- ◆ Each participating group is the Sponsor for their participants (unless otherwise agreed).
- ◆ In summary:

Country	Recruiting group(s)	Sponsor
Canada	NCIC	NCIC
United Kingdom	MRC	EORTC
United States	RTOG	RTOG
Australia/New Zealand	COGNO CTC	COGNO CTC
Other countries	EORTC	EORTC

- ◆ The EORTC is the coordinating group in this trial and therefore centrally manages 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 participating group / Sponsor locally manages the notification/submission of all necessary documents to the Competent Authorities and/or Ethics Committees and gets 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 17 are fully applicable to all groups. Chapters 18-21 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 in the Group Specific Appendixes annexed at the end of the protocol.
- ◆ The patient information sheets and informed consent templates (Appendix F, Appendix G, Appendix H) 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 or of your national group (should you have any difficulty in identifying such a group, please contact the EORTC Headquarters).
- ◆ Investigators members of several groups participating to the trial should select one of these groups for the framework of this trial and 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).
- ◆ The investigational drug will be supplied by Merck.
- ◆ This is an academic trial with an educational grant support from Merck.

1 Background and introduction

1.1 Anaplastic glioma

About 20-30% of all newly diagnosed primary brain tumors in adults are considered to be WHO grade III tumors or anaplastic glioma: anaplastic astrocytoma, anaplastic oligoastrocytoma and anaplastic oligodendroglioma. Usually, patients who are newly diagnosed with these tumors are treated similarly to patients with glioblastoma multiforme, the most malignant primary brain tumor in adults. It is unclear whether that assumption is correct. Recent studies show that anaplastic glioma differ both at the clinical level and at the molecular level from glioblastoma multiforme (and from grade II tumors). For example, an important difference exists between recurrent anaplastic oligodendroglioma, oligoastrocytoma or astrocytoma and recurrent glioblastoma multiforme in sensitivity to PCV or temozolomide chemotherapy.(Ref. 1, Ref. 2, Ref. 3, Ref. 4, Ref. 5) Genetic analysis has shown that oligodendroglioma are characterized by combined loss of 1p/19q which can be found in 60-70% of anaplastic oligodendrogliomas but which is much less frequent in anaplastic oligoastrocytoma.(Ref. 6, Ref. 7) In particular these 1p/19q loss tumors are now known to be very sensitive to chemotherapy, with virtually all tumors responding to PCV chemotherapy.(Ref. 8)

1.1.1 Molecular classification of anaplastic glioma

Because of the sensitivity to chemotherapy of oligodendroglial tumors both the RTOG and EORTC have investigated whether these tumors benefit from adjuvant PCV chemotherapy. These studies, EORTC study 26951 and its North-American counterpart RTOG 9402, both showed that the addition of (neo)adjuvant PCV chemotherapy (consisting of procarbazine, CCNU and vincristine) to 59.4 Gy radiotherapy does increase progression free survival (PFS) without improving overall survival in anaplastic oligodendroglioma and anaplastic oligoastrocytoma.(Ref. 9, Ref. 10) A major finding of both studies is the large difference in prognosis of patients with and without combined 1p/19q loss. In patients with 1p/19q loss median survival is well over 6-7 years, but only 2-3 years for patients without 1p/19q loss. The latter survival in non-codeleted anaplastic glioma is in line with the survival usually observed in anaplastic astrocytoma. Based on these differences in survival and the clear different outcome in anaplastic oligodendroglioma with 1p/19q loss, it is no longer rational to treat these patients according to histology without taking the genotype of these tumors into account. For this and other current neuro-oncological studies it is therefore proposed to classify high grade glioma into glioblastoma multiforme (median survival 12-15 months), anaplastic glioma without 1p/19q loss (median survival 2-3 years) and anaplastic oligodendroglial tumors with loss of both 1p and 19q (1p/19q co-deleted; median survival more than 6-7 years). The present study proposal considers the non-1p/19q co-deleted anaplastic glioma.

1.1.2 Concomitant and adjuvant temozolomide in anaplastic glioma

The recent large randomized EORTC study 26981-22981/NCI-C CE3 showed that combined radiotherapy and temozolomide chemotherapy provides a superior outcome for patients with newly diagnosed glioblastoma as compared to adjuvant treatment with radiotherapy only.(Ref. 11) Correlative studies suggest that the benefit of combined alkylating agent chemotherapy and radiotherapy may be limited to patients whose tumors have a methylated (and thus silenced) MGMT gene promoter (Ref. 12). It is however far from clear that these results can be extrapolated to anaplastic glioma without 1p/19q loss.

Both toxicity and efficacy issues may be different for anaplastic glioma as compared to glioblastoma multiforme. Reviews of old RTOG/ECOG studies suggested a decreased survival in more aggressively treated anaplastic astrocytoma patients (Ref. 13). These data were obtained from

historical comparisons over several trials, so the conclusions should be viewed with caution. Similarly though, in contrast to the reported 40-50% response rates to temozolomide if given prior to irradiation in newly diagnosed glioblastoma, trials of pre-irradiation chemotherapy in anaplastic glioma yielded disappointing response rates, with only 17% to 30% of patients responding.(Ref. 14, Ref. 15, Ref. 16, Ref. 17) Radiotherapy may cause delayed neurological side-effects, in particular a subacute leuko-encephalopathy with mental slowing, memory disturbances, gait disorder and micturition problems. It is at present not known whether combined modality treatment with radiotherapy and temozolomide increases delayed neuro-toxicity in patients with longer survival. The study of combined modality treatment in glioblastoma did not explore whether this increased late toxicities. Other treatments in which radiotherapy to the brain was combined with chemotherapy (e.g., primary CNS lymphoma) do suggest however that there may be a real risk. This becomes an even more relevant question in patients with a better prognosis who are at risk of developing these toxicities over a longer period of time.

Thus, it cannot be taken for granted that approaches leading to a better outcome in glioblastoma will also provide a superior outcome in anaplastic astrocytoma.

1.1.3 The relevance of progression free survival

Both EORTC study 26951 and RTOG 94-02 showed an increase of progression free survival after adjuvant treatment. Many glioma patients deteriorate at the time of progression, and thus prolonging time to progression may help to keep patients in a good clinical condition for a longer period. Thus, postponing progression in patients with glioma (either low grade or high grade) may have a significant impact on the quality of life. This has not yet been investigated however with proper measures in any of the large randomized phase III neuro-oncological trials.

1.1.4 Further considerations for anaplastic glioma

Neither the role of adjuvant chemotherapy after radiotherapy nor the role of concurrent chemo-irradiation has been established in anaplastic glioma. Various surveys among clinicians underline the absence of evidence based consensus on how to treat these patients: different institutions have adopted various strategies, including radiotherapy only, radiotherapy followed by adjuvant chemotherapy (with a variety of regimens), and concurrent chemo-irradiation with or without further adjuvant treatment.

Moreover, if indeed adjuvant treatment does not increase overall survival in this patient population (as suggested by both EORTC 26951 and RTOG 9402), postponing chemotherapeutic treatment until recurrence will avoid the continuation of an inactive treatment in unresponsive patients. This would shorten initial treatment considerably, and would be an argument to stop treatment at the end of irradiation and to withhold further treatment until progression. On the other hand, postponing progression by adjuvant treatment may help to keep patients in a better condition.

Because of significant toxicity of the PCV regimen in EORTC 26951 and RTOG 9402 studies (Ref. 9, Ref. 10) and good tolerability of temozolomide overall and in the EORTC 26981 study (Ref. 11), temozolomide serves as preferred drug for future trials of radiochemotherapy.

These considerations and the concern for late toxicities require a prospective trial to examine the role of adjuvant and concurrent temozolomide chemotherapy in non-1p/19q co-deleted anaplastic glioma.

1.2 Study outline

The present study will establish whether concurrent and adjuvant temozolomide improves the outcome of patients with non-codeleted 1p/19q anaplastic gliomas. Patients will be randomized in a 2 x 2 design to radiotherapy (with further treatment including chemotherapy if indicated at the time of progression), radiotherapy with concurrent temozolomide, radiotherapy followed by adjuvant temozolomide and radiotherapy with concurrent temozolomide followed by adjuvant temozolomide. In view of the large impact of methylation of the MGMT promoter gene on the outcome in glioblastoma, patients will be stratified for MGMT status. Molecular diagnostic assessment of both MGMT and 1p/19q status prior to the start of radiotherapy is required. Patients will be followed after progression to assess whether the initial treatment with temozolomide prolongs time to neurological deterioration. An abbreviated neuro-psychological test will establish whether initial treatment with temozolomide increases the risk of treatment-related cognitive deterioration.

Patients can be randomized on the basis of either local histological and 1p/19q diagnosis, or on central histological and 1p/19q diagnosis. The patients will first be registered to the trial. At this step, for all patients tumor and blood samples must be sent for histology review, 1p/19q analysis and MGMT assay. If inclusion is based on central pathology and 1p/19q diagnosis the patient can be randomized into the trial once found eligible at central assessment. Centers must decide prior to study activation whether they will include patients based on local or on central diagnosis of histology and 1p/19 status.

2 Objectives of the trial

2.1 Primary objectives

- ◆ To assess whether concurrent radiotherapy with daily temozolomide chemotherapy improves overall survival as compared to no daily temozolomide in patients with non-1p/19q deleted anaplastic glioma.
- ◆ To assess whether adjuvant temozolomide chemotherapy improves survival as compared to no adjuvant temozolomide chemotherapy in patients with non-1p/19q deleted anaplastic glioma

2.2 Secondary objectives

- ◆ To assess whether concurrent and adjuvant temozolomide treatment prolongs progression free survival and neurological deterioration free survival in patients with non-1p/19q deleted anaplastic glioma.
- ◆ To assess the safety of concurrent and adjuvant temozolomide in patients with non-1p/19q deleted anaplastic glioma, including late effects on cognition.
- ◆ To assess the impact of concurrent and adjuvant temozolomide treatment on the quality of life in patients with non-1p/19q deleted anaplastic glioma.

2.3 End-points

2.3.1 Primary endpoint

The primary endpoint of the study is overall survival, as measured from the day of randomization.

2.3.2 Secondary endpoints

Secondary endpoints of the study are progression free survival, neurological deterioration free survival, quality of life, toxicity, and development of cognitive deterioration.

3 Patient selection criteria

All patients are initially registered into the trial as soon as possible after surgery. After this point, material must be sent for 1p/19q analysis and MGMT promoter methylation assay. This should again be done as soon as possible. Patients can only be randomized into the trial within 8 days from the start of radiotherapy; at this time, all baseline requirements for the study must have been fulfilled.

3.1 At the time of registration

- ◆ Histologically confirmed newly diagnosed anaplastic oligodendroglioma, anaplastic oligoastrocytoma or anaplastic astrocytoma by local diagnosis
- ◆ Availability of tumor material for central 1p/19q assessment, central MGMT promoter methylation assessment and central pathology review.
- ◆ Previous surgery for a low grade tumor is allowed, provided histological confirmation of an anaplastic tumor is present at the time of progression
- ◆ WHO performance status 0-2
- ◆ Age ≥ 18 years
- ◆ All patients must use effective contraception if of reproductive potential. Females must not be pregnant or breast feeding
- ◆ Absence of known HIV infection, chronic hepatitis B or hepatitis C infection
- ◆ Absence of any other serious medical condition that can interfere with follow-up
- ◆ Absence of any medical condition which could interfere with oral medication intake (e.g., frequent vomiting, partial bowel obstruction)
- ◆ No previous other malignancies, except for any previous malignancy which was treated with curative intent more than 5 years prior to registration, and except for adequately controlled limited basal cell carcinoma of the skin, squamous carcinoma of the skin or carcinoma in situ of the cervix.
- ◆ Absence 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
- ◆ No prior chemotherapy (including no treatment with BCNU containing wafers (Gliadel®))
- ◆ No prior radiotherapy to the brain
- ◆ Before patient registration, written informed consent must be obtained, according to ICH/GCP, and national/local regulations.

3.2 Randomization step

- ◆ The combination of:
 - ◆ Histologically confirmed newly diagnosed anaplastic oligodendroglioma, anaplastic oligoastrocytoma or anaplastic astrocytoma by local diagnosis
 - AND
 - ◆ Absence of combined 1p/19q lossboth of which must have been determined by either local testing or central review
- ◆ Availability of tumor material for central 1p/19q assessment, central MGMT promoter methylation assessment and central pathology review
- ◆ WHO performance status 0-2
- ◆ Age ≥ 18 years
- ◆ Previous surgery for a low grade tumor is allowed, provided histological confirmation of an anaplastic tumor is present at the time of progression
- ◆ Start of radiotherapy within 8 days from randomization
- ◆ Start of radiotherapy within 7 weeks (49 days) from surgery (extra 2 days could be allowed)
- ◆ Patients must be on a stable or decreasing dose of steroids for at least two weeks
- ◆ No prior chemotherapy (including no treatment with BCNU containing wafers (Gliadel®))
- ◆ No prior radiotherapy to the brain
- ◆ No concomitant treatment with other anti-cancer agents or with any other experimental agent
- ◆ Adequate hematological, renal and hepatic function according to all of the following laboratory values (to be performed within 28 days prior to randomization):
 - ◆ neutrophils greater or equal to 1.5×10^9 cells/l
 - ◆ platelets greater or equal to 100×10^9 cells/l
 - ◆ bilirubin < 1.5 times upper limit of laboratory normal
 - ◆ alkaline phosphatase, ASAT and ALAT < 2.5 times upper limit of laboratory normal
 - ◆ serum creatinine lower than 1.5 times upper limit of laboratory normal
- ◆ All patients must use effective contraception if of reproductive potential. Females must not be pregnant or breast feeding
- ◆ Absence of known HIV infection, chronic hepatitis B or hepatitis C infection
- ◆ Absence of any other serious medical condition that could interfere with follow-up
- ◆ Absence of any medical condition which could interfere with oral medication intake (e.g., frequent vomiting, partial bowel obstruction)
- ◆ Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.
- ◆ Before patient randomization, written informed consent must be given according to ICH/GCP, and national/local regulations.

- ◆ Patients with a buffer range from the normal values of $\pm 5\%$ for hematology and $\pm 10\%$ for biochemistry are acceptable.

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 randomized phase III study investigates the optimal treatment in patients with newly diagnosed anaplastic glioma without combined 1p/19q loss. Patients will be randomized after surgery to one of the four following therapeutic options:

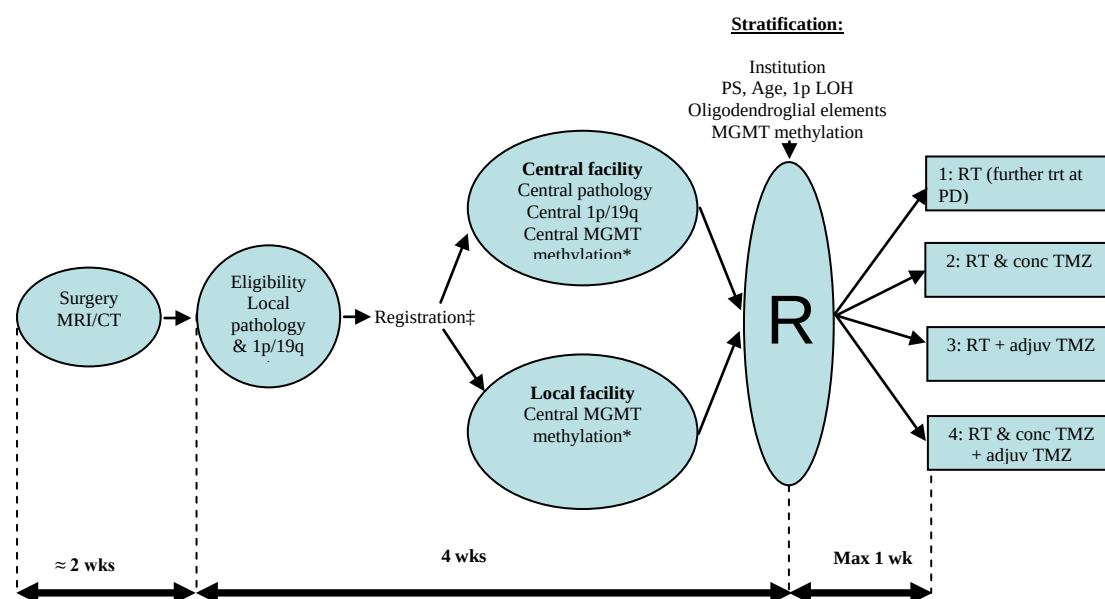
Arm 1: Radiotherapy and further treatment including chemotherapy if indicated at progression

Arm 2: Radiotherapy & concurrent temozolomide

Arm 3: Radiotherapy + adjuvant temozolomide for 12 cycles

Arm 4: Radiotherapy & concurrent temozolomide + adjuvant temozolomide for 12 cycles

For patients randomized to receive adjuvant temozolomide, twelve months of adjuvant treatment is foreseen. Patients will be included based on the 1p/19q status of the tumor. Centers with known expertise in 1p/19q testing will be allowed to include patients based on their local diagnosis, with central review for both the histological diagnosis and 1p/19q testing. For sites without access to 1p/19q testing a central facility is available. Methylation status of the MGMT promoter gene will be a stratification factor. Clinical follow-up must be continued after the diagnosis of first progression to allow assessment of time to neurological deterioration and to assess Quality of Life.



† Institution must choose to evaluate 1p/19q LOH locally or use central facility.

‡ After registration, all material is centrally reviewed for MGMT methylation status.

* Investigators can't randomize a patient:

- If the central facility is used: before the histological diagnosis, diagnosis of no combined 1p/19q LOH has been centrally confirmed and the MGMT methylation status (methylated/unmethylated or indeterminate) has been communicated by the EORTC Data Centre. The randomization is based on the central histological and 1p/19q LOH evaluation.

- If the local assessment is used: before the MGMT methylation status (methylated/unmethylated or indeterminate) has been communicated by the EORTC Data Centre. The randomization is based on the local histological and 1p/19q LOH evaluation.

5 Therapeutic regimens, expected toxicity, dose modifications

5.1 Drug information

5.1.1 Temozolomide

5.1.1.1 General information

Temozolomide is commercially available.

5.1.1.2 Packaging, dispensing and storage

Temozolomide is available as hard gelatin capsules (5mg, 20mg, 100mg, 250mg).

Temozolomide should be stored between +2°C - +30°C and protected from moisture.

Temozolomide should be administered in a fasting state at least one hour prior to eating.

5.1.1.3 Temozolomide accountability

The investigator/pharmacist must maintain an accurate record of dispensing of temozolomide in a drug accountability ledger, a copy of which must be given to EORTC at the end of the study. An accurate record of the date and amount of study drug dispensed to each patient must be available for inspection at any time.

5.2 Initial dose and schedule

5.2.1 Radiotherapy

Radiotherapy will consist of a conventionally fractionated regimen, delivering a total dose of 59.4 Gy in 6.5 weeks, in a once daily schedule of 1.8 Gy per fraction for a total of 33 fractions.

Treatment should start within 7 weeks of surgery and 8 days from randomization

A single phase treatment volume will be used throughout treatment – a cone-down or boost volume is not normally used (other than for shielding organs which have reached a tolerance limit e.g optic chiasm at 55 Gy).

Whenever possible, target volume definition should be based on magnetic resonance imaging (MRI). Image fusion (= co-registration) of the MRI scans and the planning CT scan should be used for target volume definition. Centers having the possibility of image co-registration should use this technique for all trial patients. The accuracy of image co-registration should remain within < 0.5 cm. Post-operative imaging after resection and debulking is preferable.

CT-based 3-D treatment planning using beam's-eye-view and the registration of Dose-Volume-Histograms is mandatory for all centers.

5.2.1.1 Gross Tumor Volume

The Gross Tumour Volume (GTV) is defined by/

1. The entire region of high signal intensity on T2 weighted MRI images or FLAIR sequences (corresponding to the hypodense area on CT images).

Plus

2. The region of enhancement on post operative CT/MRI if available or the region of enhancement on pre operative CT/MRI if post op imaging is not available (usually contained in 1 above)

Plus

3. The tumour resection margin (usually contained in the above)

In some tumours no area of enhancement can be seen and the GTV is defined entirely on the T2 abnormality.

In case of complete or subtotal removal, the position of the tumour bed can have shifted, and the GTV should take the new position of the abnormalities on the planning CT scan and any post-operative imaging into account. Postoperative imaging is not mandatory, and it is acceptable to define GTV based on pre-operative scans and a planning CT.

5.2.1.2 Clinical Target Volume

The Clinical Target Volume (CTV) is defined by a 1.5 - 2 cm volumetric expansion of the GTV

The CTV extends to the contralateral hemisphere only when midline structures such as the corpus callosum and the contralateral hemisphere are invaded by tumor. The tentorium and meninges should be considered as anatomical borders and therefore a margin of 7-10 mm is sufficient to encompass the microscopic spread at these borders.

Volumetric expansion may also be reduced in areas adjacent to sensitive structures.

5.2.1.3 Planning Target Volume

The Planning Target Volume (PTV) will take into account uncertainties of planning and setup. This margin should be based upon known departmental values, but will usually be of the order of 0.5-0.7 cm.

All margins should be added using a three-dimensional (3-D) growth algorithm where possible.

5.2.1.4 Planning procedure

Patient either supine or prone depending on site of lesion, in an immobilization device (any fixation system with relocation accuracy < 5 mm).

The use of a Planning CT is mandatory. The use of a contrast medium, a maximum CT slice thickness of 3 mm in order to obtain good quality of Digitally Reconstructed Radiographs (DRR's) and margin definition is recommended.

Co-registration of CT and MRI data is strongly recommended for centers having implemented this function. For centers not having this possibility, a manual/visual fusion with the MRI shall be done.

Conventional or virtual simulation is mandatory. Planning with beams-eye-views (BEV's) of each beam is mandatory.

Use of shielding blocks or a multi-leaf collimator is mandatory.

Planning should conform to ICRU 50/62 criteria for target volume coverage, dose normalization and homogeneity. (Ref. 18)

5.2.1.5 Treatment technique

Treatment must be delivered with a linear accelerator with a minimal nominal beam energy of 4-6 MV. The volume should be treated by multiple field technique, all fields treated at each fraction.

The use of a vertex field is optional. If used it requires either a diagram or photograph of treatment position.

NOTE: the use of a strict vertex field may result in increased dose to the thyroid and whole body!

Treatment position verification is carried out by at least weekly portal imaging or portal films according to the institute's standards.

For 3DCRT: The prescription dose is specified and reported at the ICRU reference point as defined in ICRU Reports #50 and #62 [ICRU 1993; ICRU 1999].

For Intensity-modulated RT (IMRT): Treatment with IMRT is allowed provided that conventional fractionation and dose prescription according to ICRU #50 and #62 is used. No simultaneous integrated boost is allowed. IMRT will be allowed providing sufficient proof of external credentialing is submitted to and approved by EORTC QART team.

Stereotactic radiotherapy, implants, brachytherapy are NOT ALLOWED.

5.2.1.6 Acute toxicity and treatment interruption

Expected acute toxicity of conventional radiotherapy includes headache, fatigue, hair loss, skin reaction, sickness sometimes, mucositis (if nasopharynx included), temporary reduced hearing (if ear canal included), and temporary loss of taste (if nasopharynx included).

No dose adjustments are recommended irrespective of length of treatment interruptions.

Maximum overall treatment time: 7 weeks (theoretical optimal treatment time: 6.5 weeks).

Individual reasons for treatment interruption, such as major worsening of neurological or mental status or any other medical condition that would preclude the continuation of radiotherapy, and conversely the decision to resume radiation therapy after interruption, will be taken on an individual basis by the local investigator.

5.2.1.7 Dose prescription, fractionation

Dose prescription and recording will according to ICRU 62-criteria. Dose homogeneity requirements in the PTV shall be -5% + 7%. The PTV should be encompassed by the 95% isodose.

The 90% isodose is acceptable in close proximity to organs-at-risk.

Total dose: 59.4 Gy; dose per fraction: 1.8 Gy in 33 daily fractions

5.2.1.8 Dose Limitation to Critical Structures

Organs-at-risk to be spared if possible-are: eyes, pituitary gland, optic chiasm, optic nerves, brainstem, ear, uninvolved brain areas.

The optic chiasm, optic nerves and brainstem (= medulla, pons and midbrain) should not receive doses higher than 60 Gy.

The eye balls including the lens and retina should not be included in any direct beam. Maximum dose for the lens: < 5 Gy, for the retina: ≤ 36 Gy.

The normal brain contralateral to the tumor location may not receive > 60% of the total dose.

5.2.1.9 Dose reporting

The isodose distributions will be calculated and printed for documentation in three planes (transverse, coronal and sagittal planes) through the isocentre.

Isodose distributions with marked PTV and isodose lines with the maximum dose, 100%, 95%, 90%, 80%, 60%, 50%, 40%, 20% of the prescription dose should be reported for a reviewer to judge the adequacy of target coverage.

The following volumes should be calculated and documented in cm³: GTV, CTV, PTV and the total volume of the brain tissue (exclusive of PTV) as well as dose volume histograms of PTV and organs-at-risk.

Weekly portal imaging or portal films will be undertaken for set-up verification

5.2.1.10 Potential Late Complications

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) 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 3.0

5.2.2 Temozolomide

5.2.2.1 Temozolomide randomization possibilities

Patients can be randomized to a) concomitant radiotherapy and temozolomide, b) adjuvant temozolomide, c) both or d) neither (this latter randomization should be understood as temozolomide chemotherapy at the time of progression).

5.2.2.2 Concomitant temozolomide dosing during radiotherapy treatment

Patients randomized to concomitant temozolomide will receive temozolomide continuously at a daily dose of 75 mg/m² during radiotherapy. The drug will be administered orally 1 hour before each session of radiotherapy during weekdays. During weekends without radiotherapy, the drug will be taken in the morning.

The dose administered will be determined using the body surface area (BSA) calculated at the beginning of the concomitant treatment. The daily dose will be rounded to the nearest 5 mg. In case of high value of BSA, an upper limit of 2.1 m² is suggested to calculate the dose. Patients should be told to swallow the whole capsules in rapid succession without chewing them. If vomiting occurs during the course of the treatment, no re-dosing of the patient is allowed before the next scheduled dose.

5.2.2.3 Resting period following radiotherapy treatment

The radiotherapy treatment is followed by a four weeks resting period.

5.2.2.4 Temozolomide dosing during adjuvant treatment

Patients randomized to adjuvant temozolomide will start adjuvant temozolomide after a 4 week resting period after the end of radiotherapy. Temozolomide will then be administered orally once a day for 5 consecutive days (days 1-5). The starting dose for the first cycle will be 150 mg/m²/day with a single dose escalation to 200mg/m²/day in subsequent cycles if no significant toxicity is observed in the first cycle. One cycle is defined as 28 days and a maximum of 12 cycles will be administered. Treatment can be discontinued earlier in case of significant toxicity interfering with further treatment and not responding to dose reductions, or at the patient wish.

The dose administered will be determined using the BSA calculated at the beginning of each treatment cycle. The dose will be rounded to the nearest 5 mg. In case of high value of BSA, an upper limit of 2.1 m² is suggested to calculate the dose. The exact dose administered should be recorded on the CRF. Each daily dose should be given with the least number of capsules. Patients should be instructed to fast 1 hour before and one hour after administration of temozolomide. Water is allowed during the fasting period. Patients should be told to swallow the whole capsules in rapid succession without chewing them. If vomiting occurs during the course of the treatment, no redosing of the patient is allowed before the next scheduled dose.

5.2.3 Summary of initial dosages and schedules

	Concomitant/RT	Adjuvant/year 1 after RT
RT	59.4 Gy, 6.5 weeks, 1.8 Gy/fractions, 33 fractions	None
TMZ	75mg/m ² /day, maximum 7 weeks	
TMZ		150-200mg/m ² /day, D1-5, every 28 days (maximum 12 cycles)

5.3 Treatment duration

The concomitant temozolomide is scheduled to last for 6.5 weeks according to the radiotherapy schedule during which temozolomide will be administered on a daily basis. In case of delays in the delivery of the radiotherapy temozolomide will be given for a maximum of 7 weeks. Adjuvant temozolomide treatment is planned for a maximum of 12 cycles.

Treatment should be administered until documented disease progression, unacceptable toxicity, patient refusal or further treatment not in patient's best interest or until the maximum treatment duration as specified in the protocol is reached.

5.4 Withdrawal criteria

Whatever the disease status, treatment will be discontinued in case of

- ◆ Patient refusal
- ◆ Unacceptable toxicity precluding further therapy
- ◆ Best interest of the patient

Patients discontinuing therapy in the absence of progression should usually not receive other cancer treatment before their disease progresses, unless this is clearly not in the interest of the patient.

After progression, further treatment will be at the discretion of the treating physician. Any anti-cancer therapy other than the study regimen described in this protocol will not be considered as part of the protocol treatment.

5.5 Dose and schedule modifications

5.5.1 General

In the general approach of the management of toxicities it is important to define to which drug the toxicities are related. After determination of the origin of the toxicity, the drug specific procedures have to be followed. For temozolomide these procedures are described in the following chapters.

If administration of temozolomide is interrupted due to unacceptable toxicities, the **patient must be evaluated at least once a week** following demonstration of the toxicity until **resolution** of the toxicity which should occur **within 14 days** allowing for re-treatment according to the guidelines below. These evaluations include: a physical examination, vital signs, hematologic tests, serum chemistries, and assessment of adverse events and concomitant medications.

5.5.2 Radiotherapy

With the type and site of radiotherapy foreseen in this protocol, interruption due to acute radiation toxicity is unlikely. Individual reasons, such as major worsening of neurological or mental status or any other medical condition that would preclude the continuation of radiotherapy and conversely the decision to resume radiation therapy after interruption will be taken on an individual basis by the local investigator.

For example, cranial irradiation can be withheld for CNS toxicity or ototoxicity greater than or equal to grade 3 attributable to radiotherapy. The overall time of interruption and over all time of radiotherapy must be recorded. Radiotherapy should not be interrupted due to haematologic toxicities or other temozolomide related toxicities. If radiotherapy is interrupted, actions regarding dosing on concomitant temozolomide are described hereunder.

- ♦ If the administration of temozolomide (see 1.1.3) is interrupted, the radiotherapy will proceed normally and no catch up days of temozolomide will be given after the end of radiotherapy.
- ♦ The concomitant treatment will last until the end of radiotherapy and may be continued up to a maximum of 7 weeks. In case of radiotherapy delays, the duration of the concomitant treatment part will **never** exceeds 49 days.
- ♦ If radiotherapy is definitely stopped for toxicity, concomitant temozolomide is to be continued as per protocol unless progression occurs.

5.5.3 Temozolomide

5.5.3.1 Dose modifications of temozolomide during concomitant treatment

During the concomitant treatment, **no dose reductions** will be made. Delay and discontinuation will be decided according to toxicity criteria and the relationship to the study drug as defined hereunder. In case of toxicity related to temozolomide, the following actions should be taken.

Please note that the delay may not exceed 2 weeks, if toxicity is ongoing at that time, concomitant treatment with temozolomide must be discontinued.

Although most of the toxicities caused by temozolomide will be of hematological origin, according to previous studies non hematological events could be expected too: nausea and vomiting, fatigue, infections, hepatic function disturbances and rash.

Averse Drug Reaction	Value	CTCAE Grading Version 3.0	Action
Haematological			
ANC	≥ 0.5 and $< 1.5 \times 10^9/L$	2-3	Delay TMZ ¹ until normalization
ANC	$< 0.5 \times 10^9/L$	4	Stop concomitant TMZ
Platelets	≥ 25 and $< 75 \times 10^9/L$	2-3	Delay TMZ until normalization
Platelets	$< 25 \times 10^9/L$	4	Stop concomitant TMZ
Non haematological			
Except fatigue, alopecia, nausea and vomiting*		2	Delay TMZ until normalization
Except fatigue, nausea and vomiting*		3-4	Stop concomitant TMZ

* For Nausea and vomiting; please refer to section 5.6.

¹ temozolomide

5.5.3.2 Dose modification of temozolomide during the adjuvant treatment

During adjuvant treatment temozolomide dose interruptions as well as modifications are allowed.

Dose modifications are based on toxicity observed during prior treatment cycle. If multiple toxicities are seen, the dose administered should be based on the dose reduction required for the most severe grade of any single toxicity.

The possible doses of temozolomide are as follows:

Dose level	Dose mg/m ² /day (1-5)	Action
-1	100	Reduction if prior toxicity
0	150	Starting dose cycle 1
+1	200	Escalated dose as of cycle 2 in absence of toxicity

The first cycle of temozolomide is administered at the dose of 150 mg/m² d1-5. The dose is escalated at 200 mg/m² /day as of cycle 2 in absence of toxicity.

♦ Dose reduction according to worst adverse drug reaction during previous cycle

Adverse drug reaction	Value	CTCAE grading Version 3.0	Action
Haematological			
ANC and Platelets	$\geq 1.5 \times 10^9/L$ $\geq LLN$	0-1 0	Escalation to Dose Level +1 (only at cycle 2)* or continue at current dose
ANC and Platelets	≥ 1 and $< 1.5 \times 10^9/L$ ≥ 50 and $< LLN$	2 1-2	Dose unchanged
ANC and/or Platelets	$< 1 \times 10^9/L$ $< 50 \times 10^9/L$	3-4 3-4	Reduce by 1 dose level
Non haematological toxicity			
Except fatigue, alopecia, nausea and vomiting*		0-2	Escalation to Dose Level +1 (only at cycle 2)* or continue at current dose
Except fatigue, nausea and vomiting*		3	Reduce by 1 dose level
Except fatigue, nausea and vomiting*		4	Stop treatment

* the dose of temozolomide may only be increased from 150 mg/m²/day to 200 mg/m²/day as of cycle 2.

* For nausea and vomiting, please see 5.6.

A **maximum of 2 dose reductions** is permitted. However, if the same (in nature and severity) non haematological toxicity occurs at 2 subsequent cycles despite 1 dose reduction, a second dose reduction is not permitted and the patient should stop the treatment. **No dose reductions below 100 mg/m² are allowed**, if 100mg/m² is not tolerated the patient should stop treatment. Once a dose has been reduced, **no dose re-escalation** is allowed.

- ♦ Treatment delay according to worst adverse drug reaction during previous cycle

Adverse Drug Reaction	Value	CTCAE Grading Version 3.0	Action
Haematological			
ANC	$< 1.5 \times 10^9/L$	2-3-4	Delay up to 2 weeks until resolution to at least grade 1. If unresolved then stop
and/or Platelets	$< 75 \times 10^9/L$	2-3-4	
Non haematological toxicity			
Except fatigue, alopecia, nausea and vomiting*		2-3	Delay up to 2 weeks until resolution to at least grade 1. If unresolved then stop
Except fatigue, nausea and vomiting*		4	Stop treatment

- ♦ For nausea and vomiting, please see 5.6. Summary of initial dose and schedule

5.6 Concomitant medications

- ♦ Prophylactic antiemetics will be administered at the discretion of the treating physician. The prophylactic use of a 5-HT-3 antagonist is strongly recommended before the adjuvant temozolomide administration, **especially on day 1-3 and should be taken 1 hour before temozolomide is administered.** During radiotherapy with concomitant daily dose of temozolomide antiemetic prophylaxis is usually not necessary, but may be considered on the first three days.
- ♦ Corticosteroids are administered at the treating physician's discretion, but the dosage should be kept as low as possible.
- ♦ Pneumocystis carinii prophylaxis is mandatory during radiotherapy-daily temozolomide concomitant treatment. Corticosteroid therapy and continuous temozolomide therapy induce lymphocytopenia. Patients are therefore at an increased risk of opportunistic infections. Therefore a prophylaxis against Pneumocystis carinii pneumonia is mandatory. It can be either pentamidine inhalations once every 4 weeks or trimethoprim-sulfamethoxazole 960 mg 3 times a week. Prophylaxis should be continued during the entire concomitant treatment or until patients have recovered from lymphocytopenia to at least grade 1.

5.7 Prohibited medications

- ♦ No other investigational treatment should be used.
- ♦ No other anti-cancer agents.
- ♦ No growth factors unless it is vital for the patient.

6 Clinical evaluation, laboratory tests and follow-up

6.1 Immediately post-surgery: registration step

For the submission of tumor material for pre-randomization 1p/19q analysis (or review) and MGMT analysis, all patients must be registered at the EORTC Headquarters as soon as possible, and material must be sent as soon as possible, as follows:

- ◆ Submission of paraffin tumor blocks or 30 unstained sections for central pathology review, for 1p/19q LOH, and for determination of MGMT promoter methylation
- ◆ Submission 20 ml whole blood collected in EDTA tube for assessment of LOH 1p/19q

6.2 Before treatment start: randomization step

All pretreatment physical, neurological and quality of life evaluations should be performed within 2 weeks of randomization but after the surgical procedure leading to the diagnosis of anaplastic glioma. All laboratory evaluations must be carried out within 4 weeks from randomization. The initial assessment of disease with MR or CT must be performed between the surgery and the start of radiotherapy, unless patients underwent a biopsy only in which case the pre-operative imaging is sufficient (and only a CT for radiotherapy planning is required). Radiotherapy and concomitant temozolomide should be started within 8 days of randomization.

The baseline evaluations include:

- ◆ Complete medical history
- ◆ Physical examination including neurological evaluation and vital signs
- ◆ Vital signs, blood pressure, height and weight
- ◆ WHO-ECOG performance status
- ◆ Mini mental status examination (MMSE)
- ◆ Quality of Life C30 and BCM20
- ◆ Corticosteroid intake
- ◆ Complete blood counts: hemoglobin, haematocrit, white blood cells and differential, platelets.
- ◆ Serum chemistry: sodium, potassium, calcium, creatinine, urea, glucose, ASAT, ALAT, total bilirubin, alkaline phosphatase, gamma-GT, total protein, LDH.
- ◆ Toxicity according to CTCAE v.3
- ◆ Gadolinium enhanced MRI or contrast enhanced CT scan of the brain
- ◆ Fresh frozen tumor material for translational research (optional)
- ◆ Cognitive exam (dedicated centers only)

6.3 During radiotherapy treatment

6.3.1 During radiotherapy with or without concomitant temozolomide treatment

Patients are seen on a weekly basis. A more detailed evaluation will take place at week 4, week 6 (= end of radiotherapy) and 4 weeks after the end of radiotherapy. Patients treated with temozolomide during radiotherapy require monitoring for side-effects, particularly hematotoxicity.

6.3.1.1 Weekly visits

- ◆ Physical examination including vital signs
- ◆ Complete blood count (*temozolomide patients only*)
- ◆ Toxicity according to CTCAE v.3

6.3.1.2 Evaluation at week 4 and 6

- ◆ Physical examination including vital signs and neurological evaluation
- ◆ WHO-ECOG performance status
- ◆ Toxicity according to CTCAE v.3
- ◆ Complete blood count, all serum chemistries including LDH (*temozolomide patients only*)
- ◆ Corticosteroids intake

6.3.1.3 Evaluation 4 weeks after the end of radiotherapy

- ◆ Physical examination including vital signs, and neurological evaluation
- ◆ Corticosteroid intake
- ◆ MMSE
- ◆ Quality of Life C30 and BCM20
- ◆ WHO-ECOG performance status
- ◆ Toxicity according to CTCAE v.3
- ◆ Complete blood count, all serum chemistries
- ◆ Gd-enhanced MRI or contrast CT scan of the brain
- ◆ Corticosteroid intake

6.4 After the end of radiotherapy

Patients are followed every three months for disease assessment; in addition patients randomized to receive adjuvant temozolomide are followed every four weeks prior to the start of the next cycle of temozolomide.

6.4.1 Three monthly disease evaluation after the end of radiotherapy

All patients would have three monthly disease and status assessment after the end of radiotherapy.

- ◆ Physical examination including neurological evaluation
- ◆ Corticosteroid intake
- ◆ MMSE
- ◆ Quality of Life C30 and BCM20
- ◆ WHO-ECOG performance status
- ◆ Toxicity according to CTCAE v.3
- ◆ Gd-enhanced MRI or contrast CT scan of the brain
- ◆ Cognitive exam; dedicated centers only, to be carried out yearly after the start of radiotherapy (e.g., 12 months, 24 months, 36 months etc)

6.4.2 During adjuvant temozolomide treatment

Patients randomized to adjuvant temozolomide will receive twelve cycles of adjuvant temozolomide, unless treatment needs to be discontinued earlier. In addition to the disease assessments, patients will be followed during this phase as indicated hereunder:

6.4.2.1 Prior to each cycle of adjuvant therapy

- ◆ Physical examination including vital signs
- ◆ WHO-ECOG performance status
- ◆ Toxicity according to CTCAE v.3
- ◆ Complete blood count, all serum chemistries

6.4.2.2 Day 21 (+/- 48 hours) of each cycle of adjuvant therapy

This is only needed in cycle 1 and in cycle 2 if the daily dosage is increased to 200 mg/m², or in case significant hematological toxicity was observed in the prior cycle:

- ◆ Complete blood count

6.5 After the documentation of first progression

The patient must be followed every 3 months, in particular for performance status, quality of life, cognition and for documentation of further treatments.

- ◆ Physical examination including neurological evaluation
- ◆ Corticosteroid intake
- ◆ MMSE
- ◆ Quality of Life C30 and BCM20
- ◆ WHO-ECOG performance status
- ◆ Documentation of further treatments

All patients will be followed until death.

6.6 Summary table

	Baseline		During radiotherapy w/wo Concomitant treatment		4 weeks after RTX	Follow up With or without adjuvant temozolomide		After first progression Every 3 months
	At registration	Within 14 -28 days prior to random.	Weekly	Wks 4 and 6		Adjuvant treatment (bef. each cy)♣	Disease /Adverse Events assessment every 3 months	
Medical history		♦						
Phys. Exam. Vital signs		♦	♦	♦	♦	♦	♦	♦
Neurological Exam		♦		♦	♦		♦	♦
WHO-ECOG PS		♦		♦	♦	♦	♦	♦
QOL questionnaire		♦			♦		♦	♦
MMSE		♦			♦		♦	♦
Haematology		♦	♣	♣	♦	♣♫		
Serum chemistry#		♦		♣	♦	♦		
Toxicity		♦	♦	♦	♦	♦	♦	
Brain Imaging		♦(£)			♦		♦	
Corticoid intake		♦		♦	♦		♦	♦
Paraffin blocks	♦							
Frozen material		∞						
Blood samples for LOH 1p/19q	♦							
Cognitive exam		∞*						

serum chemistry: electrolytes, transaminases, gamma-GT, alkal.phosph., creatinine, LDH, glucose

♦ mandatory

♣ mandatory only for temozolomide treated patients

♫ to be repeated at day 21 of the first cycle of adjuvant temozolomide; and in case the dosage in the second cycle is increased; and in case of significant hematological toxicity during the previous cycle

∞ optional translational research, dedicated centers only; * at baseline and at yearly intervals

(£) The initial assessment of disease with MR or CT must be performed between the surgery and the start of radiotherapy, unless patients underwent a biopsy only in which case the pre-operative imaging is sufficient (and only a CT for radiotherapy planning is required).

7 Criteria of evaluation

7.1 Progression free survival

Disease progression is defined as radiological or neurological/clinical progression (which ever occurs first); progression free survival (PFS) is the time interval between the date of randomization and the date of disease progression or death which ever occurs first. If neither event has been observed, the patient is censored at the date of the last follow up examination.

PFS will be assessed following the target lesion(s) as defined hereunder.

7.1.1 Schedule of disease evaluation

The initial assessment of disease (including MRI or CT) must be performed between the surgery and the start of radiotherapy, unless patients underwent a biopsy only in which case the pre-operative imaging is sufficient.

Follow-up assessments (including MRI or CT) will be performed as described in chapter 6 here above until disease progression (even after treatment discontinuation), or until the start of another treatment.

The use of MRI is strongly recommended.

7.1.2 Definition of progression

Special attention should be given so as to avoid labeling progressive enhancement or edema which develops immediately after the end of radiotherapy as tumor progression. Pseudo-progression within the first three months from completion of radiotherapy is recognized to occur. (Ref. 19) Such pseudo-progression may continue for months, and may be accompanied by clinical signs and symptoms. Therefore, only in exceptional cases should the adjuvant treatment be discontinued or cancelled within 3 months of radiotherapy. In addition, surgery may cause increased contrast uptake, which should be differentiated from tumor progression. The clinical follow-up must dictate how the initial progression of the lesion should be labeled. If the course of events shows that true progression indeed occurred, the date of the first increase is to be considered as the date of progression. The study coordinator may be contacted for further discussions on a case by case basis.

7.1.2.1 Radiological progression

For follow-up it is required that the patients are followed with the same type of imaging throughout the whole study. The lesion –whether contrast enhancing or not- must be measured in the two largest perpendicular diameters, the area is defined as the product of these two diameters.

- ◆ Increase of contrast enhancing area on MRI or CT scans of more than 25% as measured by two perpendicular diameters compared to the smallest measurements ever recorded for the same lesion by the same technique.
- ◆ The appearance of new lesions with or without contrast enhancement
- ◆ In case of predominantly non-enhancing tumors: an increase of 25% in bi-dimensional perpendicular product of signal hyperintensity area on MRI T2 weighted images or FLAIR images, or area with hypodensity on CT scan

If there is radiological evidence of progression only before the first cycle of adjuvant treatment, patients may stop radiotherapy but should be continuing the adjuvant treatment. Such cases will be reviewed.

7.1.2.2 Clinical /neurological progression

Clinical/neurological progression is defined as the presence of the following conditions:

- ◆ decrease in WHO performance status
 - ◆ for patients with baseline WHO performance status 0: deterioration to WHO performance status 2 or worse for which no other explanation is present
 - ◆ for patients with baseline WHO performance status 1 or 2: deterioration to WHO performance status 3 or worse for which no other explanation is present
- ◆ deterioration of neurological functions
- ◆ appearance of signs/symptoms of increased intracranial pressure (headache, nausea and vomiting without other explanations)
- ◆ and/or start of corticosteroid or increase of corticosteroid dosage by 50% for control of neurological signs and symptoms

7.1.2.3 Considerations in the diagnosis of clinical/neurological progression

At all times in case of clinical/neurological progression, radiological confirmation of the progression is recommended.

In case no clear progression is visible as compared to recent neuro-imaging procedures older images must be used for comparison to detect progression.

If no clear progression is visible on neuro-imaging other explanations for the deterioration must be sought (e.g., anticonvulsant medication, metabolic disturbances)

7.2 Neurological deterioration free survival

This study will assess neurological deterioration as a secondary endpoint to investigate if the prolongation of progression free survival translates into a better preservation of neurological function. Neurological deterioration is defined as a decrease in WHO performance status as follows:

- ◆ decrease in WHO performance status
 - ◆ for patients with baseline WHO performance status 0: deterioration to WHO performance status 2 or worse for which no other explanation is present, and which is maintained for at least three months
 - ◆ for patients with baseline WHO performance status 1 or 2: deterioration to WHO performance status 3 or worse for which no other explanation is present and which is maintained for at least three months

The date of neurological deterioration will be the first date the persistent decrease in performance status was diagnosed. Neurological deterioration free progression is the time interval between the date of randomization and the date of neurological deterioration or death which ever occurs first. If neither event has been observed, the patient is censored at the date of the last follow up examination.

7.3 Evaluation of cognitive function

Short cognitive screening with the *Mini-Mental State Examination* (MMSE) will take place at randomisation, 4 weeks after radiotherapy and then at every scheduled follow-up visit as indicated in chapter 6. This 30-point test includes questions on orientation to time and place, registration, attention, calculations, recall, language, and visual construction. (See Appendix L)

Additional more comprehensive neurocognitive testing will be performed at dedicated centers only, as a side study to this protocol. (See Appendix I)

7.4 Overall survival

All patients will be followed until death. The duration of survival is the time interval between randomisation and the date of death due to any cause. Patients not reported dead or lost to follow up will be censored at the date of the last follow up examination.

7.5 Evaluation of toxicity

7.5.1 Adverse events and side effects

All adverse events will be recorded on the case report forms; the investigator will decide if those events are drug related (unrelated, likely related, not assessable) and his decision will be recorded on the forms for all adverse events.

Adverse events not drug related (i.e. reported as unrelated) will not be considered as side effects or toxicity.

7.5.2 General evaluation of side-effects

This study will use the International Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, for toxicity and adverse event reporting. A copy of the CTCAE can be accessed from the CTEP home page (<http://ctep.cancer.gov/forms/CTCAEv3.pdf>). A link to this page is provided on the EORTC web site <http://www.eortc.be/>; if the location is moved to another site, this link will be updated. Investigators who do not have any access to Internet can contact the EORTC Headquarters to receive a copy by mail.

Hematological toxicity will be assessed on the basis of blood counts as indicated in chapter 6. The nadir count will be assessed for each cycle of therapy, and graded according to the International CTCAE v3.

Non-hematological acute side effects will be assessed and reported separately for each cycle of therapy, and graded according to the International CTCAE v3.

7.5.3 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 on
Reporting adverse events)

7.5.4 Toxic deaths

Toxic death is defined as death due to toxicity. This must be reported on the summary form: the cause of death must be reported as "toxicity".

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

7.5.5 Evaluability of toxicity

All patients receiving treatment will be considered evaluable for toxicity.

8 Statistical considerations

8.1 Statistical design

8.1.1 Sample size

This is a 2 by 2 factorial design with Overall Survival as the primary endpoint when comparing:

- ◆ Patients receiving RT alone or RT + adjuvant TMZ to those receiving RT & concurrent TMZ or RT & concurrent TMZ + adjuvant TMZ.

[Question I: test for superiority of the concurrent TMZ chemotherapy]

- ◆ Patients receiving RT alone and RT & concurrent TMZ to those receiving RT + adjuvant TMZ or RT & concurrent TMZ + adjuvant TMZ.

[Question II: test for superiority of the adjuvant TMZ chemotherapy]

The hypotheses are the following:

- ◆ In the EORTC trial 26951 for Anaplastic Oligodendroglioma and Oligoastrocytoma tumors, patients with no combined 1p/19q LOH treated by RT alone had a median survival of 24 months. In the EORTC trial 26882 for Anaplastic Astrocytoma, patients treated by RT alone had a median survival of 24 months.
- ◆ No interaction is anticipated between the concurrent and adjuvant temozolomide treatment that are assumed to contribute equally to the survival improvement.
- ◆ In the EORTC trial 26981, comparing RT & Concurrent TMZ + adjuvant to RT alone, the estimated Hazard Ratio was 0.63 and its 95% Confidence Interval [0.52-0.75].

The following table summarizes the statistical parameters of the design. A Hazard Ratio (HR) of 0.775 is assumed for both questions.

RT		No adjuv CT (median OS)	Adjuv CT (median OS)	Question I	
				Median OS	HR
No conc CT		24 m	31 m	(24+31)/2=27.5	0.775
Conc CT		31 m	40 m	(31+40)/2=35.5	
Question II	Median OS	27.5	35.5		
	HR	0.775			

For both questions, to detect a reduction of the risk of death of 22.5%, based on a two-sided logrank test, at an overall significance level of 5% and a power of 83%, a total of 534 events are needed. With an estimated accrual rate of 150 patients per year, a total of **748** patients should be recruited within approximately 5 years. A minimum follow-up of 2 ½ years will be needed to observe the required number of events. One interim analysis for efficacy is planned when 41% of the events have been observed (219). To perform this interim look, 11 additional events are necessary. Power of the trial was slightly increased in order to compensate for the loss of information due to patients dropping out before starting the adjuvant treatment. It is estimated that 10% of the patients will fail during or within the month following radiotherapy.

After evaluation of the first 183 patients entered, it appeared that the rate of patients not randomized was underestimated (45% vs 10%). The targeted registration sample size was re-estimated to approximately 1360. Recruitment will be continued till the planned **748** patients can be randomized.

8.1.2 Randomization and stratifications

Patients will be centrally randomized (for practical details, see chapter on registration / randomization procedure). A minimization technique will be used for random treatment allocation stratifying by:

- ◆ Institution,
- ◆ WHO Performance Status (0 vs >0),
- ◆ Age (≤ 50 vs > 50),
- ◆ The presence of 1p LOH only (yes vs no) ,
- ◆ The presence of oligodendroglial elements (yes vs no) and
- ◆ MGMT promoter methylation status (methylated vs unmethylated vs indeterminate).

8.2 Statistical analysis plan

8.2.1 Primary and secondary endpoints

8.2.1.1 Overall survival (primary endpoint)

Overall Survival (OS) is calculated from the date of randomization up to the date of death (any cause). For patients still alive at the time of analysis, OS will be censored at last follow-up visit date.

8.2.1.2 Progression-free Survival (secondary endpoint)

The Progression-free Survival (PFS) is calculated from the date of randomization up to the date of first progression or death (any cause) whichever comes first. In case a patient is still alive and without progression at the last follow up visit date, PFS will be censored at the date of last follow up visit date.

8.2.1.3 Neurological deterioration-free survival (secondary endpoint)

The neurological deterioration-free survival (NPFS) is calculated from the date of randomization up to the date of first neurological deterioration (see 7.2) or death (any cause) whichever comes first. In case a patient is still alive and without neurological deterioration at the last date of assessment of the WHO performance status, NPFS will be censored at that date.

8.2.1.4 Toxicity (secondary endpoint)

The assessment of safety will be based on the frequency of Adverse Events graded according to the NCI-CTCAE version 3.0 scoring system.

8.2.1.5 Mini Mental State Examination (MMSE) (secondary endpoint)

The Mini Mental State Examination (MMSE) is a brief, standardized tool to grade patients' cognitive function. It is an 11-question measure that tests five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. The maximum score is 30. Since its creation in 1975 by Folstein et al (Ref. 20), the MMSE has been validated and extensively used in both clinical practice and research. Following Tangalos et al. (Ref. 21) and as previously used by Brown et al (Ref. 22) a decline of more than 3 points in the MMSE score will be considered to represent clinically significant deterioration. Following Brown et al, the patient's cognitive

function will be considered ‘impaired’ if the MMSE score is 26 or less and ‘normal’ if it is 27 or more. MMSE questionnaire can be found in appendix L.

8.2.2 Analysis populations

- ◆ Intention-to-treat population: All randomized patients will be analyzed in the arm they were allocated by randomization.
- ◆ Per protocol population: All patients who are eligible (including 1p/19q LOH status at central review) and have started their allocated treatment (ie RT started in all arms).
- ◆ Safety population: All patients who have started their allocated treatment (ie RT started in all arms). The safety of patients excluded from the safety population is separately reported.

A patient will be considered to be eligible if he/she did not have any major deviations from the patient entry criteria listed in chapter 3 of the protocol. Eligibility will be assessed by the Study Coordinator based on the review of each patient file.

8.2.3 Statistical methods

8.2.3.1 Analyses populations

All the analyses of the efficacy endpoints (overall survival and progression-free survival) will be performed in the intention-to-treat population.

All the analyses of the safety endpoints will be performed in the safety population.

8.2.3.2 Analyses methods for efficacy endpoints

For the primary analysis of overall survival and progression-free survival, the Cox proportional hazards model will be fitted with a question indicator variable (one for each question, I and II) and adjusted by the stratification factors at randomization. For overall survival the nominal significance level to be used at the interim look and final analysis is described in section 8.3 below.

In the final report, important secondary analyses of overall survival will be 1) the Cox models with adjustment of the questions by MGMT promoter methylation status after randomization and the other stratification factors. 2) the Cox models with adjustment of the questions by IDH1 mutation status (in replacement of MGMT promoter methylation status) and the other stratification factors. Significance level used for these two secondary analyses is the same as for the primary analysis. All analyses of progression free survival will be performed at a 5% significance.

The Kaplan-Meier technique will be used to obtain estimates of the overall survival and progression-free survival. The hazard ratios will be estimated with their 95% confidence intervals. Medians will be presented with 95% confidence interval provided by the Reflected Method (Ref. 23). 5 year survival and progression-free survival rates will be presented with 95% confidence interval calculated by Greenwood formula's estimation of the standard deviation.

8.2.3.3 Analyses methods for safety endpoints

The safety analyses will be presented overall and by period as defined below:

- ◆ The baseline (BL) period will include all information recorded up to the randomization date.
- ◆ The radiation therapy (RT) or chemo/radiation period (RT&TMZ) will start on the day the radiation therapy is first given and end the day of the last administration of radiation therapy treatment plus 28 days.

- ◆ The adjuvant chemotherapy period (RT+TMZ) will start 29 days after the last dose of radiation therapy treatment and end-up 27 days after the first day of administration of the last cycle of adjuvant chemotherapy.
- ◆ The follow-up period (FUP) will start 29 days after the last dose of radiation therapy treatment or 28 days after the first day of administration of the last cycle of adjuvant chemotherapy.

The safety assessments include hematological toxicity, laboratory measurements and adverse events. Only the safety assessments performed before progression or within 7 days of progression and before start of any further anti-cancer therapy will be included in the analysis.

8.2.3.3.1 Hematological parameters

For the whole treatment period, the worst value of each hematological parameter will be calculated for each patient. The worst value of each parameter will then be coded and the frequency of each category will be tabulated. A table with grade 3 or 4 rates will be provided.

8.2.3.3.2 Biochemical parameters

For the whole treatment period, the worst value of each biochemical parameter will be calculated for each patient. The worst value of each parameter will then be coded and the frequency of each category will be tabulated. A table with grade 3 or 4 rates will be provided.

8.2.3.3.3 All AEs

The worst grade of each AE item will be calculated as the maximum grade reported **regardless of seriousness or relationship** for that item over the whole treatment period. The frequency of the worst grade of each AE item will be tabulated. A table with grade 3 or 4 rates will be provided.

8.2.3.3.4 Related AEs

The worst grade of each AE item will be calculated as the maximum grade reported **as likely related** for that item over the whole treatment period. The frequency of the worst grade of each AE item will be tabulated. A table with grade 3 or 4 rates will be provided.

There will be no formal comparison of safety endpoints. No p-value will be carried out.

Baseline AE grades will not be accounted for in any AE analyses.

8.2.3.4 Analysis of MMSE

The distribution of the MMSE at each time point of evaluation (see chapter 6) will be described on the four treatment arms separately using means and their associated standard error (a longitudinal plot will be considered). Median and range will also be computed.

Box-plots will be used to represent MMSE score distribution at baseline and at key time-points of evaluation (eg. Baseline, 4 weeks of radiotherapy, at every 3 monthly visit where form compliance is sufficient). The proportion of patients with 'normal' and 'impaired' MMSE score will also be displayed.

Similarly to Brown et al. the changes in MMSE scores over time will be summarized in the four treatment groups by the proportion of patients with significant increase (> plus 3 points), stable (- 3 points to + 3 points) or significant decrease (> minus 3 points) of the MMSE score at the key time points of evaluation. For both questions (I and II), the distributions will be compared at each evaluation point using a Chi-square test for trend. A Bonferroni adjustment of the type I error rate will be used to correct for multiple testing.

8.2.3.5 Quality of Life analysis

See chapter 10.

8.2.4 Pre-planned sensitivity or exploratory analyses

8.2.4.1 Pre-planned sensitivity analyses

If the percentage of patients ineligible and/or who did not start allocated treatment is superior to 10%, sensitivity overall survival and progression-free survival analyses will be performed by fitting the Cox proportional hazard with a question indicator variable (one for each question, I and II) and adjusted by the stratification factors at randomization in the per protocol population.

8.2.4.2 Pre-planned exploratory analyses

In addition to the questions, pairwise comparisons of overall survival and progression-free survival between the three chemotherapy arms and the radiotherapy alone arm will be performed.

All comparisons will also be performed in each stratum of the following covariates: MGMT promoter methylation, 1p and 19q LOH and histological diagnosis. Factor or treatment by covariate interaction tests will be computed. Hazard Ratios with 99% confidence intervals will be tabulated. Forest Plots will be presented.

The distribution of MGMT promoter methylation status, 1p and 19q LOH in each histological diagnosis will be presented.

8.2.5 Prognostic factor analyses

Prognostic factor (PF) analyses for overall survival are prospectively planned. The main PF analysis will include: both questions (I and II), clinical covariates (WHO Performance Status, Age, Extent of Surgery, Tumor location, Previous surgery for Low Grade Glioma), Presence of oligodendroglial component, 1p/19q LOH status and MGMT promoter methylation status, histopathology parameters and biomarkers available at the time of analyses.

In the univariate stage, depending on its scale, each question and covariate will be screened by an appropriate two-sided logrank test (heterogeneity or trend). Kaplan-Meier curves will be computed. The Peto' interaction test will be computed between questions and between questions and covariates. Main effects and interactions with $p < 0.15$ will be considered for inclusion into the multivariate modeling stage. If an interaction is detected the main effects and interaction term will be included in the multivariate models. Variables will be included with their full categorization, no regrouping or selection of categories is allowed.

All selected covariates will be included into a multivariate Cox proportional hazards model. Both the automatic backward and stepwise selection method (significance to enter and/or stay in the model at 0.05) will be tested. The differences between the two selection methods will be documented. Nevertheless, in case of discrepancies, the selection of main effects and interactions provided by the stepwise selection method will be considered for the final model. As an internal validation, the bootstrap resampling technique will be used to estimate the probability of inclusion of each main effect or interaction term in Cox proportional hazards models with stepwise selection at 5% significance and identified the 10 models with the variables selected with the highest frequency. Only main effects or interactions with more than 60% probability of inclusion will be included in the final model.

If the final model of the main PF analysis includes interactions, additional models might be fitted in each question and/or chemotherapy arm separately applying the methodology described above.

The calibration, discrimination ability (Harrell's C-index) and Akaike's criteria (AIC) of final models will be estimated. Bootstrap technique will be used to correct parameters for "optimism" (Ref. 25).

Nomograms estimating individual patient's risk of progression or death before starting treatment and to predict medians and 2 years probabilities (other relevant endpoints might be considered) will be developed.

Proportional hazard assumptions will be checked by plotting the scale Schoenfeld residuals (Ref. 24) and by time-by-covariate interactions. If the data clearly do not follow proportional hazards, medical explanations should be identified and statistical solutions should be discussed with EORTC Applied Statistical Research group on non-proportional hazards models.

These analyses might be completed by analyses based on new techniques or methods available by the time of PF analyses.

8.2.6 Data recoding 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. 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 (eg. re-treatment delays) are presented as continuous variables using the median and range.

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 (UNL) and the degree to which it is above the UNL (for example > 2.5 x UNL, > 5 x UNL, > 10 x UNL). 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 ...) will be presented using the median and range (minimum, maximum).

If appropriate, continuous data may also be presented in categories.

8.3 Interim analyses

One formal interim analysis is planned for both questions when 219 events (41%) have been observed. Based on the assumption of the statistical design, the interim analysis should take place approximatively 4 years after the start of the trial when about 600 patients have been recruited.

Only the rejection of H₀, the hypothesis of no efficacy, will be considered. Based on stopping boundaries from the Rho family (Rho=2), at the interim analysis, the nominal significance level for rejecting H₀ will be of 0.0084. The final analysis will be performed at a significance level of

0.0453. Power simulations were performed with EAST v 4.0.1.34 the results are presented in the table below based on 10000 simulations.

Scenario	Prob. of rejection of H_0		Overall Power
	Interim analysis	Final analysis	
<i>HR=0.63 (-ln(HR)=0.462)</i>	79%	21%	99.9%
HR=0.775 (-ln(HR)=0.255)	23%	61%	83%
<i>HR=0.80 (-ln(HR)=0.223)</i>	16%	56%	72%
<i>HR=0.825 (-ln(HR)=0.192)</i>	11%	47%	59%

The probability of early stopping the assumption of the design is 23% at the interim analysis and 61% at the final analysis. The design still performs well if the true treatment effect is somewhat smaller than expected: for HR=0.80 the overall power is 72% with a 16% probability of early stopping at the interim analysis. For the pessimistic scenario of HR =0.825 the design will have a poor performance and the overall power will drop to 59%. Should the true difference between the treatment arms be comparable to the one observed in the EORTC 26981 (HR=0.63) trial, the probability of early stopping after the interim look increases to 79%.

The opportunity to stop the trial for futility (rejection of H_1) was investigated. It was not possible to find a design allowing for rejection of H_1 with sufficient power at an appropriate time of assessment before the end of the accrual period.

8.4 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 analysis of the primary endpoint as defined in the protocol
3. The database has been fully cleaned and frozen for this analysis

9 Data monitoring

A Data and Safety Monitoring Board (DSMB) will monitor the recruitment, the reported adverse events and the data quality at least twice a year. Problems which are identified will be discussed with the Study Coordinator who will take appropriate measures. Relevant information (including relevant safety data) will be included in the study status reports which serve as a basis of discussion during EORTC Group meetings. These reports will be made available to investigators participating in the study and to the EORTC Independent Data Monitoring Committee (IDMC) if interim analyses (planned or not planned) are carried out.

If interim analyses are carried out, the interim monitoring of efficacy and safety data will be performed according to the Statistical Considerations chapter and the EORTC policy on “Independent Data Monitoring Committees and Interim Analyses”.

The results of the interim analyses are confidential and are discussed by the EORTC IDMC. The IDMC will subsequently recommend to the EORTC Group whether any changes should be made to the study.

No efficacy results will be presented at EORTC Group meetings or elsewhere before the trial is closed to recruitment and the data are mature for the analysis of the primary endpoint, unless recommended otherwise by the EORTC IDMC.

10 Quality of life assessment

Reducing mortality and morbidity is still the most important factor in 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 the quality of life (QoL) even when survival is extended. Progress in the acceptance of new cancer therapies is sometimes critically dependent on their QoL consequences. Health related QoL is a multidimensional concept, which represents the physiological, psychological and social influences of the disease and the therapeutic process from the patients' perspective. It comprises four principal components: physical, psychological and social well-being, and daily-life functioning.

10.1 Rationale / objectives and hypothesis (background literature)

Patients with anaplastic glioma can have a poor QOL, but this has not been frequently assessed in large scale studies. It is highly likely that these patients will experience similar symptoms as recently reported in the 26951 and 26981 trials. That is, that patients can suffer from considerable levels of fatigue, have sleep problems, communication deficits, motor dysfunction and leg weakness with impairments in emotional and social functioning and express uncertainty regarding the future and an overall reduced QOL. Therefore, in this study, QOL is an important secondary endpoint. The main objective of QoL assessment within this clinical trial is to determine the impact of no adjuvant chemotherapy versus adjuvant therapy until progression for anaplastic glioma on overall health/QoL. Based on the recent EORTC study 26981, the hypothesis is that we expect no differences between arms using the global QOL scale during treatment, but there may be a later benefit to the adjuvant therapy arm if disease progression is achieved, thereby leading to a better global QOL. Several past neuro-oncological trials have shown an increased progression free survival after more intense initial treatment, without an effect on overall survival. At present the impact of progression of high-grade glioma on the quality of life is not clear. It is not clear if increasing progression free survival is translated into a longer period with a better preserved quality of life. If that is the case, improvement of progression free survival would become a goal in itself. With this trial we will assess if QOL is decreased at the time of first progression, and if a longer progression free period is translated in a better QOL. To meet these objectives QOL questionnaires will also be administered after the first progression.

A secondary objective is to evaluate the effect of temozolomide on the various 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. Based on the past study, we may see a slight increase in fatigue and reduction on social functioning in the adjuvant chemotherapy arm. However, once off treatment, we expect to see no differences

10.2 QL measures

Quality of life will be assessed with the EORTC Quality of Life Questionnaire (QLQ-C30) version 3. This is composed of multi-item and single scales. These include five functional scales (physical, role, emotional, social, and cognitive), 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 [Aaronson et al., Ref. 26]. While this standard is used in EORTC studies, it lacks some dimensions that pertain to the QL issues in certain cancers in brain cancer. Therefore we will use the EORTC Brain Cancer module (QLQ-BN20) is designed for use with patients undergoing chemotherapy 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 validation study has been performed with English-speaking patients from Canada, the UK and the USA. (Osoba et al 1996, Ref. 27). An additional validation analysis is planned and will be completed within the time frame of this clinical trial.

10.3 Study design

Patients are eligible for the quality of life assessment in this study if they fulfill the eligibility criteria (Section 3) and, more importantly, complete the baseline quality of life questionnaire before randomization. Given the importance of QOL in this study, being able to provide a completed QOL form is an important eligibility criterion. Of course, should the QOL forms not be available in the required language then this should not exclude the patient from participating in the study. Patients will be informed in the patient informed consent form that they will have their quality of life assessment regularly while involved in this trial. QoL will be a secondary outcome and evaluated in a longitudinal design for in all patients entered in this study.

10.3.1 QoL data collection - Timing and where and how

QoL questionnaires must be filled out at the hospital when the patient comes for a scheduled visit. The questionnaire will be handed out to the patients by the investigator or a study nurse prior to seeing the doctor for clinical evaluations. Patients will be asked to fill out the questionnaires as completely and accurately as possible. The average time to complete the entire questionnaire is approximately 10-15 minutes. Master copies of the QoL questionnaires (EORTC QLQ-C30 and the QLQ-BN20) will be sent to the institution together with the CRFs. The clinical forms will include a question whether the QoL forms have been filled in -and if not, the reason why. Data collection procedures should be followed using the EORTC guidelines in Appendix D. Time windows for eligible follow-up assessment will be (+/-) 3 weeks the scheduled follow-up assessment.

The questionnaire should be completed within 14 days prior to randomization, then at 4 weeks off radiotherapy, then at every 3 monthly visit. After treatment discontinuation of treatments, QoL measurements are carried out every 3 months, at each follow-up visit up during coming five years or death if it occurred earlier. Even if patient's progress, QOL forms should still be collected every three months until death.

10.3.2 Compliance

Missing data may hamper assessment of QL in clinical trials. This may be because centers do not collect the questionnaires at the appropriate time (unit non-response), and because patients may miss questions within the questionnaires (item non-response). The latter problem occurs less than 2% on average and should not be a problem. The former problem will be minimized by ensuring that participating centers are properly informed and motivated towards QL assessment.

During the study, compliance with completing QoL questionnaires will be investigated at each time point. The compliance of the QoL assessments will also be reviewed twice a year and will be a part of the descriptive report by the EORTC Headquarters for the Group's plenary sessions. Having high compliance is imperative to this QOL study and all reasonable attempts to collect QOL data must be made. The compliance data by institutes should be presented to the entire group in order to help identify centers that are struggling to obtain maximum QOL compliance levels and efforts to improve this should be included as corrective methods (e.g. Education to nurses and doctors about the importance of the data and how to collect it)

The compliance rate between the 2 arms will be compared at each time point using a chi-square test. In order to adjust for the multiplicity of the tests, a Bonferroni adjustment will be made by which each test will be performed at the 0.01 significance level. Should serious volumes of missing questionnaires occur then the protocol writing committee would review the QL assessment in the trial. If compliance levels fall below 70% at any time point protocol writing committee would need to take remedial action to improve the position.

10.4 Statistical considerations

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 QL. The primary QL endpoints that are considered relevant to this trial are global QOL. The QOL data will inform the hypothesis that we expect no differences between arms using the global QOL scale during treatment, but there may be a later benefit to the adjuvant therapy arm if disease progression is achieved, thereby leading to a better global QOL. Hence, the global quality of life scale of the QLQ-C30 will be used as the primary QL outcome of interest. Based on the work of Osoba et al. (Ref. 27), a difference of 10 points on a 100 point scale between the two treatment arms will be considered as clinically significant. The standard deviation of the global QoL scale is approximately 20 points. With a minimal effect size of 0.5 (i.e. one-half standard deviation), with alpha set at 0.5 and beta at 0.20 (power 0.80), a minimum of 64 patients per treatment arm is required. The other scales of fatigue and social functioning will be analyzed as secondary QOL endpoints. The remaining scales will only be analyzed on an exploratory basis. Data will be scored according to the algorithm described in the EORTC QLQ-C30 scoring manual. All scales and single items are scored on categorical scales and linearly transformed to 0-100 scales where:

A high score for a symptom scale or item represents a high level of symptoms or problems.

A high score for a functional scale represents a high or healthy level of functioning.

A high score for the global health status/QoL represents high QoL.

When performing a QoL analyses complications may arise due to large quantities of missing data. This issue has a bearing on whether a valid comparison of the treatment arms is being made.

In QoL research there are two main types of missing data: (1) item non-response, (2) unit non-response (the whole questionnaire is missing for a patient.) As item non-response occurs less than 2% on average in the QLQ-C30 it is not such a major problem and thus the methods described in the EORTC QLQ-C30 scoring manual for handling item non-response will be used. For missing questionnaires, it is necessary to identify both the extent of missing questionnaires and the main

process of missing data. Three different types of missing data processes may exist: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR, informative dropout mechanism). These have distinct consequences for data analysis.

If the missing data process is considered to be non-ignorable (MNAR) then the quality of life will be compared between groups using longitudinal data modeling techniques (i.e. Proc mixed in SAS with either selection models or pattern-mixture models) in combination with a logistic regression for the dropout process.

If the missing data mechanism can be considered ignorable (MAR), then standard longitudinal data analysis will be used (PROC mixed in SAS).

If the data are MCAR then complete case analysis can be used without biasing the results.

Statistical tests will be performed using a two-sided significance level of 5%.

For all quality of life domains and items, cross-sectional descriptions of the average scores will be presented by treatment arm at each time point of assessment together with confidence intervals and a graphical display of the patterns of change over time will be provided.

10.5 Additional analysis of the QOL scales as possible prognostic factors

In addition, recent evidence from our last study (Bottomley et al 2005), suggested baseline QOL may be of some prognostic value, when combined with clinical variables. Hence, we also plan to undertake a prognostic factor analysis with the relevant clinical information and key QOL scales that have been shown to be prognostic in study 26981-22981/NCI-C CE3. These scales include cognitive functioning, fatigue, physical functioning, social functioning and the MMSE. We will use baseline scores to predict outcome, with the hypothesis that worse scores are related to poorer survival outcomes. This analysis will include the Cox modeling, along with a sensitivity analysis using the bootstrap validation technique.

11 Translational research

11.1 Generalities

The timeframe of this study necessitates anticipating translational research projects to be performed in 5 years, when all patients are accrued and all collected biological material will be available. Thus, the main goal at this time is to organize the structure for collection and preservation of biological patient material in an efficient way for future analysis. This strategy will allow adjustment of the translational research project by integrating the latest advances in cancer research and taking advantage of progresses in molecular biology techniques. A definitive comprehensive translational research project will be proposed at the latest at completion of accrual by a translational research committee formed by representatives of the trial steering committee and the translational research committee of the BTG, interested members of the BTG, and representatives of participating groups. Any translational research project using the material and data of this trial will require approval of the translational research committee of this trial, and formal approval by the EORTC protocol review committee.

11.2 Rational

Little molecular data is available for anaplastic glioma that are relatively rare, difficult to define by pathology, and consist of a morphologically heterogeneous group of tumors (astrocytoma grade 3, anaplastic oligoastrocytoma, and oligodendroglioma grade 3, for this study with the exception of tumors with 1p/19q deletions). This study provides a unique opportunity to fill this gap allowing association of molecular profiles and clinical parameters with response to therapy. Furthermore, respective comprehensive translational research projects are ongoing or planned in other trials of the EORTC Brain Tumor Group for low grade glioma (EORTC LGG 22033-26033), and glioblastoma (EORTC 26981/22981, NCIC CE.3; RTOG 0525, EORTC) that all test response to Temozolomide treatment, although using different modalities. Since most of the tumors will recur, cross over of therapies are expected, thus, informed consent needs to be acquired for optional translational research also on subsequently resected tumor tissue (frozen or paraffin embedded).

11.3 Goals

Global Molecular Profiling of tumors to establish correlations with tumor classification, prognosis, response to treatment, and overall survival. Development of evidence based, individually tailored patient management.

- ◆ **Classification** of tumors based on their molecular patterns to improve reproducible diagnosis.
- ◆ Identification of **predictive factors** (e.g. differentially expressed genes/proteins, methylation patterns) associated with response to therapy and outcome.
- ◆ Test predictive value of candidate genes/proteins on tissue arrays constructed from a large panel of gliomas representative for the distinct experimental arms and for EORTC and RTOG/NCIC centers.
- ◆ Identification of **new therapeutic targets**
- ◆ **Rational design** of new clinical trials for anaplastic glioma
- ◆ **Improve understanding of molecular mechanisms** driving tumor progression and resistance to treatment.

11.4 Approaches

Based on our preliminary findings in the EORTC/NCIC study we propose that global molecular profiling should be a high priority in this EORTC/RTOG trial. Frozen tumor tissue is most suitable for high quality molecular profiling using high through put analysis for gene expression, genomic copy number aberrations, aberrant promoter methylation, proteomics, etc., although efforts are ongoing to adapt the methodology to include also paraffin embedded tissues. Thus, collection of frozen tumor tissue is a high priority, beside collection of tissue blocks.

The obtained information will allow generating a statistically evaluable data base for correlations with treatment response, currently badly missing in this field. This data base may serve as reference for studies investigating molecular mechanisms of classical or targeted cancer drugs allowing integration of information obtained in *in vitro* model systems or murine models. Furthermore, this data would be a strong link to the database we have from the EORTC/NCIC trial. Molecular Profiling should include gene expression profiling, array-CGH or SNP chip analysis, global analysis of inappropriate promoter methylation, and integrated proteomics. Gene expression profiling should be performed on a widely used platform for comparability. SNP-chip analysis in addition allows determination of polymorphisms relevant for treatment response. This investigation requires availability of normal DNA from each patient (DNA derived from PBLs) that is also asked for in

the context of 1p/19q deletion analysis. The analysis of polymorphisms in key genes has been shown to be of importance for the cancer process.

11.5 Collection of patient material

To reach these goals the following biological patient material is collected:

The informed consent for trial participation will explain the need for material for translational research of the initial resection, and including subsequent resections.

- ◆ **frozen tumor biopsies**
- ◆ **paraffin blocks**
- ◆ **respective serum and blood lymphocytes**
- ◆ construction of **tissue arrays** from paraffin embedded material of tumor biopsies

11.6 Routing and banking of biological patient material

For EORTC, the tumor material and blood should be sent to Erasmus Medical Centrum, Rotterdam by **express carrier** (as specified in chapter 17.3.3). Details on the procedure are to be found in the appendix “Procedures and routing of tumor and blood samples prior to randomization” (Appendix K). The procedure for other participating group is detailed in the corresponding Group Specific Appendix.

11.7 IDH mutations analysis

Recently discovered, isocitrate dehydrogenase (IDH) mutations in glial tumors are mainly found in grade II and grade III glial tumors, and in secondary glioblastoma. The presence of these mutations confers a much better overall prognosis.

Indeed, shortly after the start of the CATNON study, a genome wide sequencing study described somatic mutations in the gene encoding IDH1 in 12% of glioblastoma (GBM) samples. (Ref. 30) The authors further observed that IDH1 mutations predominantly occur in patients of lower age and in glioblastomas that have progressed from lower grade gliomas (‘secondary’ GBM), and that IDH1 mutations were associated with a longer survival. Subsequent studies have shown a 60-80% mutation rate in grade II and grade III glioma, both in tumors with 1p/19q co-deletion and TP53 mutations. (Ref. 31) These observations, together with follow-up studies showing a consistent pattern of IDH1 status over time suggest that IDH1 mutations mark an early event in grade II and III glioma. Moreover, clinical studies show that IDH1 mutated tumors have an improved outcome, regardless of other prognostic factors. (Ref. 32, Ref. 33)

Therefore, further investigation into IDH genes has become crucial for the understanding of the outcome of clinical trials in glioma. For this reason, the tumors of the patients treated within CATNON will also be investigated for mutations in IDH genes.

Material: tumor at initial diagnosis (FFPE block or 30 unstained slides) which is already covered by the material requested before randomization (no extra material is needed to perform the test).

Methods: Tumor DNA will be extracted from FFPE block or unstained slides. IDH mutations will be investigated by PCR and/or immunohistochemistry. (Ref. 34)

Statistics: See section 8.2.5 (Prognostic factors analysis)

12 Publication policy

The final publication of the trial results will be written by the Study Coordinator from the EORTC on the basis of the final analysis performed at the EORTC Headquarters. After revision by the EORTC Headquarters, other co-authors and Merck, the manuscript will be sent to a major scientific journal.

The authors for the EORTC will include at least the Study Coordinator and two members of the EORTC Headquarters who have contributed to the trial. Other EORTC co-authors will be the investigators who have included most patients by order of inclusion.

Any publication that would be performed by collaborating groups with the data issued from this study should be prospectively agreed on by the Trial Steering Committee (if applicable) and the Coordinating group and/or DC.

The EORTC Group Chairman, the Study Coordinator and the EORTC Headquarters Team must approve all publications, abstracts and presentations of data pertaining to patients included in this study.

This is applicable to any individual patient registered/randomized in the trial, or any subgroup of these. Such publications must comply with the terms specified in the EORTC Policy 009 “Release of Results and Publication Policy”. Therefore, such a publication cannot include any comparisons between randomized treatment arms (for randomized trials) or an analysis of any of the study end-points unless the final results of the trial have already been published by the Study Coordinator.

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 21: Administrative responsibilities, for non-EORTC investigators: see your group specific appendix):

- ◆ The updated signed and dated Curriculum Vitae of the Principal Investigator
- ◆ 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.
- ◆ A Commitment Statement and Study Agreement between EORTC and Principal Investigator, 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.
 - ◆ A signed conflict of interest disclosure form will be required only if a possible conflict is declared on the Commitment Statement and Study Agreement.
- ◆ 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. In case patients receive treatment at a satellite institution,

i.e. outside the authorized institution, details on the satellite institution, including the CV of the local investigator, normal lab ranges and the approval of an ethics committee will have to be transmitted to the EORTC Headquarters. **Please keep in mind that all communication is done ONLY between the primary institution and the EORTC Headquarters.**

- ◆ 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 and randomization procedure

14.1 Registration before molecular testing (step 1)

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

A patient can only be registered only after verification of eligibility. This must be done **before molecular testing**.

An exhaustive list of questions to be answered during the registration procedure is included in the registration checklist, which is part of the case report forms. This checklist should be completed by the responsible investigator before the patient is registered.

STANDARD INFORMATION REQUESTED:

- ◆ institution number
- ◆ protocol number (26053-22054)
- ◆ step number: (1 – New patient)
- ◆ name of the responsible investigator
- ◆ patient's code (maximum 4 alphanumerics)
- ◆ patient's birth date (day/month/year)

PROTOCOL SPECIFIC QUESTIONS

- ◆ all eligibility criteria will be checked one by one
- ◆ actual values for the eligibility parameters will be requested when applicable

Stratification factors

- ◆ date of written informed consent (*day/month/year*)

Date foreseen for protocol treatment start

At the end of the registration procedure, a sequential patient identification number (“seqID”) will be allocated to the patients. This number is to be recorded on the registration checklist, along with the date of registration. The completed checklist must be signed by the responsible investigator and returned to the Data Center with the baseline data of the patient.

All SAMPLE SHIPMENTS and REPORTS must be identified with the EORTC Id (Seqid) attributed at registration

14.2 Blinded MGMT methylation status (Step 2)

Blinded for the sites and performed by the EORTC HQ. MGMT methylation status is used for stratification at randomization.

14.3 Randomization (Step 3)

A patient who has not been registered before the molecular testing will not be accepted for the study at a later date and cannot be randomized for the second step of the study.

An exhaustive list of questions to be answered during the randomization procedure is included in the registration checklist, which is part of the case report forms. This checklist should be completed by the responsible investigator before the patient is randomized.

Standard questions

- ◆ institution number
- ◆ protocol number (**26053-22054**)
- ◆ step number: (**3 – Existing patient**)
- ◆ name of the responsible investigator

The patient will have to be selected in the list of patients that have already been registered in the first step. Once the patient has been identified in the list, select the corresponding patient’s code. The patient’s code and date of birth will automatically be inserted in the identification screen.

Protocol specific questions

- ◆ eligibility criteria
 - all randomization criteria will be checked;
 - actual values of the eligibility parameters will be requested when applicable
- ◆ stratification factors

At the end of the procedure, the treatment will be randomly allocated to the patients, as well as a patient sequential identification number. This number and the allocated treatment have to be recorded on the randomization checklist, along with the date of randomization. The completed checklist must be signed by the responsible investigator and returned to the Data Center with the initial data of the patient. The sequential identification number attributed to the patient at the end of the randomization procedure identifies the patient and must be reported on all case report forms.

All participants from non-EORTC groups should contact the Data center mentioned in their Group Specific Appendix.

All EORTC participants should randomize patients directly on the EORTC online randomization system (ORTA = online randomized trials access), accessible, 24 hours a day, 7 days a week, through the internet. To access the interactive randomization program, the investigator needs a username and a password (which can be requested at: www.eortc.be/random).

In case of problems EORTC participants can phone the EORTC Headquarters from 9.00 am to 5.00 pm (Belgian local time) from Monday through Friday to randomize patients via the EORTC call center. Randomization via the phone is not available on Belgium holidays. A list of these holidays is available on the EORTC web site (www.eortc.be/random) and it is updated annually.

Through Internet: www.eortc.be/random

In case of problems by phone: +32 2 774 16 00

15 Forms and procedures for collecting data

15.1 Case report forms and schedule for completion

Data will be reported on the **forms specifically designed by the EORTC Headquarters for this study. Those forms will be used by all cooperative groups. Each group can eventually customize the heading frame but not the contents of the forms. Appropriate forms will be distributed to each investigator by their own Data Center.**

All participants from non-EORTC groups should send forms to the Data Center mentioned in their Group Specific Appendix.

All EORTC participants should send forms directly to the EORTC Headquarters:

BTG Data Manager
EORTC Headquarters
Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique

A. Before the treatment starts:

- ◆ The patient must be registered/randomized through your Data Center.
- ◆ The registration checklist should be returned to your Data Center.

The optimal way to work is to complete the registration checklist first and to register/randomize the patient as soon as it is completed. The date of registration/randomization and patient sequential identification number are then completed on the checklist, and this form can be sent to the Data Center.

B. During/after treatment

The list of forms to be completed for this study and their submission schedule is appended to the set of case report forms.

**ALL Forms must be dated and signed by the responsible investigator
or one of his/her authorized staff members**

15.2 Data flow

The case report forms must be completed, dated and signed by the investigator or one of his/her authorized staff members as soon as the requested information is available.

The list of staff members authorized to sign case report forms (with a sample of their signature) must be sent to the investigator's group Data Center (the one mentioned in the particular Group Specific Appendix for non-EORTC investigators; EORTC Headquarters for EORTC investigators) by the responsible investigators before the start of the study.

In all cases, it remains the responsibility of the principal investigator to check that original case report forms are sent to the adequate Data Center as soon as possible and that they are filled out completely and correctly.

The original copy must be immediately returned to the investigator's group Data Center and the investigator must keep a copy.

The EORTC Headquarters will perform extensive consistency checks on the CRFs and issue Query Forms in case of inconsistent data. These Query Forms will be sent via the group Data Center to non-EORTC investigators and directly to EORTC investigators. They must be immediately answered and signed by the investigator (or an authorized staff member). The original must be returned to the investigator's group Data Center and a copy must be attached to the CRF copies stored by the investigator.

When satellite institutions are involved all contacts are done 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 original form has been returned to the investigator's group Data Center, he/she should notify the group Data Center by using the Data Correction Form. The original Data Correction Form should be sent to the group Data Center and a copy should be kept with the other CRF copies.

The investigator's copy of the CRFs may not be modified unless modifications are reported on a Query Form or a Data Correction Form and the Query Form or Data Correction Form reference is indicated on the CRF.

16 Reporting of Serious Adverse Events

ICH GCP and the 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 were more severe)
- ◆ requires inpatient's hospitalisation or prolongation of existing inpatients' hospitalisation
- ◆ results in persistent or significant disability or incapacity
- ◆ is a congenital anomaly or birth defect
- ◆ results in any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalisation but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above), e.g. secondary malignancy, AE as a result of an overdose

SAR: A Serious Adverse Event (SAE) which is considered related to the protocol treatment is defined as a **Serious Adverse Reaction**

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 or in-patient's hospitalisation: A patient who is admitted to a hospital or clinic for at least one overnight stay.

16.2 Exceptions

The following situations are not considered to be SAEs and should not be reported on the SAE form:

- ◆ Elective hospitalisation for pre-existing conditions that have not been exacerbated by trial treatment
- ◆ A hospitalisation which was planned before the patient consented for study participation and where admission did not take longer than anticipated
- ◆ 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 (social and/or convenience admission to a hospital, 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.

By EORTC convention, clinical events related to the primary cancer progression are not to be reported as SAEs, even if they meet any of the seriousness criteria from the standard SAE definition, unless the event is more severe than expected and therefore the investigator considers that their clinical significance deserves reporting.

16.3 Severity assessment

The severity of all AEs (serious and non-serious) in this trial should be graded using CTCAE v3.0 (http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf).

16.4 Causality assessment

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

Relationship to the protocol treatment	Description
UNRELATED	There is no evidence of any causal relationship to the protocol treatment
LIKELY RELATED	There is (some) evidence to suggest a causal relationship to the protocol treatment and influence of other factors is unlikely or absent.
NOT ASSESSABLE	There is insufficient or incomplete evidence to make a clinical judgment of the causal relationship to the protocol treatment.

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 Serious Adverse Event form, if necessary with the reasoning of the principal investigator.

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 document:

- ◆ For Temozolomide: Summary of Product Characteristics (SmPC) which can be found on the European Medicines Agency's website.

16.6 Reporting procedure for investigators

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

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

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

All SAE data must be collected on the study-specific SAE form.

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.

All additional documents in local language must be accompanied by a translation in English, or the relevant information must be summarized in a follow-up SAE report form.

Investigators participating through **EORTC** must fax all SAE-related information to:

EORTC Pharmacovigilance Unit:

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 EORTC 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. Complete information requested on the SAE form of any reported serious adverse event must be returned within 7 calendar days of the initial report. If the completed form is not received within this deadline, the EORTC Pharmacovigilance unit will make a written request to the investigator.

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

All forms need to be dated and signed by the principle investigator or any authorized staff member (i.e. on the signature list).

16.7 Reporting to investigators and competent authorities

The EORTC Pharmacovigilance Unit will forward all SAE reports within 24 hours of receipt to the appropriate persons within the EORTC Headquarters, the EORTC Study Coordinator and the pharmacovigilance contact at Merck.

All SUSARs will additionally be notified to all EORTC participating investigators, Ethics committees (of EORTC centers) and all central Data Managers of all Cooperating Groups.

The EORTC Pharmacovigilance Unit will take in charge the expedited reporting to all Competent Authorities and EVCTM, whenever applicable.

The EORTC Pharmacovigilance Unit will prepare the Annual Safety Report/ Development Safety Update Report and distribute it to the central Data Managers of all Cooperating Groups, the European Competent Authorities and Merck.

Every Group shall be responsible for distribution of Safety information to their investigators and respective Ethics Committees, 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 Pharmacovigilance Unit of the respective group Data Center within the same timelines as an SAE (within 24 hours) on a Pregnancy Notification Form. The outcome of a pregnancy should be followed up carefully and any abnormal outcome of the mother or the child should be reported. This also applies to pregnancies following the administration of the investigational product to the father prior to sexual intercourse.

- ◆ Any pregnancy in a female subject or in a female partner of a male subject diagnosed during the treatment period or within 30 days after last study treatment administration must be reported to the Pharmacovigilance Unit of the respective group Data Center
- ◆ This must be reported within 24 hours of first becoming aware of the event by fax, to the Pharmacovigilance Unit on a Pregnancy Notification Form/Fax
- ◆ If a Serious Adverse Event (SAE) occurs in conjunction with the pregnancy, please also complete an SAE form as explained in the SAE chapter
- ◆ Upon notification of a pregnancy, it will be the responsibility of the pharmaceutical company, Merck, to follow-up the development and outcome of the pregnancy.

17 Quality assurance

17.1 Control of data consistency

Data forms will be entered into the database of the EORTC Headquarters by a double data entry procedure. 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 by the data manager. Inconsistent forms will be kept "pending" until resolution of inconsistencies.

17.2 Audits

The EORTC Quality Systems and Compliance Unit (QS&C) regularly conducts audits of institutions participating in EORTC protocols. These audits are performed to provide assurance that the rights, safety and wellbeing of subjects are properly protected, to assess compliance with the protocol, processes and agreements, ICH GCP standards and applicable regulatory requirements, and to assess the quality of data.

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 anytime 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 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 onsite facilities related to the study conduct could be visited during an audit (e.g. pharmacy, laboratory, archives, ...).

If a regulatory authority inspection is announced, the investigator must inform the EORTC Headquarters QS&C unit immediately (contact at: qualitysystemandcompliance@eortc.be). In this way EORTC can provide help in preparing and/or facilitating the inspection.

17.3 External review of histology and molecular diagnosis

17.3.1 Central review of histology

Samples shipments should be addressed to [REDACTED] (see section 17.3.3 for instructions). The central pathology review will be carried out by [REDACTED].

For the review, material embedded in paraffin must be sent to the above laboratory (same block will be used for the determination on 1p/19q, see section 17.3.3).

17.3.2 Central review of molecular diagnosis

Eligible for this study are patients with a histological diagnosis of an anaplastic astrocytoma, anaplastic oligoastrocytoma and anaplastic oligodendroglioma, without combined 1p/19q loss. Patients can be entered into the study either based on the local diagnosis or on central histology review and 1p/19q assessment. Centers must decide prior to the site initiation whether they will include patients based on local or on central histology and 1p/19q diagnosis.

Different techniques are available to assess loss of 1p and 19q (FISH, LOH, array CGH). Only centers that fulfill minimum quality requirements for 1p/19q testing and that are cleared by the EORTC Headquarters will be allowed to enter patients based on local diagnosis (see Appendix J). This must be determined prior to study activation by the EORTC datacenter and the study coordinator. Tumors from patients from centers that use central 1p/19q testing for eligibility assessment will simultaneously undergo histological review; patients are only eligible if at least one of the two central reviewers has confirmed the histological diagnosis and in the absence of combined 1p/19q loss.

To allow stratification of the patients according to MGMT status immediate post-surgery shipping of tumor material together with the required blood samples is an absolute requirement. **This also concerns tumor material from patients from centers that enter patients based on local 1p/19q**

testing. Stratification for MGMT status will be either ‘methylated’, ‘non-methylated’ or ‘undeterminate’. Patients in whom MGMT status cannot be determined because of insufficient material, material not timely received etc will still be eligible for the study (and will be stratified for MGMT status as ‘undeterminate’).

Both the 1p/19q testing and the MGMT promoter methylation determination are essential for the study. The submission of tissue for these assays is therefore **mandatory**. The procedures for Europe are explained below. For non-European centers, a similar procedure is covered by Group Specific Appendices.

For patients that are included in the trial based on local determination the histological and molecular diagnosis will be centrally reviewed. Thus, for all patients 1p/19q status will be centrally assessed as part of the trial.

17.3.2.1 Centers without local 1p/19q testing

Centers relying on inclusion based on central histological review and 1p/19q testing must submit tumor material to the Erasmus University Hospital for eligibility assessment. Only samples received from sites that have activated the study will be reviewed and investigated for 1p/19q loss. Both the center and the EORTC will receive the 1p/19q test result and the histology review outcome. The central pre-randomization histology review and 1p/19q testing requires the registration of patients with an eligible local histological diagnosis at the EORTC DataCenter after obtaining patient approval using the registration consent form. This form covers the submission of tumor material and blood for central testing. Once the patient is found eligible at both central histology review and 1p/19q assessment he can be entered into the study.

17.3.2.2 Centers with local 1p/19q testing facilities

Patients with eligible histologies as diagnosed by the local pathologist and in whom local testing has assessed intact 1p, 19q or both can be randomized directly into the trial. However, because pre-radiotherapy assessment of MGMT status is vital for the study stratification, it is still requested to submit a tumor sample and a blood sample as soon as possible. The patient must therefore as soon as possible be registered at the EORTC Headquarters after obtaining approval using the registration consent form. This form covers the submission of tumor material and blood for central testing. The result of the central histology review and 1p/19q assessment will be made available to the center after randomization.

17.3.2.3 Central review for MGMT

MGMT central testing requires shipment of a tumor sample to the central Laboratory. MGMT status determination may be time consuming and may therefore not be compatible with the maximum time to elapse between diagnosis and start of radiotherapy which is of 7 weeks. The central facility will be set up but central MGMT status determination will not be made mandatory during the first year to test the feasibility. If central testing for MGMT is deemed to be feasible, it will be enforced for the rest of the trial. Regardless, it will be tried to determine MGMT determination prior to study entry in all patients.

The material requested for MGMT testing will be sent by the central histopathology laboratory in Rotterdam to MDxHealth (Liège, Belgium).

17.3.3 Sample requirements and routing

Following registration of the patient the following items must be collected:

- ◆ A paraffin embedded tumor sample (preferably a tumor block, otherwise 30 unstained slides)
- ◆ The local pathology report (including local diagnosis of 1p/19q status if available)
- ◆ 20 ml whole blood collected in EDTA tubes for 1p/19q status determination
- ◆ the pathology review and 1p/19q form (in case of local evaluation) with the fax number of the center.

and must be sent by **express carrier** to:



This material must be sent as soon as possible after surgery, once the patient has given consent for the shipment of his material and after he has been registered at the EORTC Headquarters into the trial (registration step). Blood samples should be sent within 24 hours from taking the sample, together with the tumor specimen.

1p/19q analysis for assessment of eligibility purposes will be made available to the site, results can be expected within 14 days. Central review of 1p/19q status will be done in batches at a later stage (after randomization), the results will not be made available to the site unless quality concerns arise. The results of the MGMT promoter methylation assay will not be made available to the local center, but only to the EORTC Headquarters.

All SAMPLE SHIPMENTS AND REPORTS must be identified with the EORTC Id (Seqid) attributed at registration

17.3.4 Post randomization tissue studies

Following central pathology review, central 1p/19q assessment and MGMT promoter methylation status determination, the H&E stained slides will be entered into the EORTC virtual tumor bank.

Thereafter, material from patients that have consented for optional translational research will be stored centrally. If tissue blocks have been made available these will be centrally stored if permission for central storage has been obtained. In case consent for optional translational research has been obtained but not for central storage of tissue blocks tissue micro arrays will be made after which the blocks will be returned to the center.

17.4 Other central review procedures

17.4.1 Central review for Imaging

The study primary end-point is survival. No central review of imaging is planned for this trial.

17.4.2 Central review for Quality Assurance in Radiotherapy

17.4.2.1 Facility Questionnaire

For participating EORTC institutes, which are not members of the EORTC Radiotherapy Group or for Brain Tumor Group members, who have not yet filled in the facility questionnaire or have filled in the questionnaire longer than 1.5 years ago, the EORTC Facility Questionnaire aiming to assess the techniques and infrastructure of each institute delivering radiotherapy in this trial must be completed prior to study activation. The Facility Questionnaire is available on the website of the EORTC Radiotherapy Group and can be downloaded and submitted online. The exact location (website address) and procedure of filling in the FQ will be explained in the starting letter being included in the starting package of this trial. At present it can be assessed at:

http://groups.eortc.be/radio/QA_general_01.htm

17.4.2.2 Case Review

The QA team of the EORTC Radiotherapy Group, including the study chairperson being responsible for radiotherapy issues will review the irradiation technique in randomly selected patients. The objectives will be to check compliance to the protocol guidelines regarding PTV definition, planning technique and documentation. This will include image co-registration and treatment technique.

17.4.2.3 Complex Dosimetry Check for IMRT

Intensity-modulated radiation therapy (IMRT) will be allowed providing sufficient proof of external IMRT credentialing is submitted to and approved by the EORTC QART team.

Chapters 18 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 chapters are superceded by procedures specific to their group.

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 (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments) 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 <http://www.ema.europa.eu/pdfs/human/ich/013595en.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 must be included on all case report forms. In order to avoid identification errors, the patient's code (maximum of 4 alphanumeric) and date of birth 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 an appendix to this protocol.

It is the responsibility of the Coordinating Investigators for this trial (sometimes called National Coordinators) to translate the enclosed informed consent document. The translated version should be dated and version controlled.

The bold sections of the informed consent document must be reflected in any translation. The content of these bold sections can either be translated literally or translated in any way that best captures the information given.

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.

19 Administrative responsibilities

19.1 The study coordinator

The Study Coordinator (in cooperation with the EORTC Headquarters) will be responsible for writing the protocol, contributing to the medical review, discussing the contents of the reports with the Data Manager and the Statistician, and for publishing the study results. He will assist the Clinical Research Physician for answering some clinical questions concerning eligibility, treatment, and the medical review of the patients.

Study coordinators:

EORTC Brain Tumour Group

[REDACTED]

EORTC Radiation Oncology Group

[REDACTED]

The study coordinators will be assisted by:



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

Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique
Fax: +32 2 7723545

Registration of patients:

<http://www.eortc.be/random>

Or

Phone (in case of problems): +32 2 774 16 00

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.be

EORTC Brain Tumour Group

Chairman:

[REDACTED]

Secretary:

[REDACTED]

EORTC Radiation Oncology Group

Chairman:

[REDACTED]

Secretary:

[REDACTED]

20 Trial sponsorship and financing

EORTC is the legal Sponsor for all EORTC participants.

The contact details of the EORTC are:

EORTC Headquarters
Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique
Phone: +32 2 7741611
Fax: +32 2 7723545
e-mail: eortc@eortc.be

The study is supported by an educational grant of Merck.

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 chapter on investigator authorization.

Patients treated at **satellite institutions** are only covered by clinical trial insurance, if these satellite institutions are properly reported to the EORTC Headquarters. For details please refer to the chapter on investigator authorization.

Appendix A: References

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Appendix B: WHO performance status scale

Grade	Performance scale
0	Able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work.
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

Appendix C: 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 3.0.

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address: <http://ctep.cancer.gov/reporting/ctc.html>.

The EORTC Headquarters web site www.eortc.be provides a link to the appropriate CTC web site. This link will be updated if the CTC address is changed.

Appendix D: EORTC Quality of Life evaluation: guidelines for administration of questionnaires (Revised June 2008)



EORTC Quality of Life evaluation: guidelines for administration of questionnaires (revised June 2008)

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?

The overall-responsible person for QoL data collection is the study-co-ordinator of the trial.

However, in each institution one person should be appointed as the responsible for the local organization of QoL data collection. This can be 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 him/herself who has to fill out QoL forms and preferably without help from others. In case a patient is too sick to fill out the questionnaire or if the patient is not able to fill out the questionnaire for reasons such as forgetting his/her glasses, another person could read the questions without making any comments and report the answers on the forms. If a patient received this type of help, please note this on the form.

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 filling out 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).

The following issues should be explained to the patient:

- ◆ The schedule of assessments.
- ◆ The questionnaire is a self administered questionnaire that should be filled out preferably by the patient him (her) self.
- ◆ 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.
- ◆ All questions should be answered.

The RP should make sure that the patient understands the instructions and that a questionnaire is available in the preferred language of the patient (questionnaires in additional languages can be obtained via the EORTC HQ).

At each subsequent assessment as defined by the protocol, the patient should receive the questionnaire from the RP or by other appropriate staff if the RP is not available.

4. Where should the patient fill out the questionnaire?

The patient should complete the questionnaire in the clinic, ideally in a quiet, private room. In general it does not take more than 5 to 10 minutes to fill out a questionnaire, but patients should be given the time they need to answer all questions.

5. When should the patient fill out the questionnaire?

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 receives a therapy, the questionnaire should be filled out before administration of the treatment. The questionnaire should not be taken home and/or mailed.

6. Review of the completed questionnaire.

After the patient has filled out the questionnaire, the person handling the questionnaire should:

- ◆ Check that the date of today is correctly filled in.
- ◆ Check the answers for omissions, for incorrectly completed questions and for inconsistent answers;

If this is the case:

- ◆ Please ask the patient for the reason for omissions or incorrect answers. If the patient prefers not to answer a question this should be noted on the form;
- ◆ Additional explanation may be provided, but the questions should not be rephrased;
- ◆ Any additional comments could be added by the person handling the questionnaire (if possible in English) followed by their name and signature.

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 date of visit should be documented on the questionnaire and returned to the person responsible for completing the CRFs (case report forms).

8. Mailing to the EORTC Headquarters

The questionnaire should be sent to the EORTC Headquarters with the CRFs.

As it is not possible to retrospectively collect missing QoL data, please make sure the patient completes the questionnaire at the time-point when he/she is supposed to fill it out.

Thank you very much for your cooperation. If you have any remarks on this leaflet or if you need further information, please contact:

Quality of Life Department - EORTC Headquarters:

Phone: 32 2 774 1678/1661

Fax: 32 2 779 45 68

**EORTC Quality of Life evaluation: instructions for Monitors**

- ◆ Check if all QoL questionnaires have been filled out on schedule
 - ◆ If not, the Monitor should inform the person in charge of data collection and explain again the schedule of the QoL questionnaires.
- ◆ Make sure the QoL questionnaires are correctly completed
 - ◆ If not, tell the responsible person to explain again to the patient how to fill out the QoL questionnaires at the next visit.

EORTC Quality of Life evaluation: instructions for Data Managers

- ◆ When a response is missing, it should be coded as “9” for missing data (cfr Scoring Manual)
- ◆ When two adjacent categories have been circled by the patient, the category which represents the worst QoL will be taken.

For a symptom item, the highest score will be taken.

For a functional item, the lowest score will be taken.
- ◆ When the response is not legible or ambiguous (eg. two categories which are not adjacent have been circled) then the response is not evaluable and it should be coded as “8”.

Appendix E: World Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
48th General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal.
After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Appendix F: Patient information sheet and Informed consent document for registration in the clinical trials including mandatory research on biological material.

“Patient information sheet and Informed consent document for registration in the clinical trials including mandatory research on biological material” is a separate document.

Appendix G: Patient information sheet and informed consent document for randomization in the clinical trial.

“Patient information sheet and informed consent document for randomization in the clinical trial” is a separate document.

Appendix H: Patient information sheet and informed consent document for future and optional research on biological material.

“Patient information sheet and informed consent document for future and optional research on biological material” is a separate document.

Appendix I: Neurocognitive testing for dedicated centers – Side study

The assessment of neurocognitive testing as specified in this appendix relates to a side study to the main protocol. This study will be performed at a number of dedicated centers, on a voluntary basis. Institutions with patients participating in the quality of life/neurocognitive function components of this study must meet certification requirements for administering neurocognitive assessments. See Appendix II for details.

1. Schedule and tests performed

Comprehensive neurocognitive testing will be performed at randomisation and at every year from randomization up to tumor progression or death.

The tests that constitute the neurocognitive function 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. Neurocognitive function has also been demonstrated to predict tumor progression and independently predict survival for patients with CNS tumors. This battery has furthermore 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. These tests are to be administered by a certified examiner and require 25 minutes or less to complete.

To reduce practice effects, parallel versions of the tests will be developed and will be made available to all participating centres.

Self-reported cognitive function will be assessed with a six-item scale developed for use in the Medical Outcomes Study (MOS scale). 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.

2. Neurocognitive Function Testing Certification

The healthcare professional (e.g., nurse, psychologist) who is responsible for test administration in this study requires pre-certification by [REDACTED] in order to participate in this protocol. For the exact procedure see appendix II.

In short, test and data recording forms are available on a password-protected website:

www.vumc.nl/neurooncology

Test instructions and administration procedures will be provided upon agreement to participate in the side-study. A training video of test administration and data collection procedures are accessible through a password-protected website at M. D. Anderson Cancer Center for review and reference during this study. This video must be reviewed with the test Instructions for the Neurocognitive Function Battery by anyone who will administer neuropsychological assessments. The post test associated with this video must be completed and faxed to [REDACTED]. Passwords for the website will be provided by [REDACTED], for which he can be contacted by e-mail (see below).

3. Statistical analysis

Overall power calculation for estimating sample size requirements were based on the following criteria: (1) 4 treatment arms, (2) a minimal effect size $f(V)$ of 0.25, (3) power $(1-\beta)$ of 0.95, and (4) 3 neurocognitive follow-up assessments after randomization. With $\alpha = 0.05$, 129 patients in total ($n=32$ per treatment arm) are needed to perform repeated measures MANOVA, with potential within and between groups interactions. With a minimal effect size $f(V)$ of 0.15 353 patients in total

(n=88 per treatment arm) are needed. Considering that not all centers will participate in the neurocognitive side-study, the present study meets these sample size requirements.

We will use various models, including the Cox proportional hazards model and mixed and hierarchical linear models. Alternatively, we can use multilevel modeling to detect differences between the four groups over time. These repeated measure analyses can also be supplemented with a psychometric analysis of changes in test performance using the Reliable Change (RC) Index [10]. The difference between the pre-treatment baseline and follow-up assessments will be evaluated by the RC index. This index is derived from the standard error of measurement (SEM) for each test in the battery. The SEM is calculated from the test-retest reliability (r) and the standard deviation of test scores (SD): $SEM = SD(1 - r)^{1/2}$. The standard error of difference is then calculated: $SE\ diff = [2(SEM^2)]^{1/2}$. A reliable change (RC) in test scores from baseline to follow-up is considered significant if it is within $\pm (1.64)(SE\ diff)$, a 90% confidence interval. For each subject, the difference between the pre-treatment baseline and each follow-up assessment will be coded (according to the RC index) as 1 (deterioration), 2 (no change), and 3 (improved). Frequency tables will show the percentage of patients in each treatment protocol who show meaningful losses or gains in the various test domains over the course of the study. Treatment group differences can be compared using chi-square analysis and Cochran's and Mantel-Haenszel statistics.

4. Data Management

All tests will be identified by the date of assessment and EORTC patient identification number (seqid). The test results from all participating centers and groups will be sent to the EORTC Headquarters together with the regular patient documentation. The EORTC Headquarters will then transfer the forms relating to the neurocognitive assessment side study to the Coordinator of the Side Study [REDACTED]

The information related to the side study will be entered in a specific database in Amsterdam. Care will be taken that the patient identification is recorded.

At the end of the clinical trial after publication of the main trial results, the information from the clinical database that is needed for the analysis of the side study data will be transferred to the Coordinator of the Side Study, after completion and approval of the Request for External Release of Data as specified in EORTC Policy number 8.

The neurocognitive side study coordinator will be responsible for assuring the statistical analysis of the neurocognitive testing results. The Study Coordinator will also lead the preparation of a publication relating to the findings of this side study. Other co-authors on this publication will be the Study Coordinators of the Clinical Trial, the statistician who performed the analysis of the side study results and other contributors to the side study. All participants to the side study will be acknowledged.

5. Scientific Committee and publication policy

This project is coordinated by the side study coordinators in collaboration with the PI of the clinical study. The PI Side Study coordinator is responsible for the preparation of the manuscript and will be the leading author. Other co-authors on this publication will be all Side Study Coordinators, the Study Coordinators of the Clinical Trial, the statistician who performed the analysis of the side study results and other main contributors to the side study according to the general EORTC BTG policy. All participants to the side study will be acknowledged.

Side study coordinators:

For EORTC (and PI Side Study):

[Redacted]

[Redacted]

[Redacted]

For CTSU:

[Redacted]

Appendix II

Certification and administration procedures for the neurocognitive test battery

General Procedures: Certification for Test Administration

The healthcare professional (e.g., nurse, psychologist) who is responsible for test administration in this study requires pre-certification by [REDACTED] in order to participate in this protocol.

- ◆ Test and data recording forms are available on the password-protected website provided by [REDACTED]. Test instructions and administration procedures are provided in Appendix III. The instructions must be reviewed along with the test forms and retained for reference.
- ◆ A training video of test administration and data collection procedures are accessible through a password-protected website at M. D. Anderson Cancer Center for review and reference during this study.
- ◆ This video must be reviewed with the “Test Instructions for the Neurocognitive Function Battery” found in Appendix III by anyone who will administer neuropsychological assessments.
- ◆ The post test associated with this video must be completed and faxed to [REDACTED].

To obtain website and password information for the training video, contact:

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

- ◆ Prior to the enrollment of any patient onto the study, the healthcare professional who will be evaluating patients must complete a “practice” assessment, including completion of test forms/score sheets, neurocognitive evaluation summary form, and complete and sign the Certification Worksheet (Appendix IV). Fax the practice tests, score sheets, neurocognitive evaluation summary form, training video post test, and signed Certification Worksheet to the attention of [REDACTED].
- ◆ If there are administration or procedural errors, [REDACTED] will discuss the test administration and scoring issues over the phone with the healthcare professional (5-10 minutes). If the health professional meets criteria for certification, notification of certification will be sent to both the site and to EORTC, and study enrollment may commence.
- ◆ The first case for each certified examiner should be faxed to [REDACTED]. Please send the test forms and all test summary and score sheets and include contact information (name, phone, email) for the certified examiner. [REDACTED] will review test forms and summary sheets 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.
- ◆ Completed test forms must be signed by the certified test administrator. [REDACTED] will be available by telephone and e-mail if questions arise about the testing procedures. [REDACTED] may be contacted at phone: [REDACTED].
- ◆ Results of the HLV-T-R, COWA, and Trail Making Tests should be recorded on the Neurocognitive Evaluation Summary Form (CS), and the original patient tests/forms will not be submitted to [REDACTED] (copies of test forms and summary sheets for the first case will be sent to [REDACTED] per Appendix II). All tests will be identified by the date of assessment and EORTC patient identification number (seqid). The test results will be sent to the EORTC Headquarters

together with the regular patient documentation. The EORTC Headquarters will then transfer the forms relating to the neurocognitive assessment side study to the Coordinator of the Side Study

Summary of Requirements for Examiner Approval for EORTC 26053_22054

Prior to testing a patient, potential examiners must:

1. Read Appendix II and III
2. Obtain copies of the neurocognitive tests
3. Watch the training video available on a password-protected website. To obtain website and password information, contact [REDACTED]
4. Complete the training video post test
5. Complete a “practice” assessment
6. Complete the Certification Worksheet (Appendix IV)
7. All materials (i.e., post test, complete practice assessment and scoring forms, certification worksheet) must be faxed to [REDACTED], who will score it and review any procedural errors with the trainee. If the trainee demonstrates competency, he/she will be notified of the approval to administer the tests to study subjects as part of EORTC 26053_22054. An approval notice will be sent to EORTC for their records and to ensure that only EORTC 26053_22054-approved examiners are testing subjects on protocol EORTC 26053_22054.
8. After certification, each examiner must fax to [REDACTED] all test forms and data summary sheets for their first case.

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. These tests are to be administered by a certified examiner and require 25 minutes or less to complete.

Cognitive Domain	Test	Time to Administer (minutes)
Memory	Hopkins Verbal Learning Test–Revised	8
Visual-motor processing speed	Trail Making Test Part A	5
Executive Function	Trail Making Test Part B	7
Verbal fluency	Controlled Oral Word Association	5
		Total time: 25 minutes

Neurocognitive Assessment – Sequencing of Alternate Forms

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 versions to be administered at pre-entry and subsequent sessions. The forms should continue to be alternated in this order for the duration of the study. The forms packet will contain alternate versions of these neuropsychological tests.

TEST	Study Registration	1 month post RT/TMZ	3 rd visit	4 th visit	5 th visit	6 th visit	7 th visit
HVLT-R	Form 1	Form 2	Form 3	Form 4	Form 5	Form 6	Form 1
COWA	‘C-F-L’	‘P-R-W’	‘C-F-L’	‘P-R-W’	‘C-F-L’	‘P-R-W’	‘C-F-L’

Additional comments:

1. Testing should be completed in one session. Test instructions must be followed verbatim with every patient at every study visit. All tests should be completed in black pen.
2. Tests should be administered in the following order to every patient and at every study visit: HVLT-R Free Recall; Trail Making Test Part A; Trail Making Test Part B; COWA; HVLT-R Delayed Recall; and the HVLT-R Delayed Recognition.
3. You may fill the 20-minute delay interval between COWA and HVLT-R Delayed Recall with QOL questionnaires.
4. Follow the instructions on the Forms Packet Index before submission of forms to [REDACTED].
5. Please keep all original test records. In the event of questions, contact [REDACTED]. Copies of the test forms and summary sheets for the first case from each site must be reviewed by [REDACTED]. Additionally, test results are not submitted to [REDACTED]. All tests will be identified by the date of assessment and EORTC patient identification number (seqid). The test results will be sent to the EORTC Headquarters together with the regular patient documentation. The EORTC Headquarters will then transfer the forms relating to the neurocognitive assessment side study to the Coordinator of the Side Study [REDACTED].
6. All test results are recorded on the Neurocognitive Evaluation Summary Form (CS), which is found in the Forms Packet. Study/case specific labels must be applied to all forms.
7. Patients should not be given copies of their tests to avoid learning the material between test administrations.
8. Before dismissing the patient, thank the patient for his/her cooperation. Remind the patient of his/her next appointment and that these tests will be repeated.
9. In the event that a patient cannot complete a given test, please write the reason(s) on the test form AND the data summary form.

Appendix III

Test instructions for the neurocognitive function battery

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

HVLT-R FREE RECALL

TRAIL MAKING TEST PART A

TRAIL MAKING TEST PART B

CONTROLLED ORAL WORD ASSOCIATION

HVLT-R DELAYED RECALL

HVLT-R DELAYED RECOGNITION

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

This test has three parts and six alternate forms:

Part A - Free Recall: Complete the three learning trials first

Part B - Delayed Recall: Complete after a 20 minute delay that includes administration of Trail Making Tests and COWA

Part C - Delayed Recognition: Complete 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 say nothing 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 words that were correctly repeated on the summary 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.
- ◆ If a word is said that is not in the list (*for example, “intrusion”*), do not write that word on the form and say nothing 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 3. Later, you can record the number of words that were correctly repeated on the summary form.

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.
- ♦ If a word is said that is not in the list (for example, “intrusion”), do not write that word on the form and say nothing 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.
- ♦ 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 am) on the designated space on the HVLT-R form .

2. TRAIL MAKING TEST [Timed Test]

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 and say:

Examiner: *“On this page (point) 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 s/he 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, 2 to 3, 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 still 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. Then say:

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). 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 s/he cannot do the task, DISCONTINUE testing and indicate the corresponding reason on the Trail Making Data Sheet. If the patient completes Sample A correctly and appears to understand what to do, proceed immediately to Part A.

Part A – Test: After the patient has completed Sample A, place the Part A test worksheet directly in front of the patient and say:

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 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). 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 Trail Making Data Sheet 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 Trail Making Data Sheet in minutes and seconds. Then say, *“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 (the bottom of the worksheet should be approximately six inches from the edge of the table) and say:

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

If the patient completes Sample B correctly, and in a manner demonstrating that s/he understands what to do, proceed immediately to Part B. If the patient makes a mistake on Sample B, 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 to 2), 2 to B (point to B), B to 3 (point to 3) 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 still cannot complete Sample B, take their hand and guide them through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on the copy. Then say:

Examiner: *“Now you try it. Remember, begin at number 1 (point to 1) and draw a line from 1 to A (point to A), A to 2 (point to 2), 2 to B (point to B), B to 3 (point to 3) 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 Trail Making Data Sheet. If the patient completes Sample A correctly and appears to understand what to do, proceed immediately to Part A.

Part B – Test:

After the patient has completed Sample B, place the Part B Worksheet directly in front of the patient and say:

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 to A), A to 2 (point to 2), 2 to B (point to B), B to 3 (point to 3), 3 to C (point to C) and so on, in order, until you reach the circle marked END (point). Remember, first you have a number (point to 1), then a letter (point to A), then a number (point to 2), then a letter (point to B), 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 Trail Making Data Sheet 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 Trail Making Data Sheet 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 (COWAT) [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 a second appropriate word is given, proceed to the test itself.

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 sheet.

If the patient has succeeded in giving two appropriate words beginning with the demonstration letter, say:

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 a minute for each letter. The first letter is ‘___’. Begin” (Start timing immediately. See scoring sheet).

****Allow exactly one minute for each letter****

- ◆ 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.

Recording and Scoring:

- ◆ The record sheet 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.
- ◆ 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 record sheet, place check marks in the boxes to indicate correct responses only.
- ◆ Count all the correct responses. The number of correct words should be indicated below each column on the recording sheet and on the summary data form that is sent to [REDACTED].

Comments on scoring:

- ◆ Note: 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.
- ◆ 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.
- ◆ Slang terms are OK if they are in general use.
- ◆ Foreign words (*for example, pasta; passé; lasagna*) can be counted as correct if they can be considered part of the lexicon of the relevant language, the criterion being their listing in a standard dictionary of that language. All incorrect and repeated responses MUST be crossed out with one single line, initialed and dated. Additionally, all duplicate entries that have been verified to have different meanings must be marked “ok”, initialed and dated. Refer to the descriptions above for guidelines for acceptability. Add the total number of correct responses in each column and input the totals where indicated on the COWA worksheet.
- ◆ 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 WORD LIST AGAIN.**
- ◆ Record the time on the clock that you start ‘Part B – Delayed Recall’ (for example, 10:20 am) on the designated space on the HVLТ-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 HVLТ-R. If the time is too short, allow the patients to complete a questionnaire.

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 HVLТ-R worksheet 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 say nothing 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, record the number of words that were correctly recalled on the summary 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 HVLТ-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).

5. Medical Outcome Studies (MOS) EVALUATION SUBJECTIVE COGNITIVE FUNCTIONING**Items from the cognitive function scale**

- (1) How much of the time during the past month did you have difficulty reasoning and solving problems, for example making plans, making decisions or learning new things?
- (2) During the past month how much of the time did you forget, for example things that happened recently, where you put things or appointments?
- (3) How much of the time during the past month did you have trouble keeping your attention on any activity for long?
- (4) During the past month how much of the time did you have difficulty doing activities involving concentration and thinking?

(5) How much of the time did you become confused and start several actions at a time?

(6) Did you react slowly to things that were said or done?

Response options: all of the time, most of the time, a good bit of the time, some of the time, a little of the time or none of the time.

Ref.: Stewart AL, Ware JE, Sherbourne CD, Wells KB. Psychological distress/well-being and cognitive functioning measures. In: Stewart AL, Ware JE, eds. Measuring functioning and well-being. The Medical Outcomes Study approach. Durham and London: Duke University Press, 1992: 102-142.

Appendix IV**Certification worksheet for test administrator****EORTC 26053_22054****PHASE III TRIAL ON CONCURRENT AND ADJUVANT TEMOZOLOMIDE
CHEMOTHERAPY IN NON-1P/19Q DELETED ANAPLASTIC GLIOMA: THE CATNON
INTERGROUP TRIAL**

This worksheet must be completed and signed by the person requesting certification and submitted to [REDACTED] prior to the registration of any patients to EORTC 26053_22054. Refer to protocol Appendix II for details.

- (Y) 1. Have you reviewed the Certification and Administration Procedures for the Neurocognitive Test Battery in Appendix II of the protocol, as well as the Test Instructions for the Neurocognitive Function Battery in Appendix III?
- (Y) 2. Have you watched the Neuropsychological Test Administration video?
- (Y) 3. Have you completed and submitted the post test associated with the training video and a “practice” Neuropsychological Assessment (See Appendix II)?

Signature of test administrator

Date

(person who read Appendix II and III, watched video and completed a “practice” Assessment)

Printed name of test administrator

Institution number/Name

Telephone number of test administrator

Fax number of test administrator

If you have any questions regarding the certification, please contact [REDACTED]. Once you have completed this form, please attach both the Neuropsychological Assessment forms from the “practice” subject and the training video post test and submit to:

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

For [REDACTED] *(to fax to EORTC +32 2 771 38 10)*

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

Signature

Date

Appendix J: Minimum requirements for local 1p/19q diagnostics

Circumscribed deletions on 1p and 19q are not restricted to oligodendroglial tumors but are also frequent in astrocytic tumors. Large deletions on 1p and 19q are very characteristic of oligodendroglial tumors and this type of deletion is associated with better prognosis and more favourable response to therapy.

1p/19q determination with FISH

1. The laboratory should have at least one year experience with clinical 1p/19q testing in gliomas.
2. There must be regular quality control/assurance procedures (e.g. validation of new batches of probe, routine - weekly/monthly - of anomaly rate)
3. Appropriate control probes for 1q and 19p should be included in each batch- to accurately determine the 1p/1q and 19q/19p ratios as well as to determine ploidy.
4. A positive deletion control should be included with each batch - a normal control is also useful.
5. Two hybridizations using two slides should be performed, a single hybridization for both 1p and 19q assessment is not appropriate
6. Each case is reviewed by a neuropathologist prior to FISH to ensure that at least 40% tumor is present and to mark the area where the technologist will count.
7. At least 60-100 nuclei need to be enumerated.
8. Cut-offs may vary from one institution to another, and should be based on normal values studies - ideally using normal brain - for the establishment of deletion (and gain) criteria. This could be defined in terms on % of cells showing twice the number of reference vs test signals (e.g. 2 and 1, 4 and 2, 6 and 3, etc., e.g., total score 20%), or an overall ratio of test to reference signals instead (e.g., cut-off of 0.8).

Loss of heterozygosity tests

1. The laboratory should have at least one year experience with clinical 1p/19q testing in gliomas.
2. There must be regular quality control/assurance procedures.
3. The LOH assays for determining losses should not be restricted to a single locus on chromosomes 1p and 19q, but multiple microsatellite probes must be used covering large area's of both 1p and 19q. A reasonable set of probes is given in (Ref. 29).
4. A comparison must be made with normal patient DNA (eg, extracted from leukocytes).
5. All samples need to be checked under the microscope for tumor content prior to analysis by a qualified neuropathologist.

Appendix K: Procedures and routing of tumor and blood samples prior to randomization

1. General remarks

- ◆ Eligible for this study are patients with
 - ◆ a histological diagnosis of an anaplastic astrocytoma, an anaplastic oligoastrocytoma or an anaplastic oligodendroglioma
 - ◆ without combined 1p/19q loss.
- ◆ Patients can be entered into the study either based on a) the local diagnosis including 1p/19q assessment or b) on central histology review and central 1p/19q assessment.
- ◆ Centers must decide prior to the activation of the center whether they will include patients based on local or on central histology and 1p/19q diagnosis. Only centers that fulfill basic quality requirements for 1p/19q testing and that are cleared by the EORTC Headquarters will be allowed to randomize patients based on the local diagnosis (see Appendix J).
- ◆ Both the 1p/19q testing and the MGMT promoter methylation determination are essential for the study. The submission of tissue for these assays is therefore **mandatory**.
- ◆ To allow stratification of the patients according to MGMT status **immediate** post-surgery shipping of tumor material together with the required blood samples is an absolute requirement for all patients regardless of the 1p/19q procedure: **this also concerns material from patients from centers that enter patients based on local 1p/19q testing**.
- ◆ Stratification for MGMT status will be either 'methylated', 'non-methylated' or 'unknown'. Patients in whom MGMT status cannot be determined because of insufficient material, material not timely received etc will still be eligible for the study (and will be stratified for MGMT status as 'unknown').
- ◆ Test results from tumor blocks are superior compared to the results from slides. All investigators are urged to send blocks.
- ◆ The procedures for Europe are explained below. For non-European centers, a similar procedure is covered by Group Specific Appendices.

2. Registration procedure

- ◆ As a first step, all patients (regardless of 1p/19q testing procedure) must be registered into the study prior to randomization using the Registration Consent form (see Appendix F). This is also necessary for patients from sites with approved local 1p/19q testing.
- ◆ The submission of the blood and tumor samples as part of the study is covered by this Registration Consent form.

3. Procedure for centers without accepted local 1p/19q testing

Centers relying on inclusion based on central histological review and 1p/19q testing must submit tumor material to the Erasmus University Hospital for eligibility assessment. Only samples received from sites that are on the list of activated centers of the EORTC Headquarters will be reviewed and investigated for 1p/19q loss.

After the registration of the patient using the Registration Consent into the trial the following items must be sent:

- ◆ A paraffin embedded tumor sample (preferably a tumor block, otherwise 30 unstained slides)
- ◆ The local pathology report (including local diagnosis of 1p/19q status if available)
- ◆ 20 ml whole blood collected in an EDTA tube
- ◆ the pathology review and 1p/19q form (with the EORTC id given at registration, the fax number of the center and with information regarding the 1p/19q status)

Samples will first be reviewed for the pathological diagnosis, if at review the tumor is considered not eligible the sample will not be tested for 1p/19q loss and the patient will not be eligible.

For eligibility, both central histology review and 1p/19q assessment must confirm eligibility. Cases that are not eligible according to the review pathologist will not be examined for 1p/19q loss and MGMT promoter gene methylation. Both the center and the EORTC will receive the 1p/19q test result and the histology review outcome, results can be expected within 14 days from arrival. Once the patient is found eligible he can be randomized into the study.

4. Procedure for centers with accepted local 1p/19q testing facilities

Patients with eligible histologies as diagnosed by the local pathologist and in whom local testing has assessed intact 1p, 19q or both can be randomized directly into the trial. However, because pre-radiotherapy assessment of MGMT status is vital for the study stratification, these patients must also as soon as possible be registered at the EORTC Headquarters after obtaining approval using the Registration Consent form. After the registration of the patient into the trial the following items must be sent:

- ◆ A paraffin embedded tumor sample (preferably a tumor block, otherwise 30 unstained slides)
- ◆ The local pathology report (including local diagnosis of 1p/19q status)
- ◆ 20 ml whole blood collected in an EDTA tube
- ◆ the pathology review and 1p/19q form (with the EORTC id given at registration, the fax number of the center and with information regarding the 1p/19q status)

Central review of 1p/19q status will be done in batches at a later stage (after randomization), the results will be made available to the site.

5. Addresses

Tumor and blood samples must be sent by **express carrier** to:

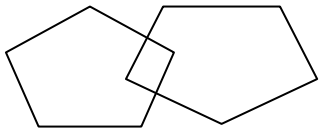


The material requested for MGMT testing will be sent by the central histopathology laboratory in Rotterdam to MDxHealth (Liège, Belgium). The results of the MGMT promoter methylation assay will not be made available to the local center, but only to the EORTC Headquarters for stratification purposes.

Appendix L: 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

Source:

Folstein MF, Folstein SE, McHugh PR: "Mini-mental state: A practical method for grading the cognitive state of patients for the clinician." J Psychiatr Res 1975;12:189-198.