Intergroup Study (EORTC 22033-26033)
(EudraCT number 2004-002714-11)

Primary chemotherapy with temozolomide vs. radiotherapy in patients with low grade gliomas after stratification for genetic 1p loss: a phase III study

Coordinating Group: EORTC Radiotherapy Group

Collaborative Groups:

Brain Tumour Group
National Cancer Institute of Canada – Clinical Trials Group (NCIC CTG)
Trans Tasman Radiation Oncology Group (TROG)
Medical Research Council – National Cancer Research Institute (MRC-NCRI)

Study Chairman: 

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 and Appendix G) 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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<th>Version</th>
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<td>May 28, 2003</td>
<td>PRC outline approval</td>
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<tr>
<td>November 23, 2004</td>
<td>Full protocol approval</td>
<td>Version 1.0</td>
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<tr>
<td>January 19, 2005</td>
<td>Administrative change 1</td>
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<td>Third amendment (non substantial)</td>
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Contact addresses

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QA radiotherapy committee

Pathology committee:
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## Protocol summary

| **Objective(s)** | A randomized study to demonstrate a difference in progression-free survival (PFS) for primary treatment with temozolomide in order to assess: whether PFS and OS can be prolonged by primary chemotherapy with temozolomide, whether the incidence of late toxicity can be decreased by using primary chemotherapy, the toxicity profile of the two treatments and the quality of life of the patients  

The impact of 1p deletions in low-grade gliomas: prognostic effect of tumors with deletion on PFS overall and by treatment group. Benefit for patients with LGGs and deletions treated with TMZ compared to radiotherapy alone with respect to survival. Interaction between treatment and cytogenetic features. |
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<td><strong>Trial design</strong></td>
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| **End-points** | Primary: PFS  
Secondary: Overall survival, Quality of life and Minimental State Examination (MMSE), Adverse events, neurocognitive function (for dedicated centers) |
| **Principal selection criteria** | At registration:  
- Histologically proven low grade diffuse glioma (Astrocytoma WHO grade II, gemistocytic, fibrillary and protoplasmatic), Oligoastrocytoma WHO grade II and oligodendroglioma WHO II); supratentorial location only  
- WHO performance status ≤ 2  
- Age ≥ 18 years  
- Informed consent  
At randomization:  
Same as above +  
- Requiring treatment as demonstrated by at least one of the following criteria (1-4):  
1. Age ≥40 years;  
2. Radiologically proven progressive lesion;  
3. Neurological symptoms others than seizures only (focal deficits, signs of raised intracranial pressure, mental deficits);  
4. Intractable seizures  
- Not candidate for treatment exclusively by surgery  
- RTOG neurological function 0-3  
- Results of genetic testing (1p) available  
- Adequate hematological, renal and hepatic function; |
No previous radiotherapy to the brain, no prior chemotherapy, patient has recovered from any surgery
No second primary tumor with the exception of adequately treated basal cell skin carcinoma

**Treatment**
- Arm A: Radiotherapy (control arm), 50.4 Gy, standard fractionation (28 x 1.8 Gy), conformal techniques
- Arm B: Temozolomide 75 mg/m2 daily x 21 days, q 28 days until progression or for max. 12 cycles (experimental arm)

**Statistical design**
Test for a difference in 5-y PFS (HR=0.68, MR=1.47) between the two treatment groups.
Assuming (EORTC 22845) a 5-y PFS rate of 45% on RT, a 2-sided logrank test at the 0.05 significance level and 80% power, entry of patients over 5 years and 2.5 years of follow-up after the last patient
- 216 events are needed in total
- 466 randomized patients

Further assuming that 2/3 of registered patients are randomized,
- 699 registered patients (one assumes patients will need treatment within 6-18 months of registration)
An exploratory analysis will investigate the presence of an interaction between the 1p cytogenetic status of the patients and the treatment effect (i.e. predictive effect of cytogenetic status for benefit of treatment). The power for this analysis will be limited.
A descriptive analysis of treatment effects within cytogenetic subgroup will also be performed, with limited power.
The prognostic value of the 1p cytogenetic status will be assessed separately within each treatment group. Since the prognostic effects are expected to be large, the data should provide a reasonably high power of detecting such effects.
Post-hoc power calculations will be provided for the interaction effects and prognostic assessments described above.

**Central Pathology**
Central pathology review will be performed.

**Genotyping**
A particularity of this study is the mandatory upfront testing and stratification according to a known genetic marker, deletions on chromosome 1p. To this purpose, one reference laboratory for Europe and Canada will be established using the same standardized procedures. This will allow to confirm and to establish prospectively the true role of these markers in the management of glioma. This will require to collection and central analysis of both paraffin-embedded tumor tissue and blood.
The paraffin-blocks are also requested to construct tissue arrays for subsequent correlation with the clinical outcome. These arrays will allow to test and verify multiple markers, both recently identified ones as well as not yet known potential markers which will become available during the course of the study.
All participating institutions are strongly encouraged to provide not only paraffin-embedded tumor tissue, but to prospectively collect and freeze
<table>
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<tr>
<th><strong>Quality of Life</strong></th>
<th>The use of primary Temozolomide may have better QoL outcomes because of deferring radiotherapy and thus late radiation-induced toxicity. QoL is included as a secondary endpoint in this study. The main objective of QoL assessment within this trial is to determine the impact of Temozolomide on seven chosen domains being primarily global QL, with role functioning, social functioning, visual disorder, motor dysfunction, communication deficit and drowsiness as other key issues. It was expected that these were likely to be most affected in patients undergoing either radiotherapy or Temozolomide. Quality of life will be assessed using the EORTC Quality of Life Questionnaire (QLQ-C30) version 3 together with the 20-question Brain Tumor Module (QLQ-BN20)</th>
</tr>
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<td>fresh tumor tissue and peripheral blood mononuclear cells (normal control). This will enable future efforts in gene expression profiling and proteomics. In dedicated centers (with the available facilities) repeat PET scanning for response measurement and relation to outcome will be performed</td>
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**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 Canada.

Each participating group is the Sponsor for their participants (unless otherwise agreed).

<table>
<thead>
<tr>
<th>Country</th>
<th>Recruiting group(s)</th>
<th>Sponsor</th>
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</tr>
<tr>
<td>Other countries</td>
<td>EORTC</td>
<td>EORTC</td>
</tr>
</tbody>
</table>

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 Appendices annexed at the end of the protocol.

The patient information sheet and informed consent template (Appendix F, Appendix G) is 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 information on Collection and Preparation of Pathological and Biological Patient Material (Appendix L) and Central Pathology Review and Molecular Diagnostics (Appendix M) are applicable 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 information on the Neurocognitive testing for dedicated centers – side study (Appendix N) is only applicable for the EORTC participants to this side study.

The appendix on Quality Assurance for Radiotherapy (Appendix P) is applicable 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 Data Center).

Investigators members of several groups participating to the trial should select one of these groups for the framework of this trial and 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 the industry.

This trial is an academic trial with a restricted educational grant support from the industry.
1 Background and introduction

Low-grade gliomas (LGG) encompass a diverse group of primary, diffuse, slow growing glial brain tumors, occurring both in children and adults. They occur most frequently in young adults, the median age at diagnosis being < 35 years. There is a slight male preponderance. In supratentorial adult tumors, seizures are the most common symptom at presentation. The yearly incidence rate is 1-2 per 100,000. LGG represent 15-20% of all gliomas; Median survival is 5-10 years for the whole group. Five to 10 percent of the low-grade glioma are of oligodendroglial and mixed origin, the rest are of astrocytic origin.

For this study patients with a supratentorial astrocytoma, oligoastrocytoma and oligodendroglioma WHO grade II are considered. Cerebellar and pilocytic astrocytoma are excluded.

1.1 Pre-therapeutic prognostic factors influencing survival

Several investigators have tried to retrospectively identify prognostic factors in LGGs. Lote et al (Ref 1) identified 379 patients with LGGs treated over 15 years at the Norwegian Radium Hospital. In an univariate analysis, younger age, good WHO PS, the absence of neurologic deficit, and the absence of contrast enhancement on imaging were all found to be associated with longer survival. Histologic subtype (oligodendroglial and oligoastrocytic versus non-oligodendroglial), the presence of seizures at diagnosis, the extent of initial surgery (debulking versus biopsy), and the use of adjuvant chemotherapy were predictive for survival. In a multivariate analysis, only PS, neurologic symptoms or initial corticosteroid dependency, contrast enhancement, and age remained statistically significant prognostic factors.

Likewise, in a subsequent study, the database from the Norwegian Radium Hospital (n = 160) was pooled with the databases from the London Regional Cancer Centre (n = 179) and the University of California at San Francisco (n = 62) (Ref 2). Prognostic classes were identified using recursive partitioning analysis of the data. Younger patients (18 to 40 years of age) with a good performance status (KPS $\geq 70\%$) had a median survival of > 10 years; younger patients with a poor PS (KPS < 70%) and older patients (> 40 years of age) with a good PS and no contrast enhancement had a median survival of > 7 years; older patients with a good PS and with contrast enhancement had a median survival of < 4 years; and older patients with a poor PS had a median survival of only 12 months. In this study there were also significant differences in survival between institutions, reflecting patient selection, management, and referral biases. This underlines the difficulties in comparing results among institutions and stresses the importance of prospective trials.

The EORTC developed a prognostic score based on two large, randomized, multicenter trials with a total of over 600 patients (Table 1, Ref 3). The first study (EORTC 22844, Ref 4) served to construct a model of prognostic factors, which was validated with the data set of the subsequent trial (EORTC 22845, Ref 5). In a multivariate analysis, age $\geq 40$ years, astrocytic tumor type, tumor size $> 6$ cm, tumor crossing the midline, and neurologic deficit at diagnosis (before surgery) were
A score was established depending on the number of unfavorable prognostic factors. A favorable (low-risk) prognostic score was defined as no more than two of these adverse factors and was associated with a median survival of 7.7 years (95% CI = 6.6, 9.3). The presence of three to five prognostic factors (a high-risk prognostic score) was associated with a median survival of 3.2 years (95% CI = 3.0, 4.0) only.

### 1.2 Radiotherapy

The optimal management of cerebral low-grade glioma is unknown and the identification of patients needing a treatment is based on prognostic factors as outlined above. Patients above the age of 40, patients with large unresectable tumors and patients with a neurological deficit are considered to be at high risk of recurrence or progression and are usually treated with radiation therapy. There is no consensus on the treatment strategy for adult patients with this tumor category. Frequently, initial treatment is limited to a biopsy or diagnostic resection only. However, recurrence or progression occurs in almost all patients over the years following diagnosis. In a previous study by the EORTC (EORTC 22845, Ref 5) an improved progression-free survival was shown for patients treated with immediate radiotherapy, however, no difference in overall survival could be demonstrated.

![Table 2: Randomized studies of radiotherapy for low-grade glioma](image)

<table>
<thead>
<tr>
<th>Study</th>
<th>Histology</th>
<th>Treatment arms</th>
<th>No</th>
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<th>P value</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>OS</td>
<td>PFS</td>
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<tr>
<td>EORTC 22844</td>
<td>Astro, OD, OA, PA</td>
<td>S+RT 45 Gy</td>
<td>171</td>
<td>58%</td>
<td>47%</td>
</tr>
<tr>
<td>(Ref 4)</td>
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<td>S+RT 59.4 Gy</td>
<td>172</td>
<td>59%</td>
<td>50%</td>
</tr>
<tr>
<td>EORTC 22845</td>
<td>Astro, OD, OA</td>
<td>Surgery</td>
<td>140</td>
<td>66%</td>
<td>37%</td>
</tr>
<tr>
<td>(Ref 5)</td>
<td></td>
<td>S+RT</td>
<td>150</td>
<td>63%</td>
<td>44%</td>
</tr>
<tr>
<td>NCCTG-RTOG-ECOG</td>
<td>Astro, OD, OA</td>
<td>S+RT 50.4 Gy</td>
<td>102</td>
<td>73%</td>
<td>55%</td>
</tr>
<tr>
<td>(Ref 6)</td>
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<td>S+RT 64.8 Gy</td>
<td>103</td>
<td>68%</td>
<td>52%</td>
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</table>

Astro, astrocytoma; OD, oligodendroglioma; OA, oligoastrocytoma, PA, pilocytic astrocytoma

Furthermore the optimal timing for additional radiotherapy is not clear: immediate radiotherapy has not been shown to offer an advantage in overall survival over deferring radiotherapy.

Another controversial issue is the radiotherapy dose to be chosen. Many radiation oncologists usually prescribe a total dose of 50 to 55 Gy. Some retrospective single arm studies suggested doses > 53 Gy being associated with a better outcome regarding survival (Ref 6, Ref 7), others did not (Ref 8, Ref 1). Two randomized studies of the EORTC and NCCTG-RTOG-ECOG showed no significant difference concerning survival between 45 Gy and 59.4 Gy and between 50.4 Gy and 64.8 Gy, respectively (Ref 4, Ref 6). Since the dose prescription used in the first studies was based on previous ICRU guidelines (Report No. 29 of the International Commission on Radiological Units) and the dose prescription to different isodose levels may have resulted in slightly higher total doses than 45 Gy in the tumor itself, a total dose of 50.4 Gy has been selected for the present trial.
1.3 Toxicity of Radiotherapy

Treatment related late toxicity is of concern, in particular in view of the rather long survival of patients with low grade glioma. Radiation therapy to the brain is associated with white matter changes, cognitive deficits and radiation necrosis. A 2-year actuarial incidence of grade ≥ 3 radiation necrosis of 2.5% has been observed in patients treated with a total dose of 50.4 Gy versus a 5% rate using 64.8 Gy in a randomized intergroup trial (NCCTG-RTOG-ECOG) (Ref 6). The effects of early versus delayed radiotherapy on quality of life and cognitive functioning have been analysed in small patient cohorts: in irradiated and non-irradiated patients with a low-grade glioma it did not differ significantly (Ref 9). However, if those patients were compared to a control group suffering from hematological malignancies, low-grade glioma patients had a significantly worse cognitive function. This was confirmed in a second multi-center study where cognitive disability in the memory domain was significantly worse in irradiated patients (Ref 10). The latter was pronounced if fraction doses exceeding 2 Gy were applied. The tumor itself seems to have the most deleterious effect on cognitive function and additionally the use of antiepileptic drugs (Ref 10).

Comparing patients treated with postoperative radiotherapy with those having undergone surgery only, a more severe leukencephalopathy and a significantly worse cognitive performance were seen even after correction for confounding risk factors as histological grading, epilepsy, tumor location etc (Ref 11). Only measuring Mini-Mental State Examination (MMSE) in these patients may underestimate the cognitive deficit in low-grade glioma patients (Ref 12). Patients who received 54 Gy compared to 45 Gy in the EORTC 22844 trial tended to report lower levels of functioning concerning quality-of-life (Ref 13). This was especially true for fatigue, insomnia and emotional functioning. As irradiated patients may develop necrosis or dementia, another high proportion of patients (about 20%) treated with chemotherapy may experience high grade toxicities (Ref 14). Also, surgical procedures can have a 6% chance of complications that might result in impaired neurologic function (Ref 14). Brown et al concluded, based on literature review that the weight of evidence suggests only sporadic, limited neurocognitive damage from focal radiotherapy at the usually prescribed doses for low-grade gliomas. (Ref 15)

The awareness of potentially disabling long term neurotoxicity led physicians to withhold treatment for as long as possible in patients with suspected low-grade tumors. This concerns in particular patients with seizures only, as these may remain stable for a prolonged period of time and have a better prognosis than patients with focal deficits. However, most if not all patients will need treatment at some point of time.

1.4 Chemotherapy

The role of chemotherapy in low-grade gliomas is far from being established. One very small randomized trial by the SWOG comparing patients treated with radiotherapy of 55 Gy alone (n=19) versus radiotherapy plus CCNU (n=35) resulted in no significant difference in median survival and response rate (Ref 16). However, this small trial was stopped early due to lack of accrual and has major statistical flaws. Adjuvant chemotherapy after radiation is being explored in a large randomized trial by the American Radiation Therapy Oncology Group (RTOG). This trial recently completed accrual, results are not yet available. Some objective responses with currently available chemotherapy have been observed, but chemosensitivity shown so far was only modest in recurrent low-grade gliomas (Ref 17, Ref 18 and Table 3). In recent years, new chemotherapeutic agents have been developed specifically for primary brain tumors. Temozolomide, a novel alkylating agent has demonstrated activity in the treatment of recurrent high-grade glioma. Recent studies have also suggested some activity in low-grade glioma.
It has been shown that gliomas can differ markedly in their response to treatment and prognosis. The outcome of oligodendrogliial tumors is superior compared to astrocytic tumors. Furthermore, oligodendrogliomas show a higher sensitivity to chemotherapy. Over the last years there is growing evidence that gliomas may be classified by their genetic abnormalities. A combined loss of 1p and 19q can be found in about 70% of oligodendrogliomas. The significance of defined genetic lesions as 1p and 19q loss and others onto the responsiven ess of the disease to treatment (radio- and chemotherapy) is unclear. Numerous studies have shown the sensitivity of oligodendroglial tumors to chemotherapy (Ref 19). Oligodendroglial morphology together with the loss of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) is associated with response rates to chemotherapy up to 95-100% of patients (Ref 23). Most of these studies have been performed in patients with recurrent anaplastic tumors, and used the PCV chemotherapy regimen. From several small studies there is evidence that low-grade oligodendrogliomas are equally sensitive to chemotherapy (Ref 24). Although the regimen is generally well tolerated, cumulative myelosuppression can be an important limitation of the PCV regimen as well as fatigue and weight loss. These side effects often necessitate treatment delays and early discontinuation of the treatment.

Table 3. Chemotherapy for recurrent low-grade glioma.

<table>
<thead>
<tr>
<th>Author</th>
<th>No</th>
<th>Response</th>
<th>Survival</th>
<th>Therapy</th>
<th>Toxicity</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van den Bent 1998</td>
<td>52</td>
<td>OD: 9/20 (45%)</td>
<td>MTP 8 months</td>
<td>PCV</td>
<td>OD, OA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OA: (33%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RR 64%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soffietti 1998</td>
<td>26</td>
<td>12% CR, 50% PR, RR</td>
<td>MTP 24 months</td>
<td>PCV</td>
<td>17 OD, 9 OA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>62%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van den Bent 2000</td>
<td>30</td>
<td>3 CR, 5 PR, RR 26%</td>
<td>MTP 14 months</td>
<td>TMZ</td>
<td>22 OD, 8 OA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pace 2003</td>
<td>43</td>
<td>4 CR, 16 PR, 17 SD,</td>
<td>6 months-PFS</td>
<td>TMZ</td>
<td>29 Astro, 10 OA, 4 OD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 PD</td>
<td>76.8%, 12 mths</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PFS 39.6%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MTP 10 mths</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Astro, astrocytoma; OD, oligodendroglioma; OA, oligoastrocytoma, PA, pilocytic astrocytoma

Table 4: Neo-adjuvant chemotherapy for patients with a low-grade glioma

<table>
<thead>
<tr>
<th>Author</th>
<th>No</th>
<th>Response</th>
<th>Therapy</th>
<th>Toxicity</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mason 1996</td>
<td>9</td>
<td>6 PR, 3 SD (2 MR)</td>
<td>PCV/I-PCV</td>
<td>I-PC: high</td>
<td></td>
</tr>
<tr>
<td>(Ref 24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soffietti 1999</td>
<td>13</td>
<td>3 PR, 10 SD (2 MR), 2/5 improved symptoms</td>
<td>PCV</td>
<td>low</td>
<td>OD, OA</td>
</tr>
<tr>
<td>(Ref 25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mason 2001</td>
<td>8</td>
<td>2 PR, 5/6 symptoms improved</td>
<td>Mini-PCV</td>
<td>moderate</td>
<td>6 OD, 2 OA</td>
</tr>
<tr>
<td>(Ref 26)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buckner 2003</td>
<td>28</td>
<td>8 PR, 17 SD, 3 PD</td>
<td>PCV</td>
<td>moderate</td>
<td>17 OD, 11 OA</td>
</tr>
<tr>
<td>(Ref 27)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Astro, astrocytoma; OD, oligodendroglioma; OA, oligoastrocytoma, PA, pilocytic astrocytoma
Temozolomide is a novel alkylating agent, which is orally active and long-term administration has been shown feasible and safe. It is usually very well tolerated and no significant drug interactions have been reported. The recent EORTC study 26971 on first line temozolomide chemotherapy in recurrent oligodendroglioma has shown a response rate of over 50% to this agent (Ref 28).

Alternative dose-intense continuous dosing schedules have been investigated (Ref 29,Ref 30) Two studies have shown the feasibility of continuous dosing schedule. In a 21 days on/7 days off schedule patients can be treated with 85-100 mg/m2 daily with double the dose intensity compared to the standard 5-day regimen. (Ref 31). In a large randomized multicenter trial by the EORTC and NCIC 287 glioblastoma patients have been treated with a low-dose TMZ schedule (75 mg/m2 daily) for 6-7 weeks continuously with concomitant radiotherapy (Ref 32). These continuous low-dose schedules have been shown safe and well tolerated, however lymphocytopenia and in particular low CD4 counts may predispose to opportunistic infections (Ref 33, Ref 34) As low-grade tumors have a limited number of cells in the proliferation phase the investigation of a drug in a more continuous administration is theoretically attractive. Furthermore, increased response is expected by the depletion of the intratumoral alkyl-transferase (AGAT), a DNA repair enzyme being consumed by chronic alkylating agent chemotherapy.

<table>
<thead>
<tr>
<th>Author</th>
<th>No</th>
<th>Response</th>
<th>Survival</th>
<th>Toxicity</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brada 2003</td>
<td>29</td>
<td>10% PR, 48% MR, 38% SD, 1 pat. PD, 17/18 improved symptoms</td>
<td>36 mths PFS: 66% 36 mths OS: 82%</td>
<td>low</td>
<td>10 OD, 17 Astro, 2 OA</td>
</tr>
<tr>
<td>Annal Oncol (Ref 35)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinn 2003</td>
<td>46</td>
<td>CR 11, PR 17, SD 16 RR 61%</td>
<td>Med PFS 22 mths 12 mths PFS: 76%</td>
<td>low</td>
<td>20 OD, 16 Astro, 5 OA, 5 OA</td>
</tr>
<tr>
<td>(Ref 36)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mason personal communication</td>
<td>4</td>
<td>3 SD (2 mPR), 1 PD</td>
<td>Response duration 15-26 months</td>
<td>1 grade 3</td>
<td>4 OD</td>
</tr>
</tbody>
</table>

Astro, astrocytoma; OD, oligodendroglioma; OA, oligoastrocytoma, PA, pilocytic astrocytoma

Table 5. Initial treatment with temozolomide in patients with low-grade glioma.

### 1.5 Seizures

Seizures are a common presenting symptom in patients with low-grade glioma. Seizure control is an important goal when taking care of these patients. Occasionally, seizure cannot be sufficiently controlled by antiepileptic therapy. Intractable seizure may be a reason for beginning therapy in patients with low-grade glioma even in the absence of radiological progression. Intractable seizures and seizure response are defined in chapter 7.1.

### 1.6 Pathologic markers

Low-grade diffuse gliomas are classified as astrocytoma, oligodendroglioma or mixed oligoastrocytoma. The diagnosis of mixed oligo-astrocytoma is made in cases in which the histology of the tumor shows both astrocytic and oligodendrogial differentiation. Since oligodendroglial lineage is rather ill-defined and in many cases is only based on the perinuclear shrinkage artefact (“perinuclear halo”), there is considerable inter-observer disagreement in making the diagnosis. Astrogliotic lineage, on the other hand, consists of the presence of cell processes and the expression of glial fibrillary acidic protein. However, in many cases it is far from clear if the GFAP-positive
cells scattered in a tumor are either true tumor cells, or, alternatively, represent reactive astrocytes, obscuring the differentiation of a pure oligodendroglioma from a mixed oligo-astrocytoma.

From the literature it is clear that only a subgroup of the mixed oligo-astrocytomas show loss of 1p and/or 19q (or, in other words, only part of the mixed gliomas have the typical oligodendrogliarial genotype). Moreover, histologic specimens may represent the infiltration rim of an oligodendroglioma and, since many reactive astrocytes are present in such tumor borders, the erroneous diagnosis of astrocytoma may be made. To complicate matters even more, not all tumors with pure oligodendrogliarial phenotype show these characteristic chromosomal losses. In summary, histology cannot reliably distinguish oligodendroglioma (or tumors with oligodendrogliarial genotype) and therefore, up-front genotyping of all (low-grade) diffuse gliomas should be performed in order to screen for predictive markers of treatment susceptibility. Both oligodendroglial and astrocytic gliomas may show genetic losses in the mentioned chromosomal parts, albeit with different reported prevalences. With the present knowledge of the genetics of these tumors, there is interest for pre-entry genetic testing for these specific chromosomal abnormalities. We therefore propose an upfront stratification for patients with and without a loss of 1p for this study, to balance for a possible differential response to treatment.

Primary treatment with chemotherapy, in particular using a well tolerated oral agent with a favorable toxicity profile, may allow postponement of radiation therapy, thus possibly reducing late radiation-induced toxicity. Furthermore, early chemotherapy may be more effective than chemotherapy after radiation, because of an intact vascular bed and thus improved delivery of the chemotherapy to the tumor. Due to the infiltrative nature of the disease, chemotherapy has also activity beyond the radiation field.

### 1.7 Imaging – multimodality imaging in radiation treatment planning and follow-up

Magnetic resonance is the most sensitive technique currently available and the gold standard in neuro-oncology imaging. The MRI-scan, with and without i.v. contrast, is best using differently weighted sequences (T1, T2, FLAIR sequences). Typically, low-grade gliomas present as a non-enhancing mass on CT and as a low-intensity lesion on T1 weighted MRI images. T2 weighted images show an increase in signal intensity resulting in a homogeneous area. Contrast enhancement may be present in 8-15% of the cases (Ref 37, Ref 38, Ref 39). Metabolic imaging with MR spectroscopy measuring metabolic tumor activity reveals that cellular infiltration of low-grade glioma tumor cells is mainly restricted to the T2 weighted hyperintensity areas on MRI. Registration of MR spectroscopy and planning CT could therefore reduce the volume of the clinical target volume (CTV) in radiotherapy planning (Ref 40).

Patterns of spread and relapse are the basis for the definition of a clinical target volume (CTV) for radiotherapy planning. Low-grade glioma rarely cross the midline with the exception of tumors involving the corpus callosum; and infratentorial extension of initially supratentorial tumors is exceptional. The majority of recurrences in low-grade glioma are local. It is therefore crucial to define the correct area of tumor infiltration on imaging. The ideal way would be the use of co-registered images, combining the information of anatomy and metabolism using CT, MRI, PET and spectroscopy, however these sophisticated techniques are currently not available in routine clinical practice. CT images have limitations in poor visualization of non-enhancing abnormalities and MRI is recommended to define tumor extension in low-grade glioma. The CTV should encompass the visible tumor and a margin of 1 to 1.5 cm depending on the imaging technique used. There is no need to extend the field to the contralateral hemisphere or the cerebellum.

18- Fluorodeoxyglucose (FDG) -positron emission tomography (PET) imaging of the brain presents unique challenges because of the high background glucose metabolism of tumor cell in comparison to normal grey matter structures. Since metabolically active tissues such as the normal brain may
mask adjacent abnormalities, the interpretation of functional PET images can be improved by correlation with anatomic imaging. Co-registration of the MRI (or CT) and FDG-PET images is essential for accurate evaluation of brain tumors. In the brain PET based on amino-acid metabolism (e.g. tyrosine or methionine) is preferred. Nuutinen et al (Ref 41) performed a C-methionine PET scan in 13 patients with low-grade astrocytoma and found a significant correlation between Standardized Uptake Value (SUV)-ratio and prognosis. Brock et al (Ref 42) published the results of a pilot study in which 9 patients with recurrent high grade gliomas were treated with temozolomide. 18F- FDG PET scanning was performed before and after treatment. The (decrease in) metabolic rate of glucose, as calculated after FDG PET scanning, as well as the relative change in SUV, provided parameters to distinguish between responders and non-responders. Roelcke et (Ref 43) al performed 18F-FDG- and C-methionine PET in a group of 30 patients with low-grade gliomas with extensive follow-up. The measured tracer uptake in tumor (T) regions and contralateral (C) brain hemisphere was quantified by calculating the T/C ratio. The value of these ratio appeared to correlate with the rate of high grade tumor recurrence (C-methionine: p = 0.086; -FDG: p = 0.035). Several other published studies have linked the results of 18F-FDG- and C-methionine PET scanning to the treatment outcome of patients with low-grade gliomas. Pre-treatment methionine PET is a prognostic indicator in patients with low-grade gliomas. This implies that PET may be a valuable tool in the clinical management of patients with low-grade gliomas (Ref 44, Ref 45).

11C-methionine PET is more sensitive in differentiating between tumor and normal brain as well as between different tumor grades. Differentiation between gliomas and non-tumor lesions by a simple threshold was correct in 79% (Ref 46). In detecting tumor recurrence the sensitivity and specificity of MET-PET scanning were determined to be 77.8 and 100%, respectively (Ref 47) 11C-methionine also avidly accumulates in brain tumors and has the advantage of low background cortical activity. The relationship between degree of uptake of these agents and tumor grade is not fully established. PET with 11C-methionine may have the potential for distinguishing between post-therapeutic lesions and tumor recurrence with a higher accuracy than CT (Ref 48). These tracers may be useful in specific clinical situations, such as tumor localization for treatment planning or evaluation of low-grade tumors. The registration of PET and MR is helpful in defining the topographical relationship of regions with increased tracer up-take with cerebral anatomy. Finally, PET has the capacity to detect regions of high focal tracer uptake within the tumor that possibly constitute regions with a higher malignancy and higher tendency to recurrence.

The current EORTC study for low-grade gliomas offers the possibility to determine the clinical value of PET (with amino-acid tracers where available) both for therapy monitoring and volume definition in a prospective manner.

1.8  Rationale

Based on the 3 randomized radiotherapy trials for patients harbouring a low-grade glioma mentioned above there seems to be no survival advantage for immediate radiotherapy or radiation doses above 45 - 50 Gy. Additionally, radiotherapy carries the risk of side effects on cognition. Survival appears to depend mainly on age, grading, histology and neurologic function. Based on the data of the two randomized EORTC trials a group of patients with an inferior prognosis who need immediate therapy can be identified. Therefore a study is proposed for patients carrying prognostic factors for a worse outcome as identified by the previous randomized studies. In this study patients for whom treatment with radiotherapy is commonly prescribed will be randomized between radiotherapy versus chemotherapy with temozolomide.

Temozolomide has been demonstrated to have an activity in low-grade glioma. In particular, several studies have shown a higher chemosensitivity for tumors with loss of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q). The latter is especially true for oligodendrogliomas. For this reason, we propose randomization only after genetic testing and stratification for LOH on 1p. The study will investigate if the use of temozolomide improves the
time to progression as compared to radiotherapy. Late toxicity, quality of life and cognitive function are important secondary endpoints.

This study design will allow defining in the future different and tailored treatment strategies not only on individual risk factors, but also on genetic particularities of some tumors. Furthermore, through additional translational research the knowledge about genetic alterations other than 1p/19q for low-grade glioma may favorably influence future diagnostic and therapeutic decisions.

The proposed study is the first randomized neuro oncology study which prospectively stratifies also for molecular markers. This may allow identifying a subgroup of patients who possibly show a particular improvement with chemotherapy.

2 Objectives of the trial

2.1 General objectives

2.1.1 Main objectives

A randomized study to demonstrate a difference in progression-free survival for primary treatment with temozolomide versus primary irradiation (primary objective) and to assess (secondary objectives)

♦ whether OS can be prolonged by primary chemotherapy with temozolomide
♦ whether the incidence of late toxicity can be decreased by using primary chemotherapy
♦ the toxicity profile of the two treatments and the quality of life of the patients

2.1.2 Cytogenetic objective

The impact of 1p deletions in low-grade gliomas: prognostic effect of cytogenetic deletions detected in tumors on PFS overall and by treatment group. Benefit for patients with LGGs and deletions treated with TMZ compared to radiotherapy alone with respect to survival. Interaction between treatment and cytogenetic features.

2.2 End-points

Primary (see chapter 7 for definition):

♦ Progression-free survival

Secondary (see chapter 7 for definitions):

♦ Overall survival
♦ Quality of life and Minimental State Examination (MMSE)
♦ Adverse events
♦ Neurocognitive function (for dedicated centers)
3 Patient selection criteria

3.1 At the time of registration

♦ Histologically proven low-grade glioma
  ♦ Astrocytoma WHO grade II (gemistocytic, fibrillary and protoplasmatic)
  ♦ Oligoastrocytoma WHO grade II
  ♦ Oligodendroglioma WHO grade II
♦ Supratentorial tumor location only
♦ WHO performance status \(\leq 2\)
♦ Age \(\geq 18\) years
♦ No previous chemotherapy or radiotherapy for brain tumor
♦ Absence of known HIV infection, chronic hepatitis B or hepatitis C infection
♦ Absence of any medical condition, which could interfere with oral medication intake (e.g., frequent vomiting, partial bowel obstruction)
♦ Availability of histopathologic slides for central pathology review (see chapter 6.1.1, “criteria of evaluation”; and chapter 13 “pathology”)
♦ Availability of tumor material (paraffin-embedded tissue blocks) and blood for molecular testing*
♦ Before patient registration, written informed consent must be obtained. Informed consent includes collection, transfer and analysis of the pathological material for molecular biology testing (1p testing) as well as treatment according to subsequent randomization. Informed consent will be obtained according to ICH GCP, and any applicable local regulations. A separate informed consent will be obtained for translational research.

* Patients having had previous 1p testing in a different laboratory than the one specified for this study, will need repeated testing in the central reference laboratory.

3.2 At the time of randomization

♦ Histologically proven low-grade glioma **

** (based on the latest performed histology, if no repeat biopsy has been performed, based on initial histology)
  ♦ Astrocytoma WHO grade II (gemistocytic, fibrillary and protoplasmatic)
  ♦ Oligoastrocytoma WHO grade II
  ♦ Oligodendroglioma WHO grade II;
♦ Supratentorial tumor location only
♦ Not candidate for treatment exclusively by surgery
♦ Requiring treatment as demonstrated by at least one of the following criteria:
  ♦ Age \(\geq 40\) years
  ♦ Radiologically proven progressive lesion
♦ New or worsening neurological symptoms other than seizures only (focal deficits, signs of raised intracranial pressure, mental deficits)
♦ Intractable seizures defined as:
  Suffering from persistent seizures, defined as having both:
  ♦ persistent seizures interfering with every day life activities other than driving a car
  **AND**
  ♦ failed three lines of anti-epileptic drug regimen, including at least one combination regimen
♦ WHO performance status ≤ 2
♦ RTOG Neurological Function 0-3
♦ central 1p testing performed (for stratification: 1p deleted versus 1p normal versus undeterminable)
♦ No previous irradiation to the brain
♦ No prior chemotherapy
♦ Patients must have recovered from prior surgery, if applicable
♦ Adequate hematological, renal and hepatic function according to all of the following laboratory values (to be performed within 6 weeks, inclusive, prior to randomization):
  ♦ Absolute neutrophil count ≥ 1.5 × 10^9/l
  ♦ Platelets ≥ 100 × 10^9/l
  ♦ Serum creatinine ≤ 1.5 times upper limit of laboratory normal
  ♦ Total serum bilirubin ≤ 1.5 times upper limit of laboratory normal
  ♦ ASAT(AST) or ALAT(ALT) ≤ 2.5 times upper limit of laboratory normal
  ♦ Alkaline phosphatase of ≤ 2.5 times upper limit of laboratory normal
♦ Absence of known HIV infection, chronic hepatitis B or hepatitis C infection
♦ Absence of any other serious medical condition according to the medical judgment of the physician prior to randomization
♦ Absence of any medical condition, which could interfere with oral medication intake (e.g., frequent vomiting, partial bowel obstruction)
♦ Absence of previous or concurrent malignancies at other sites with the exception of surgically cured carcinoma in-situ of the cervix and non-melanoma skin cancer
♦ All patients of reproductive potential (male and female) must use effective contraception for the whole duration of the treatment and until 6 months thereafter. Females must not be pregnant or lactating
♦ Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule as discussed with the patient before randomization
♦ Completion of baseline quality of life questionnaires (QLQ-C30 + BN20) must be obtained before randomization (see Appendix D, Appendix I and Appendix J)
Completion of baseline neuropsychological testing must be obtained before randomization (see Appendix M) for selected centers. Patients can be registered and randomized in this trial only once.

4 Trial Design

This is a prospective randomized phase III study with an initial registration step.

In order to enter the study and proceed to molecular testing, patients are required to sign an informed consent and will be registered at the EORTC data center. Patients may be registered at initial pathological diagnosis even if their disease does not yet necessitate therapy.

Whenever the evolution of their disease necessitates treatment and once the results of molecular testing are available, eligible patients will be randomized 1:1 to an active treatment: either radiotherapy (RT) alone or temozolomide (TMZ) alone. If the interval between initial histological diagnosis (registration) and subsequent progression (randomization) is > 12 months, repeat biopsy is recommended, but not mandatory. However, in patients who would already be progressive at the time of initial pathological diagnosis (registration), there is no minimum time interval to randomization except the one needed to obtain the results of the 1p testing (usually 2-3 weeks).

Treatment should start within 6 weeks after randomization.

A separate informed consent is required for the optional translational research.

- **Arm 1:** Radiotherapy (control arm), 50.4 Gy, standard fractionation (28 x 1.8 Gy), conformal techniques
- **Arm 2:** Temozolomide 75 mg/m2 daily x 21 days, q 28 days until progression or for max. 12 cycles (experimental arm)

Stratification will be performed by:
- institution
- 1p deleted versus 1p normal versus undeterminable
- contrast enhancement: +/- contrast on MRI
- age: <40 years versus ≥ 40 years
- WHO performance status: 0 or 1 versus 2
5 Therapeutic regimens, expected toxicity, dose modifications

5.1 Radiotherapy
Radiotherapy will consist of a conventionally fractionated regimen, delivering a total dose of 50.4 Gy, once daily 1.8 Gy per fraction, 5 days per week, for a total of 28 fractions.

Treatment should start within 6 weeks of randomization.

5.1.1 Physical Factors
Patients will be treated on megavoltage equipment i.e., linear accelerator beams with minimal nominal energy of 6 MV. Source Axis Distance (SAD) should be at least 100 cm. Electrons, particles and implants are not permitted.

5.1.2 Planning volumes
Target volume definition should be based on magnetic resonance imaging (MRI). Whenever possible, image fusion (= co-registration) with MRI and/or PET scans should be used for target volume definition. Throughout the whole study the same PET tracer for every patient shall be used for diagnosis, planning and follow-up. The tracer used in each institute will be documented. Centers having the possibility of image co-registration should use this technique for all trial patients. Accuracy of image co-registration should stay within < 0.5 cm. Imaging, documenting the progression or post-operative residual tumor (within 3 months) is mandatory.

CT-based 3-D treatment planning using beam’s-eye-view and the registration of Dose-Volume-Histograms is mandatory for all centers. Centers, receiving the equipment for 3D planning later during the course of the study shall then switch to 3D-planning

♦ The Gross Target Volume (GTV) is defined by the region of high signal intensity area on T2 weighted MRI or FLAIR sequences corresponding to the hypodense area on CT images including any possible areas of enhancement on CT and/or tracer uptake on PET.

♦ If the patient has undergone surgery previously, postoperative imaging is mandatory and the GTV should be defined on post-operative imaging as the operative cavity and the residual tumour.

♦ The Clinical Target Volume (CTV) is defined as the GTV plus a margin to account for unseen microscopic spread using 3-D volumetric expansion (1-1.5 cm is recommended).

♦ The CTV extends to the contralateral hemisphere only when a midline structure as the corpus callosum is invaded by tumor as visualized on T2 weighted MRI. The tentorium and meninges should be considered as anatomical borders and therefore a margin of 5 mm is sufficient to encompass the microscopic spread at these borders.

♦ The Planning Target Volume (PTV) will depend on treatment set-up uncertainties and CT slice thickness, method of immobilization etc. Likely margins to be added to the CTV are 0.5-0.7 cm.

♦ Margins have to be added by 3-D volume extension.
5.1.3 **Planning procedure**

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

♦ Planning CT is mandatory

♦ A maximum CT slice thickness of 3 mm for a good quality of Digitally Reconstructed Radiograph (DRR) and margin definition is recommended.

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

♦ PET co-registration is recommended if available.

♦ Conventional or virtual simulation is mandatory.

♦ Planning with beams eye views of each beam is mandatory.

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

♦ Planning should be conformed to ICRU 50/62 criteria for target volume coverage, dose normalization and homogeneity (see 5.1.6).

5.1.4 **Treatment technique**

♦ A linear accelerator with a minimal nominal beam energy of 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. **WARNING**: 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.

♦ Treatment with intensity-modulated radiotherapy is allowed provided that a conventional fractionation and dose prescription according to ICRU is used. No simultaneous integrated boost is allowed.

♦ Stereotactically guided radiotherapy is allowed as long as conventional fractionation and dose prescription according to ICRU is used.

5.1.5 **Acute toxicity and treatment interruption**

♦ Expected acute toxicity of conventional radiotherapy include headache, fatigue, hairloss, skin reaction, 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: 6.5 weeks (theoretical optimal treatment time: 5.5 weeks (40 days).

♦ Individual reasons of 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.
5.1.6 Dose prescription, fractionation and intervals

- Dose prescription and recording according to ICRU 62-criteria (Ref 49).
- Dose homogeneity requirements in the PTV shall be -5% + 7%. This also applies to IMRT and stereotactic radiotherapy.
- The PTV should be encompassed by the 95% isodose. The 90% isodose is acceptable in close proximity to organs-at-risk.
- Total dose: 50.4 Gy
- Dose per fraction: 1.8 Gy in 28 daily fractions

5.1.7 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 higher doses than 107% of the maximum 55 Gy.
- The eye balls including the lens and retina should not be included in any direct beam. Maximum dose for the lens: < 5Gy, for the retina: ≤ 40 Gy.
- The contralateral (to the tumor location) normal brain may not receive >50-60% of the total dose.

5.1.8 Dose reporting

- The isodose distributions will be calculated and printed for documentation: in three planes through the isocentre (transverse, coronal and sagittal planes).
- 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 ccm: 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 must be used for set-up verification.

5.1.9 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 (see section 7.6).
5.2 Temozolomide

5.2.1 General drug information

Generic name: Temozolomide
Commercial name: Temodal
Chemical names: 3,4-Dihydro-3-methyl-4-oxoimidazo-[5,1-d]-1,2,3,5-tetrazin-4-(3H)-one 8-Carbamoyl-3methylimidazol[5,1-d]1,2,3,5-tetrazin-8-carboxamide
Empirical Formula: C₆H₆N₆O₆
Molecular weight: 194.15
Appearance: White to light tan/light pink powder
Melting point: Decomposes at 206°C
Stability: As a solid temozolomide is thermally stable and does not decompose when exposed to normal light conditions. In solution, temozolomide rapidly hydrolyses in a basic environment. Temozolomide demonstrates improved stability in an acid environment, but hydrolyses when heated. Temozolomide 20mg and 100mg capsules are projected to be stable for 30 months, when stored between 2°C and 30°C in amber glass bottles. Temozolomide 5mg and 250mg capsules are projected to be stable for 12 months under the same conditions. The product label recommends storage between 2°C and 30°C.
Half life: 1.24 hours at 37°C in phosphate buffer (0,2M) at pH 7.4

5.2.2 Dosing of Temozolomide

Treatment should start within 6 weeks of randomization. Treatment with temozolomide will be continued until disease progression but no longer than 12 treatment cycles (approx. 1 year).

Temozolomide will be administered continuously at a daily dose of 75 mg/m² daily x 21 days, q 28 days. The drug will be administered orally once a day. The dose administered will be determined using the body surface area (BSA) calculated at the beginning of the treatment. The BSA will be calculated from the height and weight obtained at the pretreatment visit.

Capsules of temozolomide are available in 5, 20 and 100, strengths. The daily dose will be rounded to the nearest 10 mg.

Patients should be told to swallow the whole capsules in rapid succession without chewing them. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose.

An anti-emetic prophylaxis is usually not required for the continuous daily dosing schedule. However, prior to administration of the initial dose, we recommend a prophylaxis with a 5-HT₃-antagonist or metoclopramide.
5.2.2.1 Temozolomide dosing modification

In case of toxicity as outlined below, chemotherapy will be temporarily suspended. IF one or more toxicities are present with the following severity:

♦ ANC < 1.0 x 10^9/L (Grade 3-4)
♦ platelet count 25-< 75 x 10^9/L (Grade 2-3)
♦ CTC non-hematological toxicity Grade 2 (except alopecia, nausea and vomiting)

THEN treatment with temozolomide should be withheld until all of the following conditions are met:

♦ ANC ≥ 1.5 x 10^9/L (Grade ≤1)
♦ platelet count ≥ 75 x 10^9/L (Grade ≤1)
♦ CTC non-hematological toxicity Grade ≤1 (except for alopecia, nausea and vomiting)

Patients with platelet count <25 (Grade 4) or treatment-related CTC non-hematological toxicity grade 3-4 (except alopecia, nausea and vomiting) should immediately and definitively discontinue treatment.

In case of hematological toxicity a complete blood count should be performed at least twice weekly until resolution.

In case of hematological toxicity with ANC grade 3-4 and/or platelet count grade 2-3, the patient should be assessed at least weekly with history, physical examination and relevant laboratory test(s). When resumed, the treatment in those patients should be restarted at a dose of 60 mg/m².

The treatment will last until progression or for maximum 12 cycles.
### Summary of TMZ delay or discontinuation

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Value</th>
<th>CTC Grade</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Worst observed grade during cycle</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANC</td>
<td>&lt; 1.0 x 10⁹/L</td>
<td>3 or 4</td>
<td>Delay TMZ until ≥ 1.5 x 10⁹/L and reduce further TMZ dose at 60 mg/m²</td>
</tr>
<tr>
<td>Platelets count</td>
<td>≥ 25 and &lt; 75 x 10⁹/L</td>
<td>2 or 3</td>
<td>Delay TMZ until ≥ 75 x 10⁹/L and reduce further TMZ dose at 60 mg/m²</td>
</tr>
<tr>
<td></td>
<td>&lt; 25 x 10⁹/L</td>
<td>4</td>
<td>Discontinue TMZ, further therapy should be discussed with the study coordinator</td>
</tr>
<tr>
<td>CTC non-hematological toxicity (except alopecia, nausea and vomiting)</td>
<td></td>
<td>2</td>
<td>Delay TMZ until recovered to CTC ≤ Grade 1</td>
</tr>
<tr>
<td>CTC non-hematological toxicity (except alopecia, nausea and vomiting)</td>
<td></td>
<td>3-4</td>
<td>Discontinue TMZ</td>
</tr>
<tr>
<td><strong>Values after maximum 3 weeks rest (from d28 of last cycle)</strong> (any of)</td>
<td>Value</td>
<td>CTC Grade</td>
<td>Action</td>
</tr>
<tr>
<td>ANC</td>
<td>&lt;LLN and ≥ 1.0 x 10⁹/L</td>
<td>1-2</td>
<td>Delay TMZ for a maximum of 4 weeks and retreat at full dose when grade 0</td>
</tr>
</tbody>
</table>

Patients who would remain in conditions not permitting treatment due to toxicity 4 weeks after normal re-treatment day (i.e.: d28 + 4 weeks) will definitively stop protocol treatment. Patients repeatedly experiencing grade 3 or grade 4 toxicity after dose reduction will discontinue protocol therapy permanently.

### 5.2.3 Drug supply

Temozolomide will be supplied free of charge by Schering Plough. Drug supply must be ordered through the Medical Department of the local Schering Plough Affiliate.
5.2.4 Packaging, dispensing and storage

Packaging and labeling of Temozolomide will be in accordance with Good Manufacturing Practice (GMP) for clinical trials. Temozolomide will be provided in amber glass bottles in strengths of 5 mg, 20 mg, 100 mg, and/or 250 mg. Each temozolomide label will indicate the dosage strength, number of capsules in each bottle, lot and/or PSR number(s), both the EORTC study number (22033-26033) and the Schering Plough study number (P03646), storage conditions, and will contain a caution statement in compliance with local requirements.

The label will also include space for the study site to record patient number, dispensation date, and bottle number.

Investigators and pharmacists should note that the clinical trial supplies may only be used for the clinical trial for which they are indicated. They must not be employed for any other trial, not even for Temozolomide studies on another type of tumor, or for any other clinical use.

Temozolomide must not be repackaged at investigational sites, rather it must be dispensed to study subjects in the original packaging with the original labeling provided.

Temozolomide must be stored in a secure hospital pharmacy according to storage conditions specified on the label. An expiration date and/or recertification information will be provided by Schering Plough. Study drug must be stored in such a way that it cannot be mixed up or confused with other medications, like clinical trial supplies or medicines for routine clinical use.

Strict recommendations will be made to the patients to keep Temozolomide in a cool dry place in the original amber glass bottle. The patients will be asked to return unused medications in order to perform appropriate drug accountability and check on patient compliance.

5.2.5 Known potential toxicities of temozolomide

Known potential toxicities of temozolomide are mainly hematological (leucopenia, lymphopenia, thrombocytopenia, and anemia) and nausea/vomiting. Further, liver enzyme abnormalities, lethargy, rash, headache, alopecia, constipation, fatigue/malaise, anorexia, hyperglycemia and diarrhea have been reported. Refer to Investigator Brochure or prescription information for more details. Rats given temozolomide in recent multidose toxicity studies have developed adenocarcinoma of the breast, fibrosarcomas, malignant Schwannomas (a variant of fibrosarcoma), keratoacanthomas and basal cell adenomas. Similar studies conducted in dogs did not reveal any similar findings. The significance of this finding for humans is not known presently.

Temozolomide is potentially mutagenic and should be handled with appropriate precautions by both staff and patients. Patients with known or suspected hypersensitivity to temozolomide should not be treated with temozolomide. There are no data available on the effect or management of temozolomide overdose.

Temozolomide when given on a continuous administration schedule may induce profound lymphocytopenia with an increased risk of opportunistic infections. Long term exposure to alkylating agent chemotherapy has been associated with myelodysplastic syndromes and secondary leukemias. This usually occurs 10-15 years after therapy.

5.3 Non-study treatment

5.3.1 Concomitant medications

In the CRF use of corticosteroids, antiepileptic drugs and anti-emetics will specifically be recorded with date of start and end of therapy.
5.3.1.1 Anti-emetics

Prophylactic anti-emetics will be administered at the discretion of the treating physician. The prophylactic use of a 5-HT3-antagonist is recommended before the initial 2-3 temozolomide doses. Most patients will not require antiemetic prophylaxis for the remainder of the treatment, mild nausea can usually be easily controlled with metoclopramide or domperidon (Motilium®). The latter is the drug of choice in patients with seizure. The continuous use of a 5HT3-antagonist is discouraged due to the risk of headaches and constipation.

5.3.1.2 Corticosteroids

Corticosteroids are administered at the treating physician’s discretion.

Dose and length of steroid-use will be reported.

<table>
<thead>
<tr>
<th>Glucocorticoid</th>
<th>Approximate equivalent dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short acting</strong></td>
<td></td>
</tr>
<tr>
<td>Cortisone</td>
<td>25 mg</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>20 mg</td>
</tr>
<tr>
<td><strong>Intermediate acting</strong></td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>5 mg</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5 mg</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>4 mg</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>4 mg</td>
</tr>
<tr>
<td><strong>Long acting</strong></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.75 mg</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>0.6-0.75 mg</td>
</tr>
</tbody>
</table>

Table: Glucocorticoid equivalencies

5.3.1.3 Pneumocystis carinii prophylaxis (Temozolomide arm)

*P. carinii* prophylaxis should be considered in patients receiving temozolomide and concomitant corticosteroids. Both, corticosteroid therapy and continuous temozolomide therapy induce lymphocytopenia. Patients receiving any of these drugs or both concomitantly are at an increased risk for opportunistic infections. For patients on temozolomide, repeat evaluation of the CD4 counts is recommended. If CD4 values are < 200/mm$^3$, PcP-prophylaxis is strongly suggested.

One of the following treatments should be considered:

- Pentamidine inhalations Once every 4 weeks
- Trimethoprim-sulfamethoxazole (Bactrim forte®) 1 tablet daily or 3 times a week
- Dapsone 100 mg daily

5.3.1.4 Anti-epileptic drugs

The use of anti-epileptic drugs is left to the discretion of the treating physician. Drug type will be recorded.
5.3.1.5  **Contraceptive measures**

All patients (including female partners of male patients) must use an effective contraception method for the whole duration of the treatment and until 6 months after the end of the treatment.

5.3.2  **Prohibited medications**

1. Growth factors should not be used to induce elevations in neutrophil count for the purposes of administration of temozolomide on the scheduled dosing interval or to allow treatment with temozolomide at a higher dose or to avoid interruption of the treatment. Erythropoietin may not be used.

2. No other investigational drugs will be allowed during the study.

3. Additionally, investigators should restrain from using substances known as radiosensitizers or radioprotectors (e.g. COX2, thalidomide, amifostine) on a regular basis during radiotherapy treatment. Occasional use of NSAIDs for pain is allowed.

5.3.3  **Prohibited other treatments**

Surgical procedures for tumor debulking, other types of chemotherapy, immunotherapy or biologic therapy must not be used until documented tumor progression.

Simultaneous integrated boost with IMRT (intensity modulated radiotherapy) is not allowed.

Adjuvant chemotherapy in the radiotherapy alone arm is not allowed.

Any other non anti-cancer therapy prior to progression is at the treating physician’s discretion, but should be documented in the patient medical files.

5.4  **Treatment in case of tumor progression**

Progression is defined in chapter 7.3.

Salvage treatments:

Any therapy given after progression is considered as off-protocol treatment and is left at the treating physician’s discretion. It is however recommended that patients treated with primary TMZ in the experimental arm shall receive radiotherapy and patients treated with radiotherapy first should be treated with temozolomide (free temozolomide for salvage treatment will however NOT be provided). The type and number of salvage treatments will be recorded on the case report forms.

6  **Clinical evaluation, laboratory tests & follow-up**

6.1  **At registration**

6.1.1  **Pathology: Pre-randomization genetic testing**

Since there is disparity between histology and genotype in gliomas, the tumors will be screened for losses of chromosome arm 1p and 19q. At randomization patients will be stratified according to 1p loss. Genotyping will be performed centrally in Europe (see chapter 17.4 and Appendix M) and in Canada.

Details of the pathological review process, the molecular subtyping, translational research and shipment and storage of material can be found in chapters 13 and 17 and Appendix L.
The following material for molecular subtyping, histopathological review and for translational research should be made available:

♦ Paraffin blocks of embedded tumor material
♦ 2 x 10 ml of citrated full blood
♦ Shipment should be accompanied by a copy of the anonymized pathology report, identifying the patient with character code, trial and sequential ID (seqid) number and date of birth (see Appendix L)
♦ Frozen tumor material and lymphocytes to be used for translational research are stored at the treating institution. (see Appendix L)

From the central molecular and neuropathology laboratory in Berlin, the samples will be further processed and subsequently sent for pathology review to the pathology review panel of the EORTC Brain Tumor Group (see chapter 17.3).

### 6.1.2 Other examinations and tests (within 6 weeks prior to registration)

♦ Complete medical history
♦ History of drug intake
♦ Physical examination with measurement of vital signs including height and weight.
♦ WHO-ECOG performance status.
♦ Evaluation of seizure status and RTOG neurologic function (see chapter 7.1 and 7.3.2 and Appendix O)

To be eligible for enrolment, the patient must meet all selection criteria as specified in chapter 3.1. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and the required evaluations, and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrolment and prior to any study-specific evaluations (e.g., Quality of Life questionnaire).

### 6.2 From registration until randomization

Documentation of patient’s status will be supplied to the Data Center at least on a 6-monthly basis.

### 6.3 Immediately prior to randomization (within 6 weeks of randomization)

♦ Complete medical history
♦ Complete history of drug intake
♦ Physical examination with measurement of vital signs including height and weight.
♦ WHO-ECOG performance status. (see Appendix C)
♦ Evaluation of seizure status and RTOG neurologic function (see chapter 7.1 and 7.3.2 and Appendix O)
♦ Mini Mental State Examination (MMSE) (see Appendix K).
♦ Neurocognitive testing for selected, specified centres (see chapter 7.2 and Appendix N)
Assessment of Quality of Life: EORTC QLQ-C30+BN20 (Brain Tumor Module) (see Appendix D, Appendix I and Appendix J).

Baseline adverse events scoring by CTCAE version 3.0

Complete blood count (including hemoglobin and hematocrit, total white blood count, differential white blood count, platelet count).

Serum chemistry (including sodium, potassium, calcium, creatinine, glucose, ASAT (SGOT) and/or ALAT (SGPT), alkaline phosphatase, total bilirubin, total protein).

Postoperative diagnostic imaging is mandatory in patients who have undergone surgical debulking within 3 months prior to study entry (should be performed within 72 hours after surgery). If no immediate postoperative imaging is available, unequivocal tumor progression should be demonstrated by two MRIs at an interval of > 1 month.

Gadolinium-enhanced MRI of the brain mandatory. PET if available

The tumor measurements will be recorded on the case report forms, as well as midline involvement (shift/involvement of midline structures)

To be eligible for enrolment, the patient must meet all selection criteria as specified in chapter 3.2. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and the required evaluations, and all regulatory requirements for informed consent.

6.4 Follow-up (during treatment and until progression)

6.4.1 The first follow-up (FU) will be performed 3 months after the start of therapy, then at 3-monthly intervals until progression.

The same schedule of evaluation must be used for patients in both treatment arms. Formal evaluation by the investigator is required for all patients:

Interim medical history

Interim history of drug intake

Physical examination with measurement of vital signs including weight.

WHO-ECOG performance status.

Evaluation of seizure status and RTOG neurologic function (see chapter 7.1 and 7.3.2 and Appendix O)

Mini Mental State Examination (MMSE) (see Appendix K).

Neurocognitive testing for selected, specified centres (every 6 months, see chapter 7.2 and Appendix N)

Assessment of Quality of Life: EORTC QLQ-C30+BN20 (Brain Tumor Module) (see Appendix D, Appendix I and Appendix J).

Adverse event scoring according to the CTCAE version 3.0 (see chapter 7). Special attention should be given to potential late radiation toxicity.

Radiological tumor assessment (every 6 months or in case of neurological progression; see chapter 7.3.2):

Gadolinium-enhanced MRI. PET if available and if done at baseline.
Note: The marker used for PET scanning should be the same as before treatment start (e.g., FDG or amino acids like methionine or tyrosine).

6.4.2 Additional examinations for patients receiving radiotherapy

Patients receiving radiotherapy are usually seen by their physician once a week during treatment. The first follow-up visit and examinations are scheduled at month 3 after the start of therapy, thus approximately 6-8 weeks after the end of radiotherapy.

6.4.3 Additional evaluations for patients receiving Temozolomide

6.4.3.1 Prior to day 1 of each cycle of TMZ

The following evaluations must be performed within 72 hours prior to day 1:

♦ Interim medical history.
♦ Physical examination (see Appendix O), vital signs and weight.
♦ WHO-ECOG performance status (see Appendix C)
♦ Complete blood count (including hemoglobin and hematocrit, total white blood count, differential white blood count, platelet count). During the initial 2 cycles, weekly complete blood counts should be performed.
♦ Adverse event scoring according to CTCAE v3.0

Prior to day 1 of cycle 1 only:

♦ Chest X-ray
♦ CD4 T-lymphocyte count

6.4.3.2 Every 3 months during treatment

♦ Serum chemistry (including sodium, potassium, calcium, creatinine, glucose, ASAT (SGOT) and/or ALAT (SGPT), alkaline phosphatase, total bilirubin, total protein)
♦ CD4 T-lymphocyte count

6.5 After disease progression

♦ Patients are followed every 6 months for survival.
### 6.6 Summary of the examinations

<table>
<thead>
<tr>
<th>At registration</th>
<th>Prior to random*</th>
<th>From treatment start until progression</th>
<th>After progression until death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Both groups unless specified otherwise</td>
<td>TMZ only Extra assessments</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>6 weeks</th>
<th>6 weeks</th>
<th>q 3-mo</th>
<th>q 6-mo</th>
<th>Prior to day 1 of each cycle</th>
<th>q 6-mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical history</td>
<td>♦</td>
<td>♦</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug intake: steroid consumption and antiepileptics</td>
<td>♦</td>
<td>♦</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical exam</td>
<td>♦</td>
<td>♦</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital signs, weight</td>
<td>♦</td>
<td>♦</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO PS</td>
<td>♦</td>
<td>♦</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure status (^1)</td>
<td>♦</td>
<td>♦</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological exam</td>
<td>♦</td>
<td>♦</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mini-mental status (^2)</td>
<td>♦</td>
<td>♦</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurocognitive function (^3)</td>
<td>(♦ )</td>
<td>(♦ )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of life forms (^4)</td>
<td>♦</td>
<td>♦</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>♦</td>
<td>♦</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology (^5)</td>
<td>♦</td>
<td></td>
<td>♦ (+ weekly for the first 2 cycles)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry (^6)</td>
<td>♦</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citrat blood for 1p (^7)</td>
<td>❇</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 count (^8)</td>
<td></td>
<td></td>
<td>♦ q 3-mo</td>
<td>♦ q 3-mo until normalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCP prophylaxis (^9)</td>
<td>♦</td>
<td></td>
<td></td>
<td></td>
<td>♦ if CD4 count ≤ 200/mm (^3)</td>
<td></td>
</tr>
<tr>
<td>Gd-MRI (^{10})</td>
<td>♦</td>
<td>(♦ )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET (if available)</td>
<td>(♦ )</td>
<td>(♦ )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest X-ray</td>
<td></td>
<td></td>
<td>♦ (cycle 1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed consent</td>
<td>♦</td>
<td>(♦ )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathology review (^7)</td>
<td>❇</td>
<td>❇</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paraffin blocks (^7)</td>
<td>❇</td>
<td>❇</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frozen tumour + lymphocytes (^13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>at any surgery (optional)</td>
<td></td>
</tr>
<tr>
<td>Survival status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* From registration until randomisation, documentation of patient status will be supplied to the Data Centre on a 6-monthly basis

♦ mandatory;

(♦ ) mandatory in selected centres, where available/if applicable, q3 and q6 months resp.

◇ in case suspected tumour progression; ❇ after registration; ❇ must be completed
| 1. | Seizures, see chapter 7.1; |
| 2. | MMSE, see appendix J; |
| 3. | Neurocognitive function for dedicated specified centers only, **q6 months**, see appendix M; |
| 4. | Quality of life: EORTC QLQ-30 + BN20 {Brain Tumor Module}, (see Appendix D, H, and I); |
| 5. | Hematology: hemoglobin; hematocrit; WBC (leucocytes) with differential: neutrophils, lymphocytes; platelets; |
| 6. | Chemistry: Na, K, Ca, serum creatinine, glucose, ASAT (GOT) and/or ALAT (GPT), alkaline phosphatase, total bilirubin, total protein; |
| 7. | For pathology review and 1p testing: send parafin embedded tumor material and 2 x 10ml of citrat full blood together with anonymized pathology report (sewid ID, initials and date of birth) to reference laboratory (see Appendix K); |
| 8. | CD4 count: before starting temozolomide, and then every 3 months during treatment and follow-up until normalization; |
| 9. | Pneumocystis carinii prophylaxis if CD4 count < 200, see chapter 5.4.1.3); |
| 10. | Attach a copy of radiology reports with the CRF and forward to data center; if no MRI available, CT admissible after approval by the Study Coordinator; |
| 11. | MRI used for baseline: should be performed within 72 hours after tumor resection. If no immediate postoperative imaging is available, unequivocal tumor progression should be demonstrated on two MRI at an interval of > 1month; |
| 12. | Resign informed consent if > 12 months since registration; |
| 13. | At any surgery, to be stored at the treating institution, whenever participating to the TR side study; |
7 Criteria of evaluation

7.1 Definition of seizure activity

Seizures pose a major threat to the well being of patients with low grade glioma, and the presence of seizures will be a secondary endpoint for this study. For this study seizures are divided into generalised tonic-clonic seizures and partial seizures with or without loss of conscience, the latter includes complex partial seizures. The number of seizures of each type during the last month will be recorded. The use and number of anti-epileptic drugs will also be noted.

The number of monthly seizures will be assessed at baseline and at every follow-up visit:

If only one type of seizures is present:

♦ A $\geq$ 50% reduction of seizures at any follow-up compared to baseline will be considered a response

♦ A $\geq$ 50% increase in seizure activity at any follow-up compared to baseline will be considered progression (regardless of the use of anti-epileptic drugs).

♦ Any change (increase or decrease) in seizure activity by <50% at any follow-up compared to baseline will be considered “no change”

If both seizure types are present a combined assessment will be made. Emphasis is put on the generalised seizures because of their greater impact on the daily functioning of the patient.

The combined assessment is as follows:

♦ A $\geq$ 50% reduction of generalized seizures activity without progression of partial seizures activity (ie: stability or response of partial seizures) will be considered a response

♦ A $\geq$ 50% increase of generalized seizures activity will be considered progression, regardless of partial seizures status

♦ A $< 50\%$ change (increase or decrease) in generalized seizures activity without progression of partial seizures activity (ie: stability or response of partial seizures) will be considered “no change”

♦ A $< 50\%$ change (increase or decrease) in generalized seizures activity with progression of partial seizures activity (ie: $\geq 50\%$ increase of partial seizures) will be considered progression

Patients without seizures in the past month are by definition seizure-free. Patients who did not have seizures prior to treatment but develop seizures at follow-up have progression of their seizures.
### Partial seizures

<table>
<thead>
<tr>
<th></th>
<th>Decrease ≥ 50%</th>
<th>Stable</th>
<th>Increase ≥ 50%</th>
<th>No Partial seizures at entry</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generalized seizures</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Decrease ≥ 50%,</td>
<td>Response</td>
<td>Response</td>
<td>Progression</td>
<td>Response</td>
</tr>
<tr>
<td>Stable</td>
<td>No change</td>
<td>No change</td>
<td>Progression</td>
<td>No Change</td>
</tr>
<tr>
<td>Increase ≥ 50%,</td>
<td>Progression</td>
<td>Progression</td>
<td>Progression</td>
<td>Progression</td>
</tr>
<tr>
<td>No generalized seizures at entry</td>
<td>Response</td>
<td>No change</td>
<td>Progression</td>
<td>Appearance of seizures = Progression</td>
</tr>
</tbody>
</table>

#### 7.2 Evaluation of neurologic function

Short cognitive screening with the *Mini-Mental State Examination* (Ref 50) will take place at randomisation 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 J)

The neurologic function status will be assessed by the RTOG neurologic function scale (see appendix N). Only symptoms related to disease or treatment should be considered when assessing neurological function.

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

#### 7.3 Progression

The primary endpoint of the study is progression free survival. Care must therefore be taken that complications of treatment, other diseases, metabolic disturbances and drug toxicities are not labelled as progression.

The following criteria should be used to assess progression:

##### 7.3.1 Radiological progression

Radiological progression is defined as

- An increase of 25% in bidimensional perpendicular product of signal hyperintensity on MRI T2 weighted images or area with hypodensity on CT scan
- Newly developed contrast enhancement or a 25% increase in contrast enhancement on T1 weighted MR images with or without increase in area of T2-weighted signal hyperintensity or area of hypodensity on CT scan

##### 7.3.1.1 Radiological requirements and considerations

For follow-up it is required that the same type of imaging (MRI) is used throughout the whole study. For centres where MRI is not available, the use of CT-scan may be admissible after exceptional approval by the study coordinator. PET should not be used for the assessment of progression. For the assessment of the increase in tumor size all comparisons must be made with the
scan showing the smallest measurement ever recorded for the same lesion by the same technique since entry in the study (i.e.: MRI)

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

Any increase in size or enhancement within the first three months following radiotherapy may be due to a transient radiotherapy effect, and should not be labelled progression too readily. In fact, early progression in low grade glioma is rare. Such changes may continue for months, and may be accompanied by clinical signs and symptoms.

Copies of the MRI reports will be collected together with the CRFs

7.3.2 Clinical/Neurological progression

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

♦ Clinical deterioration due to neurological signs and symptoms to either
  ♦ WHO performance status 3 or 4 and for which no other clear explanation is present
  ♦ RTOG neurologic function status 4; or a 2-step worsening of RTOG neurologic function status from best observed level since entry on study.
  ♦ And/or an increase or start in steroids medication for control of neurologic signs and symptoms

For considerations and interpretation of deterioration within 3 months after the end of radiotherapy, please refer to paragraph 7.3.2.1

For scoring RTOG NF, only the neurological signs and symptoms related to the disease or the treatment should be considered.

7.3.2.1 Considerations in the diagnosis of clinical/neurological progression

In all cases of suspected neurological/clinical progression neuro-imaging must be obtained.

In case of no clear progression on neuro-imaging 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).

Early post-radiotherapy deterioration (within 3 months from the end of radiotherapy) including a need for steroids (or need for increased dosage of steroids) may indicate a transient radiotherapy effect. This holds especially true in low grade glioma, as an early deterioration is in general not likely. This may require further follow-up before a final diagnosis can be made. If at follow-up tumor progression is indeed diagnosed, the date of first deterioration (either MRI or clinical or both) should be taken as the date of progression.

In case of doubt a) on the diagnosis of progression or b) suspicion of progression within the first three months from radiotherapy the study coordinator should be contacted. In such cases central scan review may be indicated.

7.4 Progression free survival (PFS)

Defining disease progression as radiological or clinical/neurological progression which ever occurs first, PFS is the time interval between the date of randomization and the date of disease progression or death, whichever comes first. If neither event has been observed, then the patient is censored at the date of the last follow up examination. The patient should consistently be followed with the same diagnostic imaging throughout the study.
7.5 Overall survival (OS)

The duration of survival is the time interval between the date of randomization and the date of death. Patients who were still alive when last traced are censored at the date of last follow up.

7.6 Evaluation of adverse events

This study will use the International Common Toxicity Criteria for Adverse Events (CTCAE), version 3.0, for the reporting of adverse events over the whole duration of the study. A copy of the CTCAE version 3.0 can be accessed from the CTEP home page (http://ctep.cancer.gov/forms/CTCAEv3.pdf). Additional information concerning this grading system can be accessed from the same web site (http://ctep.info.nih.gov/reporting/ctc.html). 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 Data Center to receive a copy by mail.

All adverse events will be recorded on the case report forms according to the schedule detailed in section 6.

7.7 Serious adverse events

Serious adverse event reporting is required by the Good Clinical Practice Guideline.

SERIOUS ADVERSE EVENTS SHOULD BE IMMEDIATELY REPORTED ACCORDING TO THE PROCEDURE DETAILED IN THIS PROTOCOL

(see chapter 17 on Reporting adverse events)

7.8 Early death

In the present protocol, early death will be defined as any death occurring before the first follow-up assessment at 3 months after the start of treatment.

7.9 Toxic deaths

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

The evaluation of toxic deaths is independent of the evaluation of response to treatment.
8 Statistical considerations

8.1 Statistical design

8.1.1 Sample size

This is a phase III difference trial. The objective is to detect a Hazard ratio of 0.68 (median ratio of 1.47) for progression-free survival between the two treatment groups.

Based on the former EORTC trial 22845, the 5-year progression-free survival on the radiotherapy arm (standard arm) is expected to be close to 45%. The difference to detect corresponds to an absolute improvement of 13% to a 5-year progression-free survival rate of 58% on the Temozolomide arm.

A total of 216 events of progression or death are needed to guarantee 80% power to detect this size of a difference with a 2-sided Logrank test at the 5% significance level.

It is anticipated that if patients are randomized over a period of 5 years, a total of 466 randomized patients would be needed for the study (this assumes an average of 93 randomized patients every year). An additional follow-up period of 2.5 years after entry of the last patient will be needed for the required number of events to be observed and to guarantee a median follow-up of 5 years for the assessment of the endpoint. Patient loss to follow-up in this population is assumed to be minimal.

Since it is anticipated that about one third of the patients registered to the trial will not be randomized, it is estimated that a minimum of 699 patients will need to be registered to the study to guarantee the required number of randomized patients. It is anticipated that it will take 6 to 18 months for a registered patient to need treatment and therefore to be randomized in the study. Therefore, one anticipates that an average of 140 patients will be registered in the trial on a yearly basis.

The study data will also be used for investigating the presence of an interaction between the 1p cytogenetic status of the patients and the treatment effect (i.e. predictive effect of cytogenetic status for benefit of treatment). This analysis will be essentially exploratory as the number of events available from the study would only provide limited power for detecting such interaction effects. Description of the observed treatment hazard ratios inside each cytogenetic subgroup will also be provided for descriptive purposes.

Finally, the study data will be studied to assess the prognostic value of the 1p cytogenetic status of the patients treated with Temozolomide and in patients treated with Radiotherapy, respectively. The available data for testing those effects will be limited, but since the prognostic effects are expected to be large, the data should provide a reasonably high power of detecting such effects.

Post-hoc power calculations will be provided for the interaction effects and prognostic assessments described above.

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 with prospective stratification for the following factors:

♦ institution
♦ 1p deleted versus 1p normal versus undeterminable
♦ contrast enhancement: +/- contrast on MRI
8.2 Analysis

8.2.1 Clinical data analysis

This is a phase III trial therefore the primary analysis of all efficacy endpoints of the study will be performed in the intention-to-treat population in the randomized patients. (i.e.: all randomized patients according to the allocated treatment). All time to event endpoints are counted from the date of randomization until the date of first event or date of last follow-up in case no event occurred for a particular patient.

Safety analyses will be reported on all randomized patients who started the allocated treatment.

The primary analysis of all time to event endpoints will involve estimation of the event-free rate over time by the Kaplan-Meier technique and Logrank tests for the comparison of treatment groups. The interaction effects will be tested by means of Cox models, as will be performed any prognostic factor analysis.

Supportive analyses of the time to event endpoints will involve treatment comparisons in a Cox model adjusted for the stratification factors described in 8.1.2 with the exception of institution, in addition to factors describing a) whether PET was used for the assessment of clinical progression, b) the baseline neurological function score c) whether the tumor was crossing the midline.

Hazard ratios will be presented together with the associated 95% confidence intervals. All tests will be two-sided.

For descriptive purposes only, the total percent of registered patients who were randomized will also be reported.

8.3 Minimental-state examination (MMSE)

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 50), the MMSE has been validated and extensively used in both clinical practice and research.

Following Tangalos et al. (Ref 51) and as previously used by Brown et al (Ref 52) 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.

The evolution of the MMSE evaluation over time will be interpreted in the light of the fact that attrition will result from the fact patients are assessed only until progression. All MMSE results will thus be conditional on the patients being otherwise free of progression.

The distribution of the MMSE at each time point of evaluation will be described on the two treatment arms separately using means and their associated standard error (a graphical display will be considered). Median and range will also be assessed.

The proportion of patients with ‘normal’ and ‘impaired’ MMSE score at baseline and at key time-points of evaluation (eg. Baseline, year 1, year 2 etc..) will also be displayed.
Similarly to Brown et al. the changes in MMSE scores over time will be summarized in the two treatment groups by the proportion of patients with significant increase (>3 points), stable (-3 points to +3 points) or significant decrease (decrease of >3 points) of the MMSE score at the key time points of evaluation. The distributions in the two 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.

8.4 Quality of life analysis

See chapter 10.

8.5 Neurocognitive testing (side study)

See Appendix N.

8.6 Interim Analyses

No formal interim comparison of the treatments with respect to the efficacy endpoints is foreseen in this study due to the expected low event number and resulting low power for any formal stopping rules.

However, a meeting of the Independent Data Monitoring Committee (IDMC) is planned to take place after 3 years of recruitment. At that occasion, all safety aspects of the trial as well as the progression-free survival rate (with special attention to the percent of patients showing progression at 1-year of follow-up) will be reviewed. The latter will be described both on the pooled patient groups and by cytogenetic features (1p deletion vs no 1p deletion vs status not assessable). The IDMC could request a formal interim analysis by treatment arm if they would suspect the presence of a very strong interaction between the cytogenetic features and the treatments on the basis of this review or in the event of an abnormally high 1-year event rate.

8.7 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. Arising problems 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 serving 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 unplanned, see below) are carried out.

If interim analyses are conducted for this study (see chapter on statistics), monitoring of efficacy and safety data will be performed according to the statistical design of the study (see chapter on
statistics) and the EORTC policy on “Independent Data Monitoring Committee and Interim Analyses”. Results of interim analyses are confidential and will be discussed by the EORTC IDMC that will subsequently advise the Group on eventual changes to be brought to the study.

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

QoL evaluation is important to get a better understanding of the treatment-related side effects of the treatment under study from the perspective of the patients. The role of chemotherapy in LGG is far from being established. In recent years, new chemotherapeutic agents like Temozolomide have been developed and suggested some activity in LGG. The major endpoint in this randomized phase III trial is to compare progression–free-survival between the experimental (primary treatment with temozolomide) and the control arm (primary treatment with radiotherapy) for patients with a poor prognosis. The use of primary Temozolomide may have better QoL outcomes because of deferring radiotherapy and thus late radiation-induced toxicity. Temozolomide is usually very well tolerated and no significant drug interactions have been reported while radiotherapy is associated with white matter changes, cognitive deficits and radiation necrosis. If treatment-related side effects influence the QoL of the patients in a negative way, possible differences in terms of progression-free survival will have to be balanced against the burden of treatment. It is for this reason that QoL is included as a secondary endpoint in this study.

The main objective of QoL assessment within this trial is to determine the impact of Temozolomide on seven chosen domains being primarily global QL, with role functioning, social functioning, visual disorder, motor dysfunction, communication deficit and drowsiness as other key issues. It was expected that these were likely to be most affected in patients undergoing either radiotherapy or Temozolomide.

The $H_0$ hypothesis will be tested that there is no difference between patients in both arms during and after treatment. A secondary objective is to evaluate the effect of the treatment on the remaining symptoms and functioning scales as treatment-related side effects may have a (temporary) negative influence on the health related domains of QoL of these patients.
10.2 QoL instrument

Quality of life will be assessed using the EORTC Quality of Life Questionnaire (QLQ-C30) version 3 together with the 20-question Brain Tumor Module (QLQ-BN20) (Ref 53; Ref 54). The EORTC QLQ-C30 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 (Ref 55; Ref 56). While this standard is used in EORTC studies, it lacks some dimensions that pertain to the QL issues in certain cancers.

In order to address particularities and special dimensions that pertain to the QoL issues in brain tumors, the QLQ Brain Cancer module (QLQ-BN20) will be added to the QoL evaluations in this trial. This module has been developed specifically for use in brain tumor patient populations. The QLQ-BN20 has shown its validity and utility in three pivotal trials evaluating the role of temozolomide in malignant glioma (Ref 53; Ref 57; Ref 58) and is currently awaiting final phase four of validation. The module consists of 20 items, grouped into 4 domains (future uncertainty, visual disorder, motor dysfunction and communication deficit) and 7 single items (headaches, seizures, drowsiness, hair loss, itchy skin, weakness of legs and bladder control).

10.3 Study design

Patients are eligible for the quality of life assessment in this study if they fulfill the eligibility criteria (Chapter 3) and, more importantly, complete the baseline quality of life questionnaire before randomization. Patients will be informed in the written patient informed consent form that they will have to undergo repeated quality of life assessments while involved in this trial. QoL will be a secondary endpoint and evaluated in a longitudinal design in all patients entered in this study. QOL is a mandatory requirement.

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 required to complete the entire questionnaire is approximately 10-15 minutes. Master copies of the QoL questionnaires (EORTC QLQ-C30, and brain module will be sent to the institution together with the CRFs. The CRF’s will include a question whether the QoL forms have been filled out -and if not, the reason why. Data collection procedures should be followed using the EORTC guidelines in appendix D.

QoL should be assessed at following time-points:

♦ Both arms: Baseline questionnaire within 6 weeks prior to randomization
♦ Follow-up: every 3 months until progression for both arms. During TMZ treatment, the assessments should be organized so as to occur during the last week of a treatment cycle (last week of cycles 3, 6, 9 and 12). For the RTX arm, the schedule should be adapted so that the first follow-up assessment occurs 3 months after treatment start.

Time windows for eligible follow-up assessment will be (+/-) 1 week the scheduled follow-up assessment. During follow-up, time windows for eligible assessment will be (+/-) 2 weeks the scheduled follow-up assessment.
10.3.2 Compliance

Missing data may hamper assessment of QoL 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 Data Center for the Group’s plenary sessions. 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 (below 65% at any assessment point) then the protocol writing committee would review the QoL assessment in the trial.

10.4 Statistical considerations

10.4.1 Sample size

The sample size calculation has been performed based on progression-free survival data. This is the primary endpoint and therefore no calculation has been performed based on changes in QoL.

The primary QoL endpoints that are considered relevant to this trial are detailed above. The QoL data will give information to support or reject the null hypothesis that there is no difference between patients in both arms during and after treatment.

Based on the work of Osoba et al (1999) (Ref 59), 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), minimum of 64 patients per treatment arm is required to examine the data for differences in QOL.

10.4.2 Scoring

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.

10.4.3 Missing data

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 modelling 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 (prox mixed in SAS).

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

10.4.4 Analysis
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.

11 Translational research
The timeframe of this study necessitates anticipating translational research projects to be performed in 6 to 10 years, when all patients are accrued and clinical data 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 biotechnology. A comprehensive translational research project should be proposed at the latest at completion of accrual. Any translational research project using the material and data of this trial will require approval of the trial steering committee with support the participating groups, and formal approval by the EORTC protocol review committee.

11.1 Goals
Low-grade gliomas have an inherent tendency to recur, commonly associated with progression to a higher grade tumor. However, the time interval to progression varies considerably. Some tumors progress rapidly, i.e. within months, while others, recur after up to ten years. Further, sub-classification of low grade gliomas is known to be particularly difficult and subjective histological criteria lead to striking interobserver differences in the range of 70% among any two neuropathologists (Ref 60). Thus, objective molecular factors predictive for progression and response to therapy need to be identified that can be reliably determined in diagnostic laboratories. Definition of molecular factors that can be used to classify the tumors according to their biology would have important clinical implications regarding the management of patients (e.g. allowing the identification of patients with high risk for malignant progression in need for a more aggressive treatment strategy) leading to development of optimal therapies adapted to individual patients. Further, the identification of novel therapeutic targets requires further insights into molecular aspects of pathogenesis in progression of gliomas.

A molecular predictive marker has recently been identified for glioblastoma, the methylation of the MGMT gene promotor. The relationship and potential correlation of MGMT gene promotor and the 1p/19q status will be evaluated in the current trial.
11.2 Strategy

To reach these goals the following strategy is proposed:

♦ Collection and banking of patient material, the informed consent for trial participation will also explain the need for material for translational research:
  ♦ frozen tumor biopsies
  ♦ respective serum and blood lymphocytes
  ♦ construction of tissue arrays from paraffin embedded material of tumor biopsies
  ♦ Generation of molecular profiles for frozen tumors.
  ♦ Classification of tumors based on their molecular patterns
  ♦ Identification of predictive factors (e.g. differentially expressed genes/proteins, methylation pattern) 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 2 experimental arms and for European and Canadian centers.
  ♦ Molecular targets for therapy: test candidate genes for role in glioma progression using functional analysis in in vitro and in vivo models.
  ♦ Rational design of new clinical trials for low grade gliomas.

The collection of the material proposed will allow investigation of molecular patterns on RNA level (gene expression profiling using micro-arrays and qRT-PCR, in situ hybridization), DNA level (array CGH, FISH, LOH, mutation analysis, array based methylation analysis), and protein level (proteomics, imaging mass spectrometry). Thus, allowing to detect deregulations important for the physiology of tumors and taking into account genetic and epigenetic alterations. The tissue array will be an efficient tool to validate candidate markers in an economic way in terms of tumor tissue and consumables.

11.3 Collection of biological patient material.

For EORTC, the tumor material and blood should be sent to the molecular reference laboratory (Heidelberg). Here all material will be logged in a central database (connected with the EORTC), with subsequent transfer of material to respective centers (e.g. European Biobank Maastricht; Erasmus Medical Centrum, Rotterdam). Details on the procedure are to be found in the Appendix “Collection and Preparation of Pathological and Biological Patient Material” (Appendix L).

The procedure for other participating group is detailed in the corresponding Group Specific Appendix.
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 Coordinating Data Center. After revision by the EORTC Data Center and other co-authors (and the Sponsor, if applicable) 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 Data Center Team who have contributed to the trial. For each participating group that contributed patients to the study, at least the Study Coordinator will be listed as co-author.

The number of additional co-authors allocated to each group will be proportionate to the proportion of the total number of patients that the group entered.

For EORTC, these additional co-authors will be the investigators who have contributed most to the study.

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 Data Center 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 or randomize patients in this trial only when they have returned 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 Principle Investigator

♦ The (updated) list of the normal ranges, in their own institution, of all laboratory data required by the protocol, preferably signed and dated by the head of the laboratory.

♦ A commitment statement / study acknowledgment form, indicating that they will fully comply with the protocol, to include an estimate of their yearly accrual and if any conflict of interest may arise due to their participation in the trial,

  ♦ A signed conflict of interest disclosure form: this document will be required only if a possible conflict is declared on the commitment form.

♦ A copy of the favorable opinion of their local or national (whichever is applicable) ethics committee mentioning the documents that have been reviewed (incl. version number and date of documents) and indicating the list of the ethics committee members.

♦ A copy of the translated, and adapted (according to all national requirements), Patient Information / Informed Consent sheet, clearly mentioning the version number and the date.
The signature log-list of the staff members with a sample of each authorized signature and the indication of the level or delegations.

The coordinates of the pharmacist who will be responsible for the trial medication (for any trial where the drug will be provided).

The accreditation letter for the laboratory. (if available for your center and/or applicable by your national law)

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 being fulfilled

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

### 14 Patient registration and randomization procedures

#### 14.1 Registration before molecular testing (step 1)

Patient registration will only be accepted from authorized investigators (see “Authorization procedure”).

A patient can 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 check-list, which is part of the case report forms. This check-list should be completed by the responsible investigator before the patient is registered.

Standard questions

♦ institution number ?
♦ protocol number ? (22033)
♦ step number: (1 – New patient)
♦ name of the responsible investigator ?
♦ patient's code (maximum 4 letters) ?
♦ patient's chart number (if available) ?
♦ patient's birth date (day/month/year) ?
Group affiliation:
♦ primary group affiliation (name of the group to which belongs the investigator; investigators belonging to several groups should complete the name of the group with which they deal for all administrative procedures for this trial) ?
♦ secondary group affiliation (name of the other group to which belongs the investigator) ?

Protocol specific questions
♦ eligibility criteria ?
  Principle eligibility criteria will be checked;
  actual values of the eligibility parameters will be requested when applicable
♦ date of written informed consent ?

At the end of the registration procedure, a patient sequential number will be allocated to the patients. This number is to be recorded on the registration check-list, along with the date of registration. The completed check-list must be signed by the responsible investigator and returned to the Data Center with the initial data of the patient.

14.2 Randomization (Step 2)
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 randomization check-list, which is part of the case report forms. This check-list should be completed by the responsible investigator before the patient is randomized.

Standard questions
♦ institution number ?
♦ protocol number ? (22033)
♦ step number: (2 – 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, chart number and date of birth will automatically be inserted in the identification screen.

Protocol specific questions
♦ eligibility criteria ?
  all eligibility 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. The patient’s sequential number and the allocated treatment have to be recorded on the randomization check-list, along with the date of randomization. The completed check-list 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 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 can register and randomize patients directly on the EORTC Data Center computer, 24 hours a day, 7 days a week, through the INTERNET network. To access the interactive registration and randomization programs, the investigator needs a username and a password (that can be interactively requested: http://www.eortc.be/random).

Alternatively, EORTC participants can telephone to the EORTC Data Center from 9.00 am to 5.00 pm (Belgian local time) from Monday through Friday to register and randomize patients. As from January 01, 2003 the phone registration and randomization will not be available on the official bank holiday of Belgium. A list of these dates will be available on our web site and updated yearly.

Telephone: +32 2 77416 00  
Internet: http://www.eortc.be/random

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 Data Center 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 on the EORTC Data Center:

EORTC Data Center  
Avenue Emmanuel Mounier, 83, bte 11  
B-1200 Brussels, Belgium

A. Before molecular testing (Step 1):

♦ the patient must be registered through your Data Center
♦ the registration check-list should be returned to your Data Center

B. Before the treatment starts (Step 2):

♦ the patient must be randomized through your Data Center
♦ the randomization check-list should be returned to your Data Center

The optimal way to work is to complete the registration/randomization check-lists 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 check-list, and this form can be sent to the Data Center.

C. The list of forms to be completed for this study and their submission schedule is appended to the set of case report forms
D. Upon occurrence of a Pregnancy

♦ Any pregnancy in a female subject or in a female partner of a male subject diagnosed during the treatment period or within 30 after last study treatment administration must be reported to the EORTC Safety Desk.

♦ This must be reported **within 24 hours** of first becoming aware of the event by fax to the EORTC Safety Desk on a Pregnancy Notification Form/Fax. The EORTC Safety Desk will notify Schering Plough Drug Safety within 24 hours.

♦ Upon notification of a pregnancy, it will be the responsibility of Schering Plough to follow up the development and outcome of the pregnancy.

♦ If a Serious Adverse Event (see chapter 16) occurs in conjunction with the pregnancy, please also complete an SAE form (89).

E. Upon occurrence of a Serious Adverse Event

♦ All Serious Adverse Events (SAE) occurring during the treatment period and within 30 days after the end of the last protocol treatment must be reported.

♦ All Serious Adverse Events related to the protocol treatment, and occurring after this 30-day period must also be reported.

♦ All Serious Adverse Events must be reported by fax on a Serious Adverse Event Form (Form 89) **within 24 hours** of the initial observation.

♦ A completed SAE-form must be sent back within 10 calendar days of the initial observation of the Serious Adverse Event.

**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 DC for EORTC investigators) by the responsible investigators before the start of the study.

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

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

The EORTC Data Center will perform extensive consistency checks on the CRFs and issue Query Forms in case of inconsistent data. Those 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 appended to the investigator's copy of the CRFs.

If an investigator (or an authorized staff member) needs to modify a CRF after the original copy has been returned to the investigator’s group Data Center, he/she should notify the Data Center in
writing (and sign the notification) and append a copy of the notification to his own copy of the CRFs.

The investigator's copy of the CRFs may not be modified unless modifications are reported on a Query Form (or a written and signed notification) and the Query Form (or notification) reference is indicated on the CRF.

16 Reporting adverse events

16.1 Definitions

An **Adverse Event (AE)** is defined as any untoward medical occurrence or experience in a patient or clinical investigation subject which occurs following the administration of the trial medication regardless of the dose or causal relationship. This can include any unfavorable and unintended signs (such as rash or enlarged liver), or symptoms (such as nausea or chest pain), an abnormal laboratory finding (including blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment. *(ICH-GCP)*

An **Adverse Drug Reaction (ADR) (marketed products)** are responses to a drug which are noxious and unintended and which occur at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function. *(ICH-GCP)*

An **Adverse Drug Reaction (ADR) (non-marketed products)** is defined as any response to a medical product, that is noxious and/or unexpected, related to any dose. *(ICH-GCP)*

   **Response to a medicinal product** (used in the above definition) means that a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

An **Unexpected Adverse Drug Reaction** is any adverse reaction for which the nature or severity is not consistent with the applicable product information (e.g., Investigators’ Brochure). *(ICH-GCP)*

A **Serious Adverse Event (SAE)** is defined as any undesirable experience occurring to a patient, whether or not considered related to the protocol treatment. A Serious Adverse Event (SAE) which is considered related to the protocol treatment is defined as a **Serious Adverse Drug Reaction (SADR)**.

Adverse events and adverse drug reactions which are considered as **serious** are those which result in:

- death
- a life threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed)
- hospitalization or prolongation of hospitalization
- persistent or significant disability/incapacity
- a congenital anomaly/birth defect
- any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above).

*(ICH-GCP)*
REMARK: In this study death due to progression of disease will not be considered as an SAE and must therefore not be reported as an SAE.

16.2 Reporting procedure

16.2.1 Non-serious adverse events and/or non-serious adverse drug reactions

Adverse Events (AE) and/or Adverse Drug Reactions (ADR) must be recorded as indicated in the protocol.

16.2.2 Serious adverse events or serious adverse drug reactions

All Serious Adverse Events (SAE), related or not to the protocol treatment, occurring during the treatment period and within 30 days after the last protocol treatment administration, must be reported. ([Ref. http://ctep.info.nih.gov/reporting/ctc.html](http://ctep.info.nih.gov/reporting/ctc.html)).

Any late Serious Adverse Drug Reaction (SADR), occurring after this 30-day period also must be reported.

This must be done by fax within 24 hours of the initial observation of the event. The principal investigator will decide if these events are related to the protocol treatment (i.e. unrelated, likely related, and not assessable) and the decision will be recorded on the Serious Adverse Event form (form 89), if necessary with the reasoning of the principal investigator.

The assessment of causality is made by the investigator using the following definitions:

<table>
<thead>
<tr>
<th>Relationship to the protocol treatment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated</td>
<td>There is no evidence of any causal relationship to the protocol treatment</td>
</tr>
<tr>
<td>Likely related</td>
<td>There is (some) evidence to suggest a causal relationship to the protocol treatment and influence of other factors is unlikely or absent.</td>
</tr>
<tr>
<td>Not assessable</td>
<td>There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship to the protocol treatment.</td>
</tr>
</tbody>
</table>

Details should be documented on the specified Serious Adverse Event Form (Form 89).

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

Investigators participating through EORTC should follow recommendations below:

PLEASE FAX THE REPORT TO:

EORTC Safety Desk:
Fax No. +32 2 772 8027

The EORTC Safety Desk will forward all Serious Adverse Event reports within 24 hours of receipt to all appropriate persons ([See Administrative chapter](#)).
Upon receipt of a safety report, from the EORTC Safety Desk, it is the responsibility of the investigators to promptly report this to the Ethical Review Board (ERB) according to the local regulation.

To enable each legal sponsor to comply with regulatory reporting requirements, completed documentation of any reported serious adverse events or serious adverse drug reactions must be returned within 10 calendar days of the initial report. If the completed form is not received within this deadline, the Safety Desk will make a written request to the investigator.

PLEASE SEND THE ORIGINAL REPORT TO:

EORTC Safety Desk:
Avenue E. Mounier, 83, bte 11
B- 1200 Brussels
Belgium

It should be recognized that Serious Adverse Drug Reactions (SADR) which have not been previously documented in the Investigators’ Brochure, or which occur in a more severe form than anticipated (i.e. they are ‘unexpected’ by nature or severity), are subject to rapid reporting to the Regulatory Authorities by the sponsor/promoter.

ANY QUESTION CONCERNING SAE OR SADR REPORTING CAN BE DIRECTED TO:

EORTC Safety Desk
Phone: +32 2 774 1676
Fax: +32 2 772 8027
e-mail: safetydesk@eortc.be

ALL FORMS MUST BE DATED AND SIGNED BY THE RESPONSIBLE INVESTIGATOR OR ONE OF HIS/HER AUTHORIZED STAFF MEMBERS.

17 Quality assurance

17.1 Control of data consistency

Data forms will be entered in the database of the EORTC Data Center either by a double data entry procedure or by using the RDC system. Sites will be asked to choose one of both options at the start of the study. 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 to be entered on the master database. Inconsistent forms will be kept “pending” until resolution of the inconsistencies.
17.2 Audits

To ensure quality of data, study integrity, and compliance with the protocol and the various applicable regulations and guidelines, the EORTC Quality Assurance Unit regularly conducts site visits to institutions participating to EORTC protocols.

The investigator, by accepting to participate to this protocol, agrees to co-operate fully with any quality assurance visit undertaken by third parties, including representatives from the EORTC, national and/or foreign regulatory authorities or company supplying the product under investigation, as well as to allow direct access to documentation pertaining to the clinical trial (including CRFs, source documents, hospital patient charts and other study files) to these authorized individuals.

The investigator must inform the EORTC immediately in case a regulatory authority inspection would be scheduled.

This procedure does not apply to non-EORTC investigators who should refer to their Group Specific Appendix for the information on eventual audits performed by their group.

17.3 External review of histology

The group of diffuse gliomas mainly consists of tumors of astrocytic or oligodendroglial lineage. The diagnosis mixed oligo-astrocytoma is used for cases with oligodendroglial as well as astrocytic features. However, a large interobserver variability in making this diagnosis of the different low-grade glioma subtypes exists.

Recently molecular changes, in particular losses on chromosome 1p and 19q have been identified as putative prognostic or predictive factors in oligodendrogliaoma and possibly also in mixed oligoastrocytoma. These losses are considered the genotypic signature of oligodendroglial lineage. Sampling errors, less classic histology and perhaps the true existence of a mixed type glioma all may offer explanations for discrepancies between histology and genotype. Combining histological diagnosis with molecular markers may allow to categorize tumors and predict outcome and response to therapy more accurately. Therefore, up-front genotyping for 1p is mandatory in this trial allowing to subsequently stratify patients by this molecular marker.

The histopathological diagnosis will be made by the pathology review panel of each participating group. For EORTC, this will be done by the pathology review panel of the EORTC Brain Tumor Group. They will adhere to the WHO criteria.

17.4 Molecular Genetics – analysis of LOH on 1p and 19q

Loss of heterozygosity will be assessed with 4 to 5 polymorphic markers on 10 and 19q each. Identical markers will be used in the European and in the Canadian reference centers. DNA will be extracted from peripheral blood leucozytes and from the tumor, respectively.

During the accrual period the reproducibility of the LOH analysis on 1p and 19q is tested once a year in a ring experiment including both the European and the NCIC reference laboratory.

Also see the appendix: Central Pathology Review and Molecular Diagnostic Tests (Appendix M).
17.5 Quality Assurance for Radiotherapy

The QA team, including the study chairpersons will review the irradiation technique. 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.

The dummy run procedure, individual case reviews including e.g. checks of treatment charts and portal images will be done preferentially via the worldwide web using digital data within the framework of the collaborative project between the EORTC RT Group and the NCI.

Centres participating in this protocol have to be credentialed at the best before randomisation can begin. Centres are credentialed once they have successfully completed the dummy run procedure.

For the description of the specific QA procedure for EORTC, see Appendix P. Other participating groups should refer to their group specific appendix for further details.

The center specific applicable list of required documents will be included in the protocol activation package, with adequate instructions as required for the questionnaires and dummy run procedure.
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) 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 for Good Clinical Practice (ref: http://www.emea.eu.int/pdfs/human/ich/013595en.pdf).

The protocol will be approved by the Local, Regional or National Ethics Committees.

18.2 Subject identification

The name of the patient will not be asked for nor recorded at the Data Center. A sequential identification number will be automatically attributed 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, patient’s code (maximum of 4 letters), date of birth and local chart number (if available) will also be reported on the case report forms.

18.3 Informed consent

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician. An example of a patient informed consent statement is given as an appendix to this protocol.

It is the responsibility of the individual investigator to translate the enclosed informed consent document. The translated version should be dated and version controlled.

The bold sections of the enclosed informed consent document are the sections that must appear in the translation.

The translated informed consent form is part of the documents to be submitted to the ethics committee for approval. The competent ethics committee for each institution must validate local informed consent documents before the center can join the study. It is the responsibility of the Local Ethical Committee to guarantee that the translation is conforming to the ICH-GCP guidelines.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient’s subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered or randomized at the EORTC Data Center. This must be done in accordance with the national and local regulatory requirements.

For European Union member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that “the written informed consent form should be signed and personally dated by the patient or by the patient’s legally acceptable representative”.

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19 Administrative responsibilities

19.1 The study coordinators

The Study Coordinators (in cooperation with the Data Center) will be responsible for writing the protocol, reviewing all case report forms and documenting their review on evaluation forms, discussing the contents of the reports with the Data Manager and the Statistician, and for publishing the study results. They will also generally be responsible for answering all clinical questions concerning eligibility, treatment, and the evaluation of the patients.

Study coordinators:

EORTC Radiotherapy Group:

EORTC Brain Tumor Group:

19.2 The EORTC Data Center

The EORTC Data Center will be responsible for reviewing the protocol, collecting case report forms, controlling the quality of the reported data, and generating reports and analyses in cooperation with the Study Coordinators. All methodological questions should be addressed to the EORTC Data Center.

EORTC DATA CENTER

83, avenue Emmanuel Mounier, Bte 11
B-1200 Brussels, Belgium
Fax: +32 2 7723545

Registration of patients:

Tel +32 2 7741600
or
http://www.eortc.be/random
The EORTC Safety Desk will forward all SAE within 24 hours of receipt to the EORTC Study Coordinator, Schering Plough Drug Safety Surveillance Department and the EORTC Data Manager.

All SUSARs will additionally be forwarded to all EORTC participating investigators and all central Data Managers of all Cooperating Groups.

The EORTC Safety Desk will take in charge the reporting to the National Authorities, whenever applicable.

The EORTC Safety Desk will send a six-monthly summary of all SAE to the central Data Managers of all Cooperating Groups (in parallel with the group meeting report)

19.3 The EORTC group

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

EORTC Radiotherapy Group

Chairman:
20 Trial sponsorship and financing

EORTC is the legal Sponsor for all EORTC participants.

The Director General of the EORTC is:
21 Trial insurance

A clinical trial insurance has been taken 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 if the treatment is given in a center authorized by the EORTC Data Center and which has obtained Ethical Committee approval (individually or centrally depending on the national regulations applicable). Therefore centers, holding an EORTC membership, will have to declare to the EORTC Data Center, other satellite institutions which may be responsible for providing protocol treatment to the patients. Details on these satellite institutions including CV for the local investigator, laboratory normal ranges and the Ethical Approval, will have to be transmitted to the EORTC Data Center. Correspondence on study issues and data collection will however only be performed with the primary EORTC institution which will assume all responsibilities and liabilities issues with the principle investigator, member of the EORTC Group.
Appendix A: References


Appendix B: 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 Data Center web site http://www.eortc.be/ provides a link to the appropriate CTC web site. This link will be updated if the CTC address is changed.

Investigators who do not have access to Internet can contact the Data Center to receive a hard copy of this document by mail.
## Appendix C: WHO performance status scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Performance scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Able to carry out all normal activity without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out light work.</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care; confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled; cannot carry on any self-care; totally confined to bed or chair.</td>
</tr>
</tbody>
</table>
Appendix D: EORTC Quality of Life evaluation: guidelines for administration of questionnaires
(Revised October 2004)
EORTC Quality of Life evaluation: guidelines for administration of questionnaires (revised January 2004)

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, for practical reasons it is strongly recommended that one person is responsible for the organization of QoL data collection in each Institution. 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. This person would also be the intermediate contact point in case of any necessary clarification asked by the Data Center.

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 and includes patient's code, date of birth and today’s date).

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.

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. If this is not possible, the waiting room is an acceptable alternative. 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 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 CRF’s (case record forms).

8. Mailing to the Data Center
The questionnaire should be sent to the Data Center with the CRF’s. As it is not possible to retrospectively collect missing quality of life data, please make sure the patient completes the questionnaire at the time-point when he/she is supposed to 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 Unit - EORTC Data Center:
Phone: 32 2 774 1678/1661
Fax: 32 2 779 45 68
EORTC Quality of Life evaluation: instructions for Monitors

♦ Check if all QL 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 QL questionnaires.
♦ Make sure the QL questionnaires are correctly completed
♦ If not, tell the responsible person to explain again to the patient how to fill out the QL questionnaires at the next visit.

EORTC Quality of Life evaluation: instructions for Data Managers

1. When a response is missing, it should be coded as “9” for missing data (cfr Scoring Manual)

2. When two adjacent categories have been circled by the patient, the category which represents the worst QoL will be taken.

3. When 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 clinical trials including mandatory research on biological material

INFORMATION FOR INVESTIGATORS:

This document is an English version of the Patient information sheet & informed consent for clinical trials (PIS & IC). The translation and national regulatory submission process of this document is the responsibility of the National Coordinator for this trial. He/she will keep you aware and informed and will send the translated and approved document as soon as available.

INFORMATION FOR THE NATIONAL COORDINATORS:

- this document represents an English version of PIS & IC to be used in the present study

- it is the responsibility of the national coordinator to:

  - translate the patient information sheet and informed consent in preparation for the submission of the dossier to the ethics committee (the submission may be the responsibility of EORTC or the investigator depending on the local regulations)

  - send a copy of the approved translated document to EORTC Data Center who will than distribute the document to other national participating investigators

- bold parts, appearing in the English template, **must** appear also in the translated version of the PIS & IC

- final translated and approved PIS & IC must have version number and date
1. Title of the research protocol 22033-26033: Evaluating primary chemotherapy with temozolomide vs. radiotherapy in patients with low grade gliomas with stratification for genetic 1p loss: a phase III study

2. Invitation to participate in the study

_The EORTC Radiotherapy and Brain Tumor Groups are initiating a clinical trial on patients that have a disease similar to yours. The study will be conducted at the European level under the supervision of doctors recognized as experts in this field of medicine. You are invited to take part to this research project after having received full information about the study._

3. Introduction

You have been diagnosed with a so-called low-grade glioma. These are usually relatively slow growing brain tumors, that tend however to become more aggressive over time. Unfortunately, no treatment is available that can cure these tumors and the goal of the presently available treatments (surgery, radiotherapy and chemotherapy) is to control the tumor growth as long as possible and to maintain or improve the condition of the patients. These tumors are also relatively rare, and the role of established treatments for brain tumors (radiotherapy, chemotherapy) is thus not clearly defined. The trial that is presently proposed to you is one of the studies that aim to improve the treatment of this disease.

Frequently, these tumors remain stable for many months or year and do not initially require any treatment. Once a low-grade glioma requires treatment the neurosurgeon will attempt to remove as much of the tumor as safely possible. However, the site of the tumor makes this often difficult or even impossible. Often only a biopsy to ascertain the nature of the tumor is performed. Many patients with low-grade glioma require some kind of postoperative treatment. This is especially the case in patients with a growing tumor in the period before surgery, if the patient has functional deficits or a tumor that causes a high pressure inside the head, if the patient has seizures that cannot be controlled with medication and in elderly patients. At present, those patients are usually treated with radiotherapy. There are still many questions though about the role of radiotherapy in low-grade glioma. In a previous large study the effect of radiotherapy was small, and there is fear that radiotherapy can contribute to difficulties with memory and concentration that are frequently observed in low-grade glioma patients.

A few small studies have investigated chemotherapy in low-grade glioma, which suggest that patients may also respond to this type of treatment. The question that we want to answer with the present study is, whether either radiotherapy or chemotherapy should be the preferred first line treatment in low-grade glioma patients requiring treatment.

In this study, patients with low-grade glioma needing therapy will be treated with either radiotherapy or with chemotherapy. This is a so-called randomized phase III protocol, which means that the two treatments are compared to each other in a large clinical study. An essential element for such a study is that if you decide to participate, the treatment you will receive will be selected at random with the aid of a computer at a central office in Brussels. Neither yourself nor your physician can choose the treatment that you will receive.
If you do not respond to the treatment or if you relapse at a later point in time your physician will discuss the treatment options that are available. This may also include the other treatment of the protocol.

4. Description of the research

All patients will receive either radiotherapy or chemotherapy with temozolomide as described below.

However, it may be possible, that your physicians decide that you currently do not need any treatment. They will follow the evolution of your health closely and neither radiotherapy nor chemotherapy is begun immediately. Nevertheless, in order to plan ahead, the tumor tissue obtained from your recent biopsy or resection needs to be reviewed and further analyzed. In order to proceed with the necessary steps, your consent is needed now.

*If you decide to participate it means you will be selected at random (often by a computer) to be in one group or another. Neither you nor your doctor can choose the treatment.*

♦ Radiotherapy

The radiotherapy will be given as an outpatient daily (Monday-Friday) in 28 sessions for a total duration of approx. 6 weeks. Prior to the radiotherapy you will have to visit the radiotherapy department for the planning of the radiotherapy and the preparation of a mask. This mask is needed to immobilize your head during the radiotherapy and the planning CT scan. In most cases an additional MRI or PET scan will also be needed before the start of treatment. It may be necessary to give you corticosteroids (cortison-type medication) like dexamethason during the radiotherapy period, to control some of the side effects.

♦ Chemotherapy

The chemotherapy consists of temozolomide (Temodal®), which will be given in monthly cycles (28 days) for up to 1 year (12 cycles). You must take the temozolomide every day during the first three weeks, followed by one week of pause. Temozolomide is administered as capsules, which you must swallow without chewing. Ideally you should take the medication in morning before breakfast. If you have to vomit shortly after the administration of temozolomide, you are not allowed to use additional temozolomide on that day. You will then receive medication against nausea and vomiting, which you must take as needed.

At the end of each of these four-week periods you must visit the outpatient clinic for a physical examination, at which time a blood test (which requires 7-15 ml blood) is also done to see if you tolerate the treatment. In case of a decrease or stabilization of the tumor, we will continue the treatment for a maximum of 12 cycles (= 1 year).

♦ The follow-up

The effects of both treatments will be monitored with scans, usually with MRI (magnetic resonance imaging). This will be done every three months in the first year after the start of treatment, thereafter every six months. During these scans you will also receive a contrast fluid by injection into a vein. In addition, some centers will also use another type of imaging, the so-called PET scans (positron emission tomography). If this is the case in your center, your physician will explain this to you.

Should the tumor recur or progress, your physician will discuss all existing treatment options with you, and he will continue to follow you afterwards. If you have received radiotherapy initially, subsequent treatment will likely be chemotherapy; and if you were initially treated with temozolomide, there is a chance that at progression radiotherapy is proposed.

Before treatment, and at the follow-up visits your physician will also ask you to fill in a questionnaire with all kind of questions regarding you daily activities and the signs and
symptoms you have. This is done because we feel it is important not only to monitor the disease by looking at the MRI scans, but also to monitor your subjective well being (“quality of life”). As part of the follow-up, your physician will also test your memory, concentration etc in a short test, which will take about five minutes.

Approximately 500 patients will participate in this study. It is expected that it will take about 6 – 8 years before the first results are available.

♦ Pathology review:

To verify the initial diagnosis (done by the pathologist in your hospital), glass slides or representative images of tumor material (taken at the time of establishing the diagnosis or during surgical procedure you undergo) will be reviewed by a pathologist(s) expert(s) in this field (generally using the microscope). The expert(s) will not necessarily be working in the hospital where you receive(d) protocol treatment, nor even the same country. In some cases, a sample of your tumor biopsy, removed at the time of establishing the diagnosis or during a surgical procedure that you may undergo, might be used to perform additional examination necessary to assure the correct diagnosis.

5. Description of foreseeable risks and discomforts

♦ Radiotherapy

The immediate side effects of the radiotherapy may consist of headaches, and some redness and soreness of the skin that is irradiated. It is also possible that pre-existing problems due to the tumor may worsen during a short time. Some patients complain about a dry mouth. Usually complete hair loss will occur in the irradiated fields, which is reversible in most patients. Areas of the skin that have received the largest dosage may not show complete recovery of hair growth. At the end of radiotherapy or shortly afterwards some fatigue, difficulties with concentration and loss of energy may occur, which usually subsides in a few weeks. It may be necessary to use dexamethasone to ameliorate this. Sometimes patients complain of reduced hearing due to problems with the eustachian tube, which can usually be easily managed with nose drops etc. Sometimes, late reactions to radiotherapy may occur which consists of some mental slowing, memory disturbances and difficulty with concentrating. Exceptionally, patients develop a severe local brain reaction to the radiotherapy (radiation necrosis), which may require treatment.

♦ Chemotherapy

The use of temozolomide can cause side effects. These side effects may be uncomfortable or painful and some are potentially dangerous or may even cause death.

Chemotherapy with temozolomide may suppress bone marrow function, resulting in a decrease in blood counts (low platelets, white blood cells and red cells (anemia)). It has been found that women have a higher incidence than men, of severe decrease in the neutrophils (white blood cells) and in the platelet count. In case of a substantial decrease of white blood cells, you may be more susceptible to infections or bleed (this condition is called aplasia). This condition may be prolonged and result in a disease called aplastic anaemia. This is rare but occurs more often when temozolomide is given for a longer period of time. If you develop fever it may be necessary to treat you with antibiotics. Very low platelets may result in a bleeding tendency; if necessary this can be treated with platelets transfusions. Anemia can also be treated with transfusions, if necessary. As a rule low blood counts recover once treatment is discontinued. After such an event it may be necessary to adapt the chemotherapy (e.g., with a lower dosage).

Other side effects of temozolomide may include fatigue, constipation, headache, loss of appetite or weight, diarrhea, rash, weakness, allergic reactions (including anaphylaxis which is a sudden and severe allergic reaction and may include breathing difficulty and drop of blood pressure,
leading to loss of consciousness or death), fever, chills, hair loss, pruritus (itching), dyspepsia (upset stomach), erythema (redness) and edema (swelling), elevation of liver enzymes (elevation of the amount of enzymes liver secretes in the blood as a sign of irritation or damage it has encountered), deep vein thrombosis (blood clots in large venous blood vessels usually in legs) and pulmonary embolism (blood clots in large blood vessels in the lung). Temozolomide may also cause nausea and vomiting, which are usually easily controlled with special medication.

Temozolomide has been reported to possibly contribute in very rare and isolated cases to the occurrence of severe mucosal and cutaneous toxicity (severe damage to skin and linings of body cavities) (as Stevens Johnson Syndrome). Secondary cancers (cancers possibly caused by the treatment of a previous cancer) such as myeloid leukemia (cancer of the blood and bone marrow), and myelodysplastic syndrome (caused by the bone marrow producing faulty blood cells) have been reported very rarely.

In case of fever, hemorrhages or other physical complaints during chemotherapy you must contact your treating physician, to ensure adequate treatments can be installed. With all chemotherapeutic treatments, there is a possibility of unexpected side effects or complications. As chemotherapy may have a detrimental effect on an embryo or a fetus, pregnant women cannot participate in this study. For the duration of the treatment (and 6 months thereafter) you must use an effective contraception.

**If you need to undergo another medical treatment, we advise you to inform the study doctor to ensure this will not have any effect on your participation to the trial.**

**Everything has been done and will continue to be done to prevent health problems occurring as a result of your taking part in this trial.**

6. **Description of the ultimate goal of the research**

The goal of this research is to find out which post-operative treatment is to be preferred in low-grade glioma: radiotherapy or chemotherapy. This will be decided after the analysis of the time that patients stay free from tumor progression and survive after treatment. It may well be that specific side effects of any of those treatments are important in this choice. For this reason the quality of life questionnaire that you will be asked to fill in on a regular basis is very important for the analysis of the data.

7. **Research on biological material - objectives and description**

*This clinical trial also involves mandatory research on biological material. This means that the biological material, obtained during the diagnostic or surgical procedure that you undergo, will be used to investigate how cancer cells develop and behave, in order to adapt and improve treatment of cancer and help patients.*

As part of the study, a sample from your tumor will be investigated for a specific chromosomal lesion, which is related to response to chemotherapy in a specific type of low-grade gliomas. The presence of absence of this lesion will not affect your eligibility for this trial, as the significance of this chromosomal lesion for the treatment of low-grade brain tumors is at present unknown. However, your permission for analysis of the tumor sample and a blood sample is required for participation to this study. This blood sample (7-10 ml) will be drawn specifically for that purpose; both the blood sample and the tumor sample will be investigated in another laboratory. This will be done prior to the start of any postoperative treatment. **The biological material will not be used to investigate any genetic (hereditary) tests.** This investigation is of fundamental importance for the present study. Therefore, if you do not agree with this, you cannot participate to this study.
Part(s) of biological material taken during diagnostic process or surgical procedure that you undergo, will be used for research under the EORTC legal and scientific responsibility, to better understand and improve cancer care. Any research project conducted with this biological material will begin only if it has been previously approved by an Ethics/Scientific Committee according to all applicable laws.

Your consent for participation in the clinical trial including mandatory research on biological material, also includes that you agree to the storage of your biological material. This material can be stored for several years, as long as there is sufficient material (also for future cancer research) to produce reliable analysis. The biological material will be handled and stored either at the institution where you are/were treated, at the institution where the tests are/were being performed, or at the EORTC Data Center in Brussels in accordance with all existing applicable laws. Your doctor should be able to inform you where the biological material(s) is (are) stored.

The mission of EORTC, being a non-profit research organization, is to do everything it can in the best interests of cancer patients. Collaboration with third parties, including private companies, may be necessary for the EORTC to develop more effective treatments. It cannot be excluded that results from use of biological material could lead to an acquisition of exclusive rights, which are based on research discoveries. You will not receive any financial return. Should there be any financial return for the EORTC, it will be reinvested in cancer research only to improve cancer care.

The results of the research studies on biological material are unlikely to be available in the foreseeable future. This is because research can take a long time and tissue samples and data must be taken from many patients before results are known.

New relevant information, that directly concerns your future health, may well be available from your treating doctor at the institution where you have been treated following the present protocol.

8. Expected benefits

The goal of both treatments is to stop the growth of your brain tumor for as long as possible. This study investigates two treatments, of which one, radiotherapy, is currently considered standard treatment but of limited efficacy. Less information is available about the efficacy of temozolomide chemotherapy in low-grade glioma.

This research will teach us more about cancer. This might enable us to improve the treatment and so help other patients with cancer like yours in the future. However, nobody can predict whether you will directly benefit from participating in this clinical trial.

9. Voluntary participation

Your participation in this clinical research project with mandatory research on biological material is entirely voluntary and you will be given sufficient time to decide whether or not you wish to participate. You are free to decide at anytime without giving any reason that you no longer wish to participate to the trial. Such decision will not affect your subsequent treatment or relationship with your treating physician or the hospital staff in any way. Medical data collected during your participation to the clinical trial as well as follow-up data which will still be prospectively collected will be kept for research and analysis unless you specify otherwise. All unused biological material will be processed as indicated unless you raise any objection.
10. Data protection

Your consent for participation in this Protocol also includes your consent to allow the use of the data in your medical/clinical record or data resulting from research on tissue to be used for research purposes. Your consent also includes allowing this data to be linked to data coming from other sources (such as cancer registries, medical/clinical records,…). Handling of biological material will be done in such a way, that scientists, analyzing it for research purposes, will not be able to find out your identity.

All data (personal, clinical, economic and data coming from research on biological material) collected on your behalf will be treated in compliance with the European and the national applicable laws."

The trial involves the collection of information contained in your medical records and which relate to your disease. It is very important that the information collected is accurate and from time to time it may be checked against your medical records. Duly authorized persons (EORTC staff, national and/or foreign health authority representatives or certain persons from the company supplying the trial medication) may have access to your medical records. With the exception of access by the duly authorized persons to your personal data on your medical record, all information will be strictly confidential.

11. Sponsorship

♦ The sponsor of this trial is EORTC

This clinical research project is conducted under the legal framework of EORTC with partial financial contribution of Schering Plough.

The EORTC, which is responsible for the conduct of this trial, has asked your treating doctor to disclose any existing conflict of interest he/she may have as a result of his/her activities related to this trial. The EORTC has set up procedures to ensure the integrity of this process.

12. Insurance

The sponsor of the Study has obtained clinical trial insurance in accordance with the applicable legislation of your country to cover risk related to your participation in this study.

13. Ethics Committee

This research protocol has been submitted to the ethics committee whose mission is to verify that all conditions with respect to your safety and rights are respected. Approval to this research has been given by the Ethics Committee of ______________ on ________________
14. Contact persons

In case of any problem or question, your doctor will be pleased to answer any further questions and may be contacted as follows:

Name of the doctor: ______________________________________
Hospital: ________________________________________________
Telephone: ______________________________________________

If you consent to join this trial, you will be given a telephone number at the hospital that you can contact at any time if you feel unwell or have further questions. With your agreement, your family doctor will also be informed about your taking part in this trial and what is involved, if you agree.

Please take your time to consider this information and do not hesitate to ask further questions to your doctor if anything is not clear. You are entitled to keep a copy of this document after you and your physician have signed it.
Acceptance of participation

☐ I have been properly informed about the clinical trial and have been given sufficient time to consider my participation.

☐ I have received a copy of the patient information sheet and the informed consent document

☐ All my rights have been clearly explained to me

☐ I agree to participate in the clinical research study entitled “Evaluating primary chemotherapy with temozolomide vs. radiotherapy in patients with low-grade gliomas with stratification for genetic 1p loss: a phase III study” and registered under EORTC study number 22033-26033.

I accept that any data resulting from this clinical research study can be linked with other resources for cancer research purposes My participation is completely voluntary and I have the possibility to withdraw my consent at anytime without explanation. This will not affect my relationship with my treating doctor. The data collected on my behalf will be strictly confidential and treated according to the European and national applicable laws.

In case of EORTC collaboration with a third party, I agree that my biological material can be used by:

☐ Another academic institution/organization

☐ Pharmaceutical company

☐ I accept that future cancer research studies may be conducted on the biological material that I provide and that any data resulting from these studies can, in the future, be linked with other resources for research purposes. My participation to this is completely voluntary and I have the possibility to withdraw my consent at any time without explanation. This will not affect my participation in the clinical study nor my relationship with my treating physician. The data collected on my behalf will be strictly confidential and treated according to the European and national applicable laws.

In case of EORTC collaboration with a third party, I agree that my biological material can be used for future cancer research by:

☐ Another academic institution/organization

☐ Pharmaceutical company

☐ I have been informed that the data collected may be used in the future for cancer scientific research purposes while confidentiality will be ensured

☐ I am aware that as part of this study a blood sample and a tumor sample will be examined for specific chromosomal lesions in another institute.

☐ I am aware that as part of this study another pathologist, affiliated to another institute, will review a sample of my tumor.
All data (personal, clinical and research on biological material) collected on my behalf will be treated in compliance with the European and national applicable laws.

My consent does not discharge the organizers of the research from their responsibilities and I keep all my rights guaranteed by the law

Patient's name: __________________________  
Patient's signature: ___________________ Date: ______________

Person designated by the investigator to participate in the informed consent process:

Name: ________________________________  
Signature: ______________________________ Date: ______________

Investigator's name: ______________________
Title/Position: ___________________________
Investigator's Signature: ___________________ Date: ______________

This document has been prepared taking the following documents into account:

− "European Union Directive (Dir/95/46/EC) on the protection of individuals with regard to the processing of personal data"
Appendix G: Patient Information Sheet and Informed consent document for optional research on biological material.

INFORMATION FOR INVESTIGATORS:

This document is an English version of the Patient information sheet & informed consent for clinical trials (PIS & IC). The translation and national regulatory submission process of this document is the responsibility of the National Coordinator for this trial. He/she will keep you aware and informed and will send the translated and approved document as soon as available.

INFORMATION FOR THE NATIONAL COORDINATORS:

- this document represents an English version of PIS & IC to be used in the present study

- it is the responsibility of the national coordinator to:

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  - send a copy of the approved translated document to EORTC Data Center who will than distribute the document to other national participating investigators

- bold parts, appearing in the English template, must appear also in the translated version of the PIS & IC

- final translated and approved PIS & IC must have version number and date
Research on biological material includes only patients who choose to take part without compromising their possibility to participate to the proposed clinical trial.

1. Title of the research protocol: EORTC 22033-26033: Evaluating primary chemotherapy with temozolomide vs. radiotherapy in patients with low grade gliomas with stratification for genetic 1p loss: a phase III study

2. Research on biological material - objectives and description

You have just consented to participate to the above mentioned trial. This trial includes specific further research on a specimen of your tumor, including review by a pathologist of a tumor sample and chromosomal analysis of a blood sample and of a tumor sample. This has been described in the informed consent form you have just signed. We now ask you for further permission to use available biological material for further and for future research. This research is “optional”, your denial of this research will not affect your participation to the therapeutic study.

Part(s) of biological material taken during diagnostic process or surgical procedure that you undergo or have undergone, may be used for research under the EORTC legal and scientific responsibility to better understand and improve cancer care. Any research project conducted with this biological material will begin only if it has been approved by an Ethics/Scientific Committee according to all applicable laws.

The further molecular analysis of tumor samples in relation to the outcome of treatment may provide a better understanding of brain tumors and may lead to improvement of treatment and patient selection for treatments. The EORTC therefore considers this type of research very important. At present this research cannot be specified, because ongoing research will influence the questions the optional research within this trial will try to answer. However, for this type of future and unspecified research we need your specific consent. At some point in the future the involved investigators and the EORTC will decide which further research shall be carried out. This biological material will not be used to investigate any genetic (hereditary) tests. It also requires no further invasive procedures, as the material already exists.

If you consent for research on biological material, this also implies you agree to the storage of your biological material. This material can be stored for several years, as long as there is sufficient material to produce reliable analysis (also for future cancer research). The biological material will be handled and stored at the institution where you are/were treated, or at the institution where the tests are/were being performed, or at the EORTC Data Center in Brussels in accordance with all existing applicable laws. Your doctor should be able to inform you where the biological material(s) is (are) stored.

The mission of EORTC, being a non-profit research organization, is to do everything it can in the best interests of cancer patients. Collaboration with third parties, including private companies, may be necessary for the EORTC to develop more effective treatments. It cannot be excluded that results from use of biological material could lead to acquisition of exclusive
rights, which are based on research discoveries. You will not receive any financial return. Should there be any financial return for the EORTC, it will be reinvested in cancer research only to improve cancer care.

3. Expected benefits

The results of the research studies on biological material are unlikely to be available in the foreseeable future. This is because research can take a long time and tissue samples and data must be taken from many patients before results are known. New relevant information, that directly concerns your future health, may well be available from your treating doctor at the institution where you have been treated following the present protocol.

4. Voluntary participation

Your participation in the research project on biological material is entirely voluntary and you will be given sufficient time to decide whether or not you are wishing to participate. You are free to decide at anytime without giving any reason that you no longer wish to participate in the research project on biological material. Withdrawal from this part will not affect your participation into the clinical research study or relationship with your treating doctor or the hospital staff in any way. In case of withdrawal, your data will not (no longer) be used in any analysis, unless it has already been completed prior to your withdrawal. All unused material will be returned to your treating institution, if requested.”

5. Data protection

Your consent for participation in the research on biological material also includes your consent to allow the use of the data in your medical/clinical record or data resulting from research on tissue to be used for research purposes. Your consent also includes allowing this data to be linked to data coming from other sources (such as cancer registries, medical/clinical records,…). Handling of biological material will be done in such a way, that scientists, analyzing it for research purposes, will not be able to find out your identity.

All data (personal, clinical, economic and data coming from research on biological material) collected on your behalf will be treated in compliance with the European and national applicable laws.

It is very important that the information collected is accurate and therefore from time to time, this collected information may be checked against your medical records. Duly authorized persons (EORTC research staff, national and/or foreign health authority representatives or certain persons of the company supplying the trial medication) may have access to your medical records. With the exception of access by the duly authorized persons to your personal data on your medical record, all information will be strictly confidential.

6. Ethics Committee

In addition to the Ethical Committee review for your participation in the clinical trial, further ethical and scientific review will be conducted prior to any research with biological material. This is to verify that all conditions with respect to your safety and rights are respected.
7. Contact persons

In case of any problem or question, your doctor will be pleased to answer any further questions and may be contacted as follows:

Name of the doctor: _____________________________
Hospital: _____________________________
Telephone: _____________________________

If you consent to give your biological material for cancer research, you will be given a telephone number of the hospital that you can contact at any time if you feel unwell or have further questions. With your agreement, your family doctor will also be informed about your taking part in this trial and what is involved, if you agree.

Please take your time to consider this information and do not hesitate to ask further questions to your study doctor if anything is unclear. You are entitled to keep a copy of this document after you and your study doctor have signed it.
Informed consent

Evaluating primary chemotherapy with temozolomide vs. radiotherapy in patients with low grade gliomas with stratification for genetic 1p loss: a phase III study- protocol number 22033-26033

☐ I have been properly informed about the research on biological material and have been given sufficient time to consider my participation.

☐ I have received a copy of the patient information sheet.

☐ All my rights have been clearly explained to me.

☐ I have been properly informed and accept collection, storage and research on biological material that I provide. I was given sufficient time to consider my participation. I accept that any data resulting from the research study on biological material can be linked with other resources for cancer research purposes. My participation is completely voluntary and I have the possibility to withdraw my consent at any time without explanation. This will not affect my participation into the clinical research study or relationship with my treating doctor or the hospital staff in any way. The data collected on my behalf will be strictly confidential and treated according to the European and national applicable laws”.

In case of EORTC collaboration with a third party, I agree that my biological material can be used by:

☐ Another academic institution/organization

☐ Pharmaceutical company

☐ I accept that future cancer research studies may be conducted on the biological material that I provide and that any data resulting from these studies can in the future be linked with other resources for research purposes. My participation to this is completely voluntary and I have the possibility to withdraw my consent at any time without explanation. This will not affect my participation in the clinical study nor my relationship with my treating doctor or the hospital staff in any way. The data collected on my behalf will be strictly confidential and treated according to the European and national applicable laws”.

In case of EORTC collaboration with a third party, I agree that my biological material can be used for future cancer research by:

☐ Another academic institution/organization

☐ Pharmaceutical company

All data (personal, clinical and research on biological material) collected on my behalf will be treated in compliance with the European and national applicable laws.
My consent does not discharge the organizers of the research from their responsibilities and I keep all my rights guaranteed by the law.

Patient's name: __________________________

Patient's signature: _______________ Date: ______________

Person designated by the investigator to participate in the informed consent process:

Name: ________________________________

Signature: ____________________________ Date: ______________

Investigator's name: ______________________

Title/Position: __________________________

Investigator's Signature: _______________ Date: ______________

This document has been prepared taking the following documents into account:

− European Union Directive on the protection of individuals with regard to the processing of personal data (Dir/95/46/EC)
Appendix H: Addendum to the patient information sheet / informed consent form – December 8th, 2006 - For NEW and ON GOING patients

Title of the clinical trial
EORTC protocol 22033-26033: Primary chemotherapy with temozolomide vs. radiotherapy in patients with low grade gliomas after stratification for genetic 1p loss: a phase III study

Changes relevant to participants in the clinical trial
The producer of TMZ (Temozolomide) used in this trial, Schering-Plough, has recently provided additional information concerning this drug.

You have already been informed there is a risk that blood may decrease and that might make you more likely to get a severe infection or bleed (this is a condition called aplasia). This condition may be prolonged and result in as called aplastic anaemia. This is rare but occurs more often when temozolomide is given for a longer period of time.

It has been found that women have a higher incidence than men, of severe decrease in the neutrophils (white blood cells) and in the platelet count.

Other side effects of temozolomide may include fatigue, constipation, headache, loss of appetite or weight, diarrhea, rash, weakness, allergic reactions (including anaphylaxis), fever, chills, hair loss, pruritis, dyspepsia, erythema and edema, elevation of liver enzymes, deep vein thrombosis and pulmonary embolism.

Temozolomide has been reported to possibly contribute in very rare and isolated cases to the occurrence of severe mucosal and cutaneous toxicity (as Stevens Johnson Syndrome). Secondary cancers such as myeloid leukemia (cancer of the blood and bone marrow), and myelodysplastic syndrome (caused by the bone marrow producing faulty blood cells) have been reported very rarely.
Addendum to the patient information sheet / informed consent for participation in the clinical trial after receiving new information concerning this drug

EORTC protocol 22033-26033: Primary chemotherapy with temozolomide vs. radiotherapy in patients with low grade gliomas after stratification for genetic 1p loss: a phase III study

I have been properly informed about the new information available as of December 8th 2006.

I have received a copy of the new patient information sheet and the informed consent form.

I fully understand the new information available as of December 8th 2006 which may affect my participation in this clinical trial.

☐ By signing below I confirm my participation in this clinical trial
OR
☐ By signing below I withdraw my participation and therefore no longer wish to be treated according to this research protocol.

<table>
<thead>
<tr>
<th>Name of patient</th>
<th>Date</th>
<th>Signature</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name of patient’s legal representative (only if applicable)</th>
<th>Date</th>
<th>Signature</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name of investigator</th>
<th>Date</th>
<th>Signature</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name of person designated by the investigator to take part in the informed consent process (only if applicable)</th>
<th>Date</th>
<th>Signature</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix I: QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____________________________
Your birthdate (Day, Month, Year): ____________________________
Today’s date (Day, Month, Year): ____________________________

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have any trouble doing strenuous activities,</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>like carrying a heavy shopping bag or a suitcase?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Do you have any trouble taking a long walk?</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Do you have any trouble taking a short walk outside of the house?</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Do you need to stay in bed or a chair during the day?</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Do you need help with eating, dressing, washing yourself or using the</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>toilet?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Were you limited in doing either your work or other daily activities?</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During the past week:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Were you limited in pursuing your hobbies or other leisure time</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>activities?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Were you short of breath?</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Have you had pain?</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Did you need to rest?</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Have you had trouble sleeping?</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Have you felt weak?</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Have you lacked appetite?</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Have you felt nauseated?</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. Have you vomited?</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please go on to the next page
During the past week:

16. Have you been constipated?  1  2  3  4
17. Have you had diarrhea?  1  2  3  4
18. Were you tired?  1  2  3  4
19. Did pain interfere with your daily activities?  1  2  3  4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?  1  2  3  4
21. Did you feel tense?  1  2  3  4
22. Did you worry?  1  2  3  4
23. Did you feel irritable?  1  2  3  4
24. Did you feel depressed?  1  2  3  4
25. Have you had difficulty remembering things?  1  2  3  4
26. Has your physical condition or medical treatment interfered with your family life?  1  2  3  4
27. Has your physical condition or medical treatment interfered with your social activities?  1  2  3  4
28. Has your physical condition or medical treatment caused you financial difficulties?  1  2  3  4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?  1  2  3  4  5  6  7
   Very poor                             Excellent

30. How would you rate your overall quality of life during the past week?  1  2  3  4  5  6  7
   Very poor                             Excellent

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## Appendix J: Brain module

### EORTC QLQ - BN20

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

<table>
<thead>
<tr>
<th>Question</th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>31. Did you feel uncertain about the future?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>32. Did you feel you had setbacks in your condition?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>33. Were you concerned about disruption of family life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>34. Did you have headaches?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35. Did your outlook on the future worsen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>36. Did you have double vision?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>37. Was your vision blurred?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>38. Did you have difficulty reading because of your vision?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>39. Did you have seizures?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>40. Did you have weakness on one side of your body?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>41. Did you have trouble finding the right words to express yourself?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>42. Did you have difficulty speaking?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>43. Did you have trouble communicating your thoughts?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>44. Did you feel drowsy during the daytime?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>45. Did you have trouble with your coordination?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>46. Did hair loss bother you?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>47. Did itching of your skin bother you?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>48. Did you have weakness of both legs?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>49. Did you feel unsteady on your feet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>50. Did you have trouble controlling your bladder?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

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Appendix K: Mini-Mental State Examination (MMSE)

Patient’s Name: ____________________  Date: ________________

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

<table>
<thead>
<tr>
<th>Maximum Score</th>
<th>Patient’s Score</th>
<th>Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td></td>
<td>“What is the year? Season? Date? Day? Month?”</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>“Where are we now? State? County? Town/city? Hospital? Floor?”</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>“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)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>“Earlier I told you the names of three things. Can you tell me what those were?”</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>“Repeat the phrase: ‘No ifs, ands, or buts.’”</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>“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.)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>“Please read this and do what it says.” (Written instruction is “Close your eyes.”)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>“Make up and write a sentence about anything.” (This sentence must contain a noun and a verb.)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>“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.)</td>
</tr>
<tr>
<td>30</td>
<td>TOTAL</td>
<td></td>
</tr>
</tbody>
</table>

*Source:*
Appendix L: Collection and Preparation of Pathological and Biological Patient Material

1. Shipment

A central database will be established at the EORTC and made available to manage flow of patient material.

**Material to be collected and sent to the central molecular reference laboratory (Heidelberg, Heidelberg for Europe):**

- Paraffin blocks of embedded tumor material
- 2 x 10 ml of citrated full blood

Please send material per express mail in appropriate containers at room temperature (to arrive within 3 days):

Collection for translational research (kept at the center, will be collected at a later stage):

- Fresh-frozen tumor tissue
- Fresh frozen serum
- Fresh frozen lymphocytes

**Material to be accompanied by the following information**

- Patient character code
- Trial and sequential ID number
- Date of birth
- Copy of the original local histopathological report (anonimyzed)

**Data to be collected on the registration from** (or online at the registration step):

- Patient character code (mandatory)
- Date of birth (mandatory)
- Gender (mandatory)
- Local pathological diagnosis (mandatory)
- Name of the responsible neuropathologist (mandatory) and e-mail (optional)
- Date and type of surgery or biopsy (mandatory)
2. Fixation of brain tumor tissues

Very good results for histological and molecular analyses are achieved with the following procedure:

1) Larger brain tumor samples should be cut into slices of 4 to 5 mm thickness.
   - Penetration of formaldehyde is approximately 0.5 mm per hour from each side.

2) Tissues should be placed in 20 volumes or more of 10% buffered Formalin. This corresponds to 4% buffered Formaldehyde.
   - Fixation with Bouin solution (0.9% picric acid, 9.5% formaldehyde, 4.8% ascetic acid) is to be strictly avoided. Bouin fixation is not compatible with retrieval of sufficient DNA for molecular analysis.
   - Concentrated Formalin corresponds to a stock solution of approximately 37% formaldehyde including roughly 10% methanol in order to inhibit oxidation to formic acid. A 1 in 10 dilution of concentrated formalin yields 4% formaldehyde.

3) Fixation time should be between 6 and 24 hours.
   - Longer fixation times result in the material becoming hard and brittle and in difficulties with DNA extraction.
   - If longer fixation times cannot be avoided (weekend etc.), fixation should be performed at 4°C.

4) Paraffin embedding is followed by histological and molecular analyses. Materials can be stored for long periods.

3. Storage of blood for molecular analysis

Very good results for molecular analyses are achieved with the following procedure:

1) 20 ml of citrated blood best taken before surgery.
   - Citrated blood is preferred to Heparin blood. Heparin chelates Mg^{++} ions. Traces of Heparin in DNA extractions require adjustments of Mg^{++} ion concentration in some buffers used at PCR amplification. However, Heparin blood will do, too.

2) Blood samples can be shipped for 4 days at room temperature.
   - If blood samples have previously been frozen, they should be shipped in frozen condition at -20°C or colder.
Appendix M: Central Pathology Review and Molecular Diagnostics

1. Material Routing and Flow Chart

1.1 Material Routing

All materials should be sent to the molecular reference laboratory for further processing. This laboratory will then transfer the material to the pathologist for the histopathological review. See appendix “Collection and Preparation of Pathological and Biological Patient Material” (Appendix L).

1.2 Flow chart for work at the molecular reference laboratory

Workday 1: Receipt of material. Login of data. Appropriate storage of material. Selection of material for further processing

Workday 2: Preparing sections for histological and molecular analysis

Workday 3-5: Staining and evaluation of histological sections, extraction of DNA from blood and paraffin embedded material

Workday 6: Transfer of H&E stained and 10 additional unstained sections for reference diagnosis to Rotterdam

Workday 6-12: Performance of LOH analysis

Workday 13-14: Evaluation of molecular data, login and transfer to EORTC data center

1.3 Flow chart for work at the histological reference laboratory

Workday 1: Receipt of H&E stained slides and the additional unstained sections, the paraffin blocks

Workday 2-5: Additional immunohistochemical analysis

Workday 6: Evaluation of histological data, login and transfer to study center. Designation of tumor region suitable for the tissue array (TA) on the H/E that ideally should be the last section cut from the block. Construction of tissue array.

2 Central Review Process

A detailed list of morphologic criteria will be filled in at the time of central review that will allow correlation of morphologic/ histopathologic features with outcome. The criteria will be agreed on by the review committees from Europe and Canada. This information will be entered into the central data base or a compatible data base.

In order to allow for future analysis of upcoming markers, a tissue array will be constructed (in triplicate).
2.1 Histological features to be evaluated

Cell density  low / moderate / high
Nuclear pleomorphism  low / moderate / high
Mitoses  n / 10 fields 40x magnification
MIB-1 LI:  n % pos. nuclei
Microvascular proliferation  yes / no
Necrosis  yes / no
Microcysts  yes / no
Aspect of tumor cells:  n % with oligodendrogial / n % with astrocytic differentiation
GFAP-positive oligodendrogial cells  yes / no

(Bold = necessary for the diagnosis low-grade glioma)
Appendix N: 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.

1. **Schedule and tests performed**

Comprehensive neurocognitive testing will be performed at randomisation and at every 6 months from randomization up to tumor progression or death.

Nurses or clinicians that are trained and certified at a single location will administer a battery of standardized neurocognitive tests. All individuals administering these tests will undergo training, including hands-on training, and training manuals, followed by certification by [insert certification body].

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

The test battery will include the following tests:

- **The Rey Auditory Verbal Learning Test (AVLT)** (Ref. 1) calls for various aspects of verbal learning and recall. The AVLT requires patients to memorize a list of 15 items for five consecutive tests (recall), to recall these 15 items after a 20-minute delay (delayed recall), and to identify the same 15 items from a list of 30 words (recognition). Measures used for analysis are memory performance on trial 1 as indicator of immediate recall, total recall after five trials, delayed recall and recognition after 20 minutes as indicators of memory consolidation into long-term memory, and a delta score as a measure of learning capacity.

- **Concept Shifting Test**, which is an adaptation of the Trailmaking Test (Ref. 1). This test, which has two conditions of complexity, predominantly measures functions associated with executive function, especially visual scanning and conceptual tracking. In all conditions, the patient will be given paper sheets with 16 circles to be crossed out. In part A, the patient will be asked to cross out randomly distributed digits (1 to 16) in the circles in ascending order. In part B, the patient crosses out 16 letters (A to P) in alphabetical order instead, and in part C, the patient will be instructed to alternate between letters and digits (1-A, 2-B etc.) Finally, the motor component of this task will be measured by two dummy conditions in which empty circles have to be crossed out twice, requiring no cognitive capacity except for graphomotor speed.

- **Executive functioning and cognitive flexibility will be measured by the Categoric Word Fluency Test** (Ref. 2) which requires the generation of words from specific semantic categories. Patients have to name as many animals as possible in a 2-minute period. To measure cognitive flexibility patients have to name as many items as possible from a semantic subcategory (i.e., insects) in an additional 1-minute period.

- **Adequate performance on the Digit-Symbol Substitution Test** (Ref. 3) entails several cognitive and perceptual functions, including attention, visual perceptual and visuoconstructive abilities, sequencing, and short-term memory. The patient is given a sheet of paper with a code indicating 9 symbols corresponding to 9 digits. Below this are horizontal rows of these symbols with an empty cell below each. The patient has to fill out as many cells as possible in 90 seconds by looking up the corresponding digit. Next, incidental memory is measured.
**Self-reported cognitive function** will be assessed with a six-item scale developed for use in the Medical Outcomes Study (Ref. 4). 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. Statistical analysis

Because consideration of group means may obscure cognitive impairment evaluation at the level of the individual, an impairment score for each patient will be calculated. This was performed by converting neuropsychologic test scores to z scores, using the mean scores of the healthy controls as a reference. Subsequently, a mean overall composite z score will be computed. Neuropsychologic impairment is defined as a test score of two SDs below the mean of the healthy controls. An overall impairment score will be calculated for each individual patient by counting all tests that meet this criterion.

Analysis of covariance (F tests), with correction for differences in age, sex, years of formal education, and duration of disease will be performed to test for differences between glioma patients receiving radiotherapy and glioma patients receiving Temozolomide. The same procedure will be performed to test for differences between glioma patients and healthy controls in mean scores for objective cognitive functioning.

Changes in neurocognitive functioning over time will be analyzed by using repeated measures analysis of variance correcting for differences in age, sex, education, duration of disease, and practice effects.

The prevalence of cognitive disability (on the basis of the previously described cutoff of 2 SD below the mean of the healthy controls, which we assume would seriously interfere with everyday life functioning) will be investigated in glioma patients receiving radiotherapy and in glioma patients receiving Temozolomide, with logistic regression analysis, corrected for differences in age, sex, education, and duration of disease. Disease duration will be defined as the time between histological diagnosis and formal neuropsychological testing. To assess the association between objective and self-reported cognitive function in glioma patients, Pearson’s correlations will be calculated between neurocognitive test outcomes and the Medical Outcomes Study scale.

To identify which tumour-related and treatment-related characteristics are associated with objective and self-reported cognitive functioning, a stepwise linear regression analysis with possible confounders (ie, age, sex, and education) entered into the model at the first step will be performed. Subsequently, duration of disease, use of radiotherapy (yes/no), use of temozolomide (yes/no), antiepileptic drug use (none vs any), tumour lateralisation (left vs right), and neurosurgical intervention (biopsy vs resection) will be entered as independent variables. The separate cognitive test scores, the Medical Outcomes Study scale, and the total number of deviant test scores based on a cutoff of 2 SD below the mean of the healthy controls (partners) will be entered as the dependent variables. The level of significance will be set at p<0.05. To identify tumour-related and treatment-related factors that are associated not only with cognitive functioning per se (ie, mean test scores), but also with cognitive disability, an additional series of logistic regression analyses will be performed. Using individual cognitive disability scores, the relative risk and 95% CI for cognitive disability will be calculated, correcting for differences in age, sex, and education, for the same variables as those used in the linear regression analysis. Probability for entry will be set at 0.05 and probability for removal at 0.10.
3. Data Management and Data Analysis

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 Data Center together with the regular patient documentation. The EORTC Data Center will then transfer the forms relating to the neurocognitive assessment side study to the Coordinator of the Side Study. The information related to the side study will be entered in a specific database in Den Haag. Care will be taken that the patient identification be 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 of the Request for External Release of Data as specified in EORTC Policy number 8.

The 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.

4. Auditory-Verbal Learning Test

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### Recognition

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<tr>
<td>Ranger</td>
<td>Towel</td>
<td>Gun</td>
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<td>Bird</td>
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<td>Turkey</td>
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<td>Nose</td>
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<tr>
<td>Drum</td>
<td>Lamb</td>
<td>Fish</td>
</tr>
</tbody>
</table>
5. Concept Shifting Test A

Concept Shifting Test A

1  2  3  4  5  6  7  8  9  10  11  12  13  14  15  16
5.1 Concept Shifting Test A – Practice

Concept Shifting Test A - Practice

1  2  3  4  5  6
6. Concept Shifting Test B

Concept Shifting Test B

L B I M E G O C A P H J N K
6.1. Concept Shifting Test B - Practice

Concept Shifting Test B - Practice
Concept Shifting Test C
7.1 Concept Shifting Test C- Practice

Concept Shifting Test C - Practice

1

C

2

B

3

A
8. **Digit-Symbol Substitution test – Incidental memory**

**Digit-Symbol Substitution Test - Incidental Memory**

Paired-Associate

| 5 | 1 | 8 | 2 | 9 | 4 | 6 | 3 | 7 |

Free Recall

| 8 | 5 | 6 | 3 | 1 | 9 | 4 | 7 | 2 |
8.1 Digit Symbol Substitution test - Coding

Digit-Symbol Substitution Test - Coding

```
1  2  3  4  5  6  7  8  9

2  1  3  7  2  4  8  2  1  3  2  1  4  2  3  5  2  3  1  4
5  6  3  1  4  1  5  4  2  7  6  3  5  7  2  8  5  4  6  3
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7  1  8  2  9  3  6  7  2  8  5  2  3  1  4  8  4  2  7  6
```
References
Ref. 3 Wechsler D. Wechsler Adult Intelligence Scale–III. San Antonio, TX: The Psychological Corporation, 1997
Appendix O: RTOG Neurologic Function Status

RTOG Neurologic function (NF) status

NF Definition

0  No neurologic symptoms; fully active at home/work without assistance.
1  Minor neurologic symptoms; fully active at home/work without assistance.
2  Moderate neurologic symptoms; fully active at home/work but requires assistance.
3  Moderate neurologic symptoms; less than fully active at home/work and requires assistance.
4  Severe neurologic symptoms; totally inactive requiring complete assistance at home or in institution-unable to work.

In this protocol, only signs and symptoms related to the disease or the treatment will be considered when scoring NF.
Appendix P: Quality Assurance Procedure for Radiotherapy (EORTC)

All participating centres accept to participate to the following QA procedure:

1. **Questionnaires:** For participating institutes, which are not members of the EORTC Radiotherapy Group, a first questionnaire aiming to assess the techniques and infrastructure of each institute will be circulated. Centres using stereotaxy, IMRT and/or image co-registration will receive specific questionnaires about image fusion procedures and its use for treatment planning.

2. **Dummy run procedure:** All centres will receive a dummy case adapted to the local techniques used and designed to incorporate one or more critical items, and asking them to plan a treatment following the protocol guidelines. Results will be analysed and independently reviewed and discussed with the local investigators. This will be done in collaboration with the NCI remote QA Center at Washington University, St Louis, MI.

3. **Individual case review:** Patients from the trial will be randomly chosen for review using the NCI facilities. Much of this will be possible using the Telesynergy programme.

4. **Site visits:** This will only be done if absolutely necessary. Much of the checks done during a site visit can be done using the NCI remote facility.
Appendix Q: NCIC CTG CE.5 Appendix

NCIC CTG Group Procedures and Instructions for Canadian Centres

Administrative Update#1 : 2006-DEC-07

NCIC CTG Contacts:

Study Chairs:

Central Office Contacts:

NCIC Clinical Trials Group
10 Stuart Street, Queen’s University
Kingston, ON Canada K7L 3N6
Phone: 613-533-6430
Fax: 613-533-2941

SECTION 1.0 - NCIC CTG PROTOCOL VARIATION

Canadian participants will not be included in the neurocognitive function testing component of the EORTC protocol.

SECTION 2.0 - ETHICAL AND REGULATORY REQUIREMENTS

All member centres in good standing of the NCIC CTG are eligible to participate in this study. Institutions which are not NCIC CTG members can either make an application for membership or submit a single study agreement document.

All investigators (principal investigators and co-investigators) must have completed NIH mandated ethics education training with respect to human subjects protection. Evidence of completion of this education must be on file at the NCIC CTG prior to approving any investigator on the Participant’s List for this study. For investigators who have not already completed this education, a recommended route for doing so is to complete an on-line training program available at
The program can be completed in approximately an hour and a half and it will issue a completion certificate, a copy of which must be forwarded to the NCIC CTG.

This study is being conducted under a Clinical Trial Application (CTA) in Canada. Accordingly, the protocol must be conducted in compliance with Division 5 of the Canadian Food and Drug Regulations and ICH-Good Clinical Practice Guidelines. Please note that the Division 5 Canadian Food and Drug Regulations pertaining to the conduct of clinical trials were amended and came into force on September 1, 2001; the conduct of this protocol must comply with these regulations.

The NCIC CTG will submit via fax to Health Canada for each participating Canadian centre prior to local activation a completed Health Canada Clinical Trial Site Information form.

Further information regarding these regulatory and ethics requirements may be accessed on the NCIC CTG private website at the following address: http://www.ctg.queensu.ca/private/ethics/default.html. Applicable guidelines/regulations are found under the “Links to Related Websites” under the “Ethics, Regulatory and Consents” section. A username and password are required to access this website. Please contact our Operations Office if you require assistance in this regard.

SECTION 3.0 – REQUIRED DOCUMENTS

3.1 The following documentation must be on file at the NCIC CTG central office prior to local activation:

3.1.1 Written documentation of full board Research Ethics Board (REB) approval of the protocol and sample consent form, including version dates of both. The REB of an institution must approve the consent form document that will be used at that centre. Please note that if the approval letter or form from the REB does not clearly indicate that a ‘full board’ review was done, then either a revised letter/form or the minutes of the REB meeting evidencing a full board review was done must be submitted.

If an REB refuses to approve this protocol (or an amendment/revision to this protocol) the NCIC CTG must be notified immediately of the date of refusal and the reason(s) for the refusal.

Completed “Confirmation of Initial Ethical Approval” form confirming the protocol was approved by a properly constituted REB and that only REB members independent of the investigator(s) conducting the study participated in deliberations or voting concerning the approval of the study.

3.1.2 Copy of the REB approved consent form on institutional letterhead.

A sample consent form is provided on the NCIC CTG CE.5 webpage. It may be modified to meet local requirements as long as the necessary elements are retained. These include a description of the purpose of the study, potential side effects, potential benefits, study design, voluntary participation and confidentiality. The consent form must contain statements giving permission for medical/study reports concerning the patient to be sent to the NCIC CTG and other sponsoring and monitoring agencies, and for representatives of the NCIC CTG and these agencies to inspect medical/study reports on-site.

Since this study is conducted under a CTA all ICH-GCP elements as listed in section 4.8.10 of the ICH-Good Clinical Practice Guideline must be included in the consent form. If a centre does modify the sample consent, no ICH-GCP elements may be eliminated in the modification process. It is important that descriptions of risks and alternative therapy are not reduced.

If any of the required elements of the consent form are changed, it is recommended that a copy be sent to the NCIC CTG for review prior to REB approval. This may help to avoid delays in your centre’s ‘local’ activation. Every effort will be made to review the consent
form before the planned REB submission date; however, please provide the study coordinator with a reasonable amount of time in which to undertake this review.

A French translation of the sample consent has been posted on the NCIC CTG CE.5 trial web page.

3.1.3 A Health Canada REB Attestation Form must be completed and signed by the REB representative. Alternatively, an attestation to the following may be included in the signed local ethics approval document:

♦ The membership of the Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations;

♦ The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practice; and

♦ The Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent for the trial which is to be conducted by the qualified investigator named at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

Completed and signed Health Canada ‘Qualified Investigator Undertaking’ form for the principal investigator only.

3.1.4 Written documentation confirming the applicable investigator brochure was forwarded to the REB. The investigator brochure must be retained and filed with the trial protocol. The confidential investigator brochure will be available on the study website.

3.1.5 Completed NCIC CTG Participant's List. For all new studies, after July 1, 2005, the new Participants List and Participants List change form must be used. These new forms include, among other things, the new delegated duties requirement. Also for new studies, participant lists must be signed by the PI. A copy of the participants list can be found on the NCIC CTG trial web page for CE.5.

3.1.6 Documentation of completed human subject's protection education for each investigator on the Participant’s List, if not already on file with the NCIC CTG.

A list of investigators with ethics education and NCI US # information is sent to all member centres twice a year by our Operations department. This list accompanies the membership roster update with which centres should already be familiar. If an investigator wishes to participate and ethics education has not been completed, the ‘Required Ethics Education’ information is available on the NCIC CTG website at http://www.ctg.queensu.ca/private/ethics/educ.html

3.1.7 All investigators randomizing through NCIC CTG must have a current CV on file. The CV date must be less than 2 years at the time of registration/randomization. If it is not, the investigator will not be permitted to randomize. CVs are now collected centrally by Operations. CVs are due by January 1st of every year. Email CVs to either

3.1.8 Current laboratory accreditation and normal values.

3.2 Continuing Review / Annual Re-Approvals:

This protocol must undergo REB approval at least once per year. Annual REB approvals for all NCIC CTG studies must be obtained by the 12-month mark (i.e. there is no grace period). For example, if an approval was granted at the convened meeting of the REB on 2005-Oct-02 this approval will be valid until 11:59pm on 2006-Oct-01.
This approval must be full board as long as patients are being accrued or any patients at the centre are undergoing protocol mandated treatments or interventions. Once the study is closed to accrual and patients are no longer receiving protocol mandated treatments or interventions, approval on an annual basis must continue as long as patients are being followed. These approvals may be full board or expedited, according to the policy of the local REB. Documentation of required REB annual re-approvals indicating the level of review (if full board review is required) must be forwarded to central office.

3.3 Amendments/Administrative Updates:
All amendments or administrative updates to the protocol must undergo review by local REBs. Amendments/administrative updates will be circulated to all participating centres in a standard format with clear instructions regarding REB review. If full board approval of an amendment is required it will be specified. Documentation of required REB amendment/administrative update approvals indicating the level of review (if full board review is required) must be forwarded to NCIC CTG central office.

SECTION 4.0 – SAFETY
4.1 Serious Adverse Event Reporting
4.1.1 Investigator Reporting Responsibilities to NCIC CTG
This study will use the Common Terminology Criteria of Adverse Events (CTCAE) Version 3. NCIC CTG investigators are to report all reportable serious adverse events (SAE) as defined in the protocol, to the NCIC CTG central office by telephone (613-533-6430) and/or fax (613-533-2941) within 24 hours of the event. SAEs must be reported on the CE.5 Serious Adverse Event Form (Form 89). PLEASE DO NOT SUBMIT SAE REPORTS DIRECTLY TO EORTC.

4.1.2 NCIC CTG Reporting Responsibilities to the Lead Group
The NCIC CTG will forward all expedited SAEs to EORTC within 24 hours of receipt.

4.1.3 NCIC CTG Responsibility for Reporting Serious Adverse Events to Health Canada
The NCIC CTG will provide expedited reports of SAEs to Health Canada for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment can not be ruled out).

4.1.4 Investigator Responsibility for Reporting Serious Adverse Events to Local Research Ethics Boards
NCIC CTG will notify all investigators of all SAEs from this trial as reported to the NCIC CTG by EORTC. This includes all adverse events that are serious, unexpected and related to protocol treatment. Investigators must notify their local Research Ethics Boards (REBs) of all reports received and documentation from the REB acknowledging receipt of these reportable adverse events must be kept on file in the centre along with the SAE report.

For this purpose, the REB submission template letter provided by NCIC CTG should be used. Please note:
♦ this letter must be either printed on institutional letterhead or contain the centre identification/ REB name;
♦ the date of REB submission must be provided;
♦ Either the Principal Investigator or the Clinical Research Assistant must sign this form.
The submission of these events to the local ethics board should be done as soon as possible. It is expected that these will be submitted for review within 30 days of the date of the letter to Investigator. The date of REB Submission for SAEs and SUs will need to be entered into the NCIC CTG CE.5 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site. See below (4.2) for instruction on the safety monitoring utility.

In addition, all expedited adverse events occurring within a centre should be reported to local REBs.

4.2 Safety Reports and Investigator Brochures (and Safety Monitoring Utility)

Safety Reports [serious adverse events (SAEs) which occur on any NCIC CTG led trial and safety updates (SUs) which occur on non NCIC CTG led trials using temozolomide] may be sent for reporting to REB during the course of the trial. Updated investigator brochures may also be sent for reporting to REB. Centres will receive an email message from central office with instruction to retrieve the report/brochure from the web-based safety report monitoring utility (Safety Reports). From this utility, the designated trial PCRA or ECRA will also be able to obtain a template to assist in reporting the event/brochure to the REB and within the utility, enter the date the report/brochure was submitted to the REB. (Instructions for this utility can be found on the Members page on the NCIC CTG website under Clinical Trials or at: www.ctg.queensu.ca/trials/default.html). Documentation of REB submission of this information must be filed in the local ethics binder for the trial but is no longer required to be forwarded to the central office as these documents will be reviewed during site auditing/monitoring visits. It is expected that these reports/brochure will be submitted to the REB within 30 days of being posted.

4.3 Consent Forms

The NCIC CTG may require changes to the local consent form throughout the course of the trial. NCIC CTG will send notification of these changes and request submission to the REB for approval (typically as part of an amendment/update) and REB approval of the changes must be documented and sent to the NCIC CTG.

If any changes are made to the consent form outside of those requested by the NCIC CTG, these changes must be REB approved and the amended/updated consent and REB approval of the changes forwarded to NCIC CTG for review. If this happens, please ensure any changes made to the consent form are clearly identified.

SECTION 5.0 – MONITORING / AUDITING

5.1 On Site Auditing

NCIC CTG on-site auditing will be conducted at active participating centres at least once every three years during the course of the study. Quality Assurance audits may also be carried out by EORTC (the lead group) and Schering, Canada (supplier of study drug).

As this trial is conducted under a CTA with Health Canada, sites may be subject to an inspection by the Health Products and Food Branch Inspectorate. More information may be obtained at the Health Canada website at: www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/insp_strat_clin_tria_te_e.html

Audits will ensure compliance with applicable regulation, including ICH-GCP and Health Canada. The visits will involve a review of source data as well as pharmacy, drug accountability, REB/ethics documents and other essential documents in your study binder. The auditors will require access to REB files to verify appropriate ethical reviews and access to patient medical records to verify the data submitted on CRFs.
SECTION 6.0 - REGISTRATION/RANDOMIZATION PROCEDURES

6.1 Patient Selection Criteria for Registration

The patient selection criteria are listed in the protocol.

6.2 Registration

Following informed consent, patients will be registered to the study. Patients may be registered at initial pathological diagnosis not yet necessitating therapy. Registrations for all NCIC CTG centres will be done through the NCIC CTG Central Office. Registrations will be accepted on Monday to Friday between 8:00 AM and 6:00 PM Eastern Time. The eligibility checklist and the registration form must be completed prior to registration. Registration may be done by telephone (613-533-6430) or by fax (613-533-2941). As soon as eligibility is verified, the EORTC will be contacted by the NCIC CTG to complete registration. The NCIC CTG will then relay the confirmation of registration information to the centre in writing. Following registration, patient specimens will be assessed for 1p loss/mutation in a central laboratory and undergo central pathology review. See the protocol and Section 9.0 below for details regarding collection of tissue and blood.

6.3 Randomization

Once the results of molecular testing are available and whenever the evolution of disease necessitates treatment, eligible consenting patients will be randomized to the clinical trial (note: there is one consent form for this trial that includes both the registration and randomization steps). Eligible patients (see the protocol for eligibility criteria) are randomized to either radiotherapy (RT) alone or temozolomide (TMZ) chemotherapy alone. Randomizations for all NCIC CTG centres will be done through the NCIC CTG Central Office. Randomizations will be accepted on Monday to Friday between 8:00 AM and 6:00 PM Eastern Time. The eligibility checklist and the randomization form must be completed prior to randomization. Randomization may be done by telephone (613-533-6430) or by fax (613-533-2941). As soon as eligibility is verified, EORTC will be contacted by the NCIC CTG to obtain the treatment assignment. The NCIC CTG will then relay the treatment assignment to the centre and confirm it in writing.

SECTION 7.0 – START-UP SUPPLIES

7.1 Protocol and Forms

All protocol related documents can be downloaded from the NCIC CTG CE.5 trial webpage.

7.2 Case Report Forms and Data Collection

Modified EORTC Case Report Forms (CRFs) will be used by all NCIC CTG institutions. CRFs should be completed and submitted along with required supporting documentation as described in the protocol to the NCIC CTG Central Office. In addition to the required forms as listed, a copy of the signed consent form must be submitted for each patient. NCIC CTG trial code, patient serial numbers as well as patient initials must be recorded on each form. Quality of life will be measured using the EORTC QLQ-C30 measures, as described in the protocol and are to be submitted according to the schedule described in the protocol. CRFs will be forwarded to EORTC by the NCIC CTG. PLEASE DO NOT SEND CRFs DIRECTLY TO EORTC. The NCIC CTG address for the submission of forms is:
7.3 **Study Drug: Temozolomide**

7.3.1 **Drug Supply**

Temozolomide will be supplied for this study by Schering, Canada. An initial supply of six vials will be sent within 72 hours of local activation. Therefore, at least 3-4 working days must be allowed between local activation and the enrolment of the first patient onto the study.

7.3.2 **Drug Re-Supply**

Download the re-supply fax form posted on the NCIC CTG CE.5 web page to order a re-supply. Complete the form and send your request to the contact information on the form. When reordering at least 3 vials must remain at your centre since each re-order will take at least 72hrs from request to delivery.

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**SECTION 8.0 - FUNDING**

8.1 **Per Case Funding**

The rate of per case funding is $3000 Cdn for each patient enrolled at each centre. For more information regarding per case funding please see our “Procedure for Centre Funding” information available on the NCIC CTG website at:

[http://www.ctg.queensu.ca/trials/generic_forms_public/centre_funding.pdf](http://www.ctg.queensu.ca/trials/generic_forms_public/centre_funding.pdf)

8.2 **Standard NCIC CTG funding** will be sent to pathologists for specimen retrievals upon receipt of Request For Payment forms.

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**SECTION 9.0 - CENTRAL REVIEWS**

9.1 **Central Molecular and Pathology Reviews and Banking**

Central molecular and pathology review for screening and diagnosis is required for all patients participating in this study. Patients will be asked to consent to initial review and screening as described in the protocol and the body of the main consent form.

9.1.1 **NCIC CTG Pathology Review (Required)**

Central pathology review is required prior to randomization. Please submit the following materials immediately when assessing patients for participation, and after registration is complete:

♦ Preferably representative paraffin embedded block(s) of tumour material, or alternatively if no paraffin blocks are available, 15 unstained slides if tumour tissue is one square centimeter or more in area, or 25 unstained sections if tumour area is less than one square centimeter.

♦ A copy of the anonymized operative and pathology reports, identifying the patient with trial number, patient id number, date of birth and patient initials

♦ A copy of the Central Pathology Review Form
DO NOT INCLUDE PATIENT NAMES ON THE SAMPLES.

9.1.2 NCIC CTG Molecular Testing (Required)

Materials to be collected and shipped for central molecular testing:
♦ 5 – 10 ml of blood in an EDTA tube
♦ Label blood vial with trial number, patient serial number, date of birth and a copy of the anonymized molecular testing form for the patient.
♦ a copy of the completed Genetic Testing 1P Loss form

Material should be sent by express courier to the molecular diagnostics laboratory at:

Please call the Molecular Diagnostics Laboratory (Monday to Friday) prior to shipping to ensure someone will be available to accept the delivery upon arrival.

SECTION 10.0 – CORRELATIVE STUDIES/BANKING

10.1 Banking for Translational Research (Optional)

Patients who participate in this study may also be asked to consent to biological research and banking of frozen tissue that is left over from the initial surgery. Participation in biological research and banking of frozen tissue is optional for centres, but is strongly recommended. Participation in biological research and banking of frozen tissue is optional for patients and a separate consent form is included for this purpose.

For those patients who consent to biological research and banking of frozen tissue, the block or slides that are submitted for central molecular screening and pathology review will be forwarded by the central pathologist to the Queen’s University Tissue Banking facility. For those patients who do not consent to biological research and tissue banking, any leftover tissue collected for central pathology review will be returned to their originating institution at the institution’s request.

Materials required:
♦ Fresh-frozen tumour tissue stored at randomizing centre (NCIC CTG CE5 Virtual Bank)
♦ Serum collected in a 10 ml SST gel tube, with serum decanted off
♦ Lymphocytes collected in an EDTA lavender topped tube
All blood samples should be accompanied by the trial number, patient’s serial number and date of birth and sent at room temperature by overnight express courier to the NCIC CTG Tumour Bank (where the serum will be aloquatted and the EDTA specimen will be frozen):

NCIC CTG Department of Pathology/Tumour Bank shipment arrival time of 8:00 AM to 3:30 PM Mondays to Fridays (excluding Canadian Holidays).

SECTION 11.0 - QUALITY ASSURANCE

11.1 Quality Assurance for Stereotactical and Conventional Irradiation (see Protocol)

A specific radiotherapy (RT) quality assurance (QA) procedure has been designed by EORTC to clarify the technical aspects of the radiotherapy in this trial and to decrease the inter-institutional variances.

Unless a NCIC CTG centre is already on file at EORTC as having completed this RT QA procedure, each participating centre is required to do so.

The RT QA procedure consists of two steps:
A) The Facility Questionnaire (FQ) must be completed and is a requirement prior to Local Activation. The questionnaire is available via the NCIC CTG CE.5 trial webpage. The completed questionnaire should be sent by email to the NCIC CTG central office, attention of the CE.5 Study Coordinator, where it will be reviewed and copied-to-file prior to submission to EORTC.

Once EORTC notifies NCIC CTG of approval, the participating centre will be locally activated.

B) The Dummy Run (DR) must be completed prior to randomization of a 5th patient at each participating centre. It consists of two parts:

1. definition and delineation of the volumes (GTV, CTV and PTV) to be done electronically.
2. “expert standard volume” for treatment planning which is part electronic and part print.

The Dummy Run will be sent by EORTC via NCIC CTG to each locally activated centre.

SECTION 12.0 – TRIAL CLOSURE

12.1 Discontinuation of the Trial

If this trial is discontinued for any reason by the NCIC CTG we will notify all centres in writing of the discontinuance and the reason(s) why. If the reason(s) for discontinuance involve any potential risks to the health of patients participating on the trial or other persons, the NCIC CTG will provide this information to centres as well.

If this trial is discontinued at anytime by the centre (prior to closure of the trial by the NCIC CTG), it is the responsibility of the principal investigator to notify the NCIC CTG of the discontinuation and the reason(s) why.
Whether the trial is discontinued by the NCIC CTG or locally by the centre, it is the responsibility of the principal investigator to notify the local Research Ethics Board and all clinical trials subjects of the discontinuance and any potential risks to the subjects or other persons.

12.2 Retention of Patient Records and Study Files
NCIC CTG will notify all Canadian investigators/institutions when trial related records no longer need to be retained, after consultation with EORTC. The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.
Appendix R: TROG Specific Appendix
TRANS-TASMAN RADIATION ONCOLOGY GROUP
INCORPORATED

In conjunction with:

EORTC Radiotherapy Group (EORTC 22033)
EORTC Brain Tumour Group (EORTC 26033)
NCI Canada

Primary chemotherapy with temozolomide vs. radiotherapy
in patients with low grade gliomas
after stratification for genetic 1p loss: a phase III study

Appendix to EORTC Protocol No 22033/26033
Version 3 ~ 12 March, 2007
INTRODUCTION

TROG has been authorised by the EORTC to undertake a co-ordinating role for Australian and New Zealand patients enrolled on the study. The Trial Centre will handle all enquiries from participating sites in Australia and New Zealand, organise all registrations and randomisations, issue patient treatment and follow up schedules, collect all CRFs, assist the EORTC Data Center with all data queries, collect all SAEs and make all appropriate notifications, and assist with QA procedures.

The involvement of TROG necessitates a number of changes to the procedures documented in the EORTC protocol. The following sections have been adjusted for TROG participants and supersede the EORTC protocol sections where relevant:

5.2 TEMOZOLOMIDE

5.2.3 Drug Supply

Temozolomide will be supplied free of charge by Schering Plough. Schering-Plough Australia is responsible for drug supply for both Australian and New Zealand sites, and has out-sourced packaging and distribution of the trial drug to Cryosite Limited, a clinical logistics company.

Drug supplies may only be ordered through the Trial Centre. Patients who have been randomised to receive Temozolomide will have the designated Drug Order Form/Packing List (Appendix R) completed by the Trial Centre Data Manager AT THE TIME OF RANDOMISATION. The Site Data Manager or Investigator will need to ensure the following information required for the Order Form is available at that time: site number, person to whom the delivery should be addressed [attn of eg the nominated dispensing pharmacist], address for delivery, contact phone number, patient sequence number, body surface area [BSA], and required delivery date [must start within six weeks of randomisation]. The Trial Centre will then calculate the daily dose of Temozolomide (75mg/m²/day for 21 days out of every 28, rounded to the nearest 10mg) for each patient, and will order the appropriate strength and number of capsules for each cycle. The drug will be packed and shipped to the Site within 2-3 working days. Once the drug order is delivered to the requesting Site, the “Acknowledgement of Receipt” section of the accompanying Drug Order Form/Packing List must be completed, and faxed to Cryosite and the Trial Centre within 2 working days. A total of six months of drug will be available initially.

The mandatory MRI scan at 6 months should be timed to allow a further order of Temozolomide to be made and delivered without any delay in the next scheduled course of treatment, assuming there is no evidence of progression. The Trial Centre will automatically make this order once the MRI result is received.

The Trial Centre should be notified if the drug order has not been delivered to the requesting Site within 7 working days of the order being placed with the Trial Centre. PLEASE DO NOT CONTACT SCHERING PLOUGH OR CRYOSITE DIRECTLY AT ANY TIME.

13. INVESTIGATOR AUTHORISATION PROCEDURE

Investigators will only be authorised to register and randomise patients in this trial when they have returned to the Trial Centre:

♦ a copy of the patient information sheet and the informed consent form approved by their HREC.
♦ the list of the members of the HREC
♦ a copy of the letter of acceptance of the protocol by the HREC
♦ their updated Curriculum Vitae.
♦ the list of the normal ranges, in their own institution, of all laboratory data required by the protocol.
the list of their staff members authorised to sign case report forms, with a sample of each authorised signature.

A Commitment Statement / Agreement has been signed on behalf of TROG Investigators by the TROG Research Manager, TROG President and Study Principal Investigator and forwarded to the EORTC.

This document indicates that all investigators will fully comply with the protocol, includes an estimate of their yearly accrual and notes any conflict of interest that may arise due to their participation in the trial.

As soon as all the documents have been received at the Trial Centre, new sites will be allocated an EORTC Institution number, and/or the new investigator will be added to the “authorisation list”, and will be allowed to register patients on the trial. Patient registration from sites/investigators not (yet) included on the authorisation list will not be accepted.

14. REGISTRATION AND RANDOMISATION PROCEDURE

14.1 REGISTRATION BEFORE MOLECULAR TESTING (STEP 1)

Patient registration will only be accepted from authorised investigators.

The registration procedure is included in the registration checklist, which is part of the case report forms (Form 1, Page 1). This checklist should be completed by the responsible investigator before contacting the Trial Centre for registration. Once eligibility has been verified by the site investigator/ data manager, the Registration checklist is to be faxed to:

The Trial Centre Data Manager will check the Registration checklist, and will confirm receipt by phone as soon as possible, within one working day. Additional relevant questions may need to be asked at that time, including the actual values of the eligibility parameters where applicable. Once satisfied that the patient is eligible, the Trial Centre will register the patient via the EORTC Data Centre. Because of the time differences, immediate registration may not be possible, so a further delay of up to one working day may be necessary before registration is completed and notified to the site data manager. At that time, a number will be allocated to the patient (patient sequential identification number). This number is to be recorded on the registration form, along with the date of registration. The additional information required at registration should then be completed. The completed registration form with all initial required patient data must be signed by the responsible investigator and returned immediately to the Trial Centre.

The sequential identification number attributed to the patient at the end of the registration procedure identifies the patient, is required for the Randomisation step, and must be reported on all case report forms.

If there are any queries at any stage, or there has been no response from the Trial Centre within one working day of faxing the Registration checklist, the Site data manager should contact the Trial Centre by phone.

Once registration has been confirmed, tissue and blood samples accompanied by the completed Genetic Testing Form (Form 2) must be sent as soon as possible to the Central Pathology (process documented in Appendix K). A copy of the completed Genetic Testing Form must be sent to the Trial Centre to confirm that the pathological material has been sent.
14.2 RANDOMISATION (STEP 2)

When the patient is considered to require treatment, the site investigator should first ensure that all parts of Step 1 are complete. A patient who has not been registered and undergone molecular testing cannot be randomised. A minimum period of three weeks between registration and randomisation will usually be necessary, to allow the results of the molecular testing to be available at the time of Registration.

The site investigator/data manager will then complete the list of questions on the Randomisation checklist to confirm that the eligibility criteria for randomisation are satisfied. In addition, prior to randomisation, the investigator must ensure that:

- there is no contra-indication (psychological, familial, sociological or geographic) to the required follow-up
- patient consent is still valid (consent form must be signed and dated again if >12 months since registration)
- the patient has completed a Quality of Life form
- treatment will commence within six weeks of randomisation and provide the treatment start date

Having completed the Randomisation checklist and additional information, the site investigator/data manager will fax the Checklist to the Trial Centre as above. The Trial Centre Data Manager will check the Randomisation checklist, and will confirm receipt by phone as soon as possible, within one working day. All eligibility criteria will again be checked by the Trial Centre, and actual values of the eligibility parameters requested where applicable. Once satisfied that the patient is eligible, the Trial Centre will randomise the patient via the EORTC Data Centre. Again, because of the time differences, a delay of up to one working day may be necessary before randomisation is completed and notified to the site data manager. The allocated treatment, along with the date of randomisation, will be recorded on the Randomisation form. The completed form must be signed by the responsible investigator and returned immediately to the Trial Centre. Please ensure that the sequential identification number is recorded on all pages.

NB: REGISTRATION AND RANDOMISATION MUST BE DONE THROUGH THE TROG TRIAL CENTRE. REGISTRATION AND RANDOMISATION DIRECTLY THROUGH THE EORTC DATA CENTRE ARE NOT PERMITTED.

15 FORMS AND PROCEDURES FOR COLLECTING DATA

15.1 CASE REPORT FORMS AND SCHEDULE FOR COMPLETION

Data will be reported on the EORTC forms supplied, and sent to:

A. Before the molecular testing (Step 1):

- the patient must be registered by the Trial Centre
- the registration check-list should be returned to the Trial Centre

B Before the treatment starts (Step 2):

- the patient must be randomised through the Trial Centre
- the randomisation check-list should be returned to the Trial Centre
The optimal way to work is to complete the registration/randomisation checklists first and to register/randomise the patient as soon as these are completed. The date of registration/randomisation and patient sequential identification number is then completed on the checklist, and the whole set can be sent to the Trial Centre.

C The list of forms to be completed for this study and their submission schedule is included with the set of case report forms

D Upon occurrence of a Pregnancy

♦ 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 Trial Data Manager.

♦ This must be reported within 24 hours of first becoming aware of the event by fax to the Trial Centre on a Pregnancy Notification Form/Fax. The Trial Centre will notify the EORTC Pharmacovigilance Unit, who in turn will notify Schering Plough Drug Safety within 24 hours.

♦ Upon notification of a pregnancy, it will be the responsibility of Schering Plough to follow up the development and outcome of the pregnancy.

♦ If a Serious Adverse Event (see chapter 16) occurs in conjunction with the pregnancy, please also complete an SAE form (89).

E Upon occurrence of a serious adverse event

♦ All serious adverse events occurring during the treatment period and within 30 days after the end of the last protocol treatment must be reported to the Trial Centre.

♦ All serious adverse events related to the protocol treatment and occurring after this 30-day period must also be reported.

♦ All serious adverse events must be reported by fax to the Trial Centre within 24 hours

♦ A serious adverse event form (form 89) must be completed and returned to the Trial Centre within 5 calendar days of the initial observation of the event.

ALL FORMS MUST BE DATED AND SIGNED BY THE RESPONSIBLE INVESTIGATOR OR ONE OF HIS/HER AUTHORISED STAFF MEMBERS.

16 REPORTING ADVERSE EVENTS

16.2 Reporting Procedures

Details of all Serious Adverse Events (SAE) or Serious Adverse Drug Reactions (SADR) as defined in the Protocol are to be documented on the specified Serious Adverse Event Form (Form 89) and reported as described in the protocol. An initial report should be faxed to the TROG Trial Centre within 24 hours of the initial observation of the event (do not wait for full details before making the report).

PLEASE FAX THE REPORT TO:

The Trial Centre will forward SAEs within 24 hours to the EORTC Pharmacovigilance Unit (e-mail: pharmacovigilance@eortc.be). The Pharmacovigilance Unit will forward all Serious Adverse Event reports within 24 hours of receipt to all appropriate persons (See Administrative chapter).

Serious Adverse Events (SAE) and Serious Adverse Drug Reactions (SADR) which have not been previously documented in the Investigators’ Brochure, or which occur in a more severe form than
anticipated (ie. Serious Unexpected Suspected Adverse Reaction or SUSAR), are subject to rapid reporting to Regulatory Authorities by the sponsor/promoter. This also applies to reports from spontaneous sources and from any type of clinical or epidemiological investigation, independent of design or purpose. The source of the report (investigation, spontaneous, other) should always be specified.

All study SUSARs and Safety Alerts received from Schering-Plough by the EORTC Pharmacovigilance Unit will additionally be forwarded by e-mail to the TROG trial Data Manager. The TROG trial Data Manager will forward SUSARs and alerts to local investigators as soon as possible. Upon receipt of a study SUSAR safety alert from the TROG trial centre, it is the responsibility of the investigators to promptly report this to their Institutional Human Research and Ethics Committee (if applicable).

To enable the EORTC Pharmacovigilance Unit/sponsor to comply with regulatory reporting requirements, completed documentation of any reported serious adverse events must be returned to the Trial Centre within 10 calendar days of the initial report. Please send the original report using the EORTC form to:

If the completed form is not received within this deadline, the Trial Centre will issue a written request to the investigator. The Trial Centre will forward the completed documentation to the EORTC Pharmacovigilance Unit.

ANY QUESTION CONCERNING SAE, SADR OR SUSAR REPORTING SHOULD BE DIRECTED TO:

Trial Centre
Phone: +61 (0)3 9656 3786

ALL FORMS MUST BE DATED AND SIGNED BY THE RESPONSIBLE INVESTIGATOR OR ONE OF HIS/HER AUTHORISED STAFF MEMBERS

17. QUALITY ASSURANCE

17.2 Audits

All sites will be subject to the Quality Assurance Procedures of TROG in agreement with the EORTC Brain Tumor Group. No on-site monitoring has been planned for TROG centres. Individual case reviews will be performed according to guidelines provided in Appendix O.

17.5 Quality assurance radiotherapy

17.5.1 Facility Questionnaire

All sites must complete this before being authorised to enter patients on study. The questionnaire can be filled in and submitted directly to the EORTC on-line. Access details will be provided to each site once the Trial Centre has received the Investigator Study Agreement and added the investigator/site to the “Authorisation List” (See Section 13).

17.5.2 Dummy run procedure

All participating sites are required to successfully complete a “Dummy Run” (DR) provided by the EORTC. This must be completed before randomisation of the fifth patient from each site and/or one year from activation of the site (whichever occurs first). If at the fourth patient the
DR procedure has not been performed, the site will not be able to enter further patients into the study until the DR has been done or problems are solved. In either case, you will be notified beforehand by the Trial Centre.

The DR consists of two parts:

♦ Part 1: Definition and Delineation of the GTV, CTV and PTV. This part is done via the world wide web. DICOM CT files can be downloaded directly from the EORTC website or provided by the Trial Centre. The files are then loaded onto the individual site’s planning computer, and the investigator completes the required volumes. The Completed volumes are returned to the EORTC in DICOM format via upload by the individual site, or by the Trial Centre.

♦ Part 2: An “expert standard volume” is downloaded in the same way as Part 1. These volumes should be treatment planned according to the protocol. The plan including the DVH should be printed in accordance with the protocol documentation, and sent by mail to the EORTC. An e-mail must be sent to the EORTC and the Trial Centre notifying that the data is in the post. Additionally an Excel DR Evaluation file must be completed and returned to the EORTC.

**Detailed information on how to complete the DR procedure will be provided to each site added to the “Authorisation List”.

### 19. ADMINISTRATIVE RESPONSIBILITIES

The Trial Centre will handle all enquiries from Australian and New Zealand sites, organize all registrations and randomisations, issue patient treatment and follow up schedules, collect all CRFs, assist EORTC Data Centre with all data queries, collect all SAEs and make all appropriate notifications, and assist with QA procedures.

The TROG study co-ordinator will be responsible for answering all clinical questions concerning eligibility, treatment, and evaluation of patients.

**TROG Study Co-ordinator (for all medical queries):**

The Trial Centre will be responsible for all registrations and randomisations, data-related issues and SAE notification.

**Coordinating Data Manager (for all randomisations, data related issues and SAE notification):**
Quality Assurance Manager (for source data verification and DR issues):

TROG Central Operations Office
Radiation Oncology
Newcastle Mater Hospital
Locked Bag 7
Hunter Region Mail Centre NSW 2310
Tel: +61 (0)2 4921 1453 Fax: +61 (0)2 4921 1465
Email: [redacted]

Schering-Plough Research Institute and Schering-Plough Australia through Cryosite will be responsible for distribution of temozolomide (Temodal®) in both Australia and New Zealand.

Drug supply: see section 5.2.3
Reporting of adverse events: see chapter 16

Appendix K: Collection and Preparation of Pathological and Biological Patient Material

1. Shipment

All sites in Australia and New Zealand must send pathological material to the central reference laboratory in Germany (Central Pathology Laboratory) for central histology review and molecular testing. **THERE WILL BE NO EXCEPTIONS**, i.e. this applies even if the diagnosis has been reviewed by a specialist neuro-pathologist in Australia or New Zealand, and/or the patient has already undergone genetic testing for 1p loss. The material to be collected is:

♦ Paraffin blocks of embedded tumour material
♦ 2x10mls of citrated full blood

All unused block material will be returned by the Central laboratory.

Pre-paid World Courier consignment packs, and instructions for pickup, will be provided to authorised sites for transport of pathological material. The Genetic Testing Form (Form 2) must be sent with the tissue/blood samples to the Central Pathology Laboratory. A copy of this form must also be sent to the Trial Centre to confirm that the pathological material has been sent.

**Material must be accompanied by the following information**

♦ Patient character code
♦ Trial and sequential ID number
♦ Date of birth
♦ Copy of the original local histopathological report (anonymized)

**The following pathological data should be recorded on the registration form (or online at the registration step):**

♦ Patient character code (mandatory)
♦ Date of birth (mandatory)
♦ Gender (mandatory)
♦ Local pathological diagnosis (mandatory)
♦ Name of the responsible neuropathologist (mandatory) and e-mail (optional)
♦ Date and type of surgery or biopsy (mandatory)
 Localization of the tumor (optional)
 Duration of symptoms prior to diagnosis in months (optional)
 Availability of additional fresh frozen material at the center (if yes, please indicate contact) (optional)
 EORTC sequential ID number

Pathological material should be sent as soon as possible after registration. It is also important to avoid unnecessary delays after samples have been collected/prepared for transport, as the material will be transported at room temperature, and will deteriorate if not processed at the Central Laboratory after four days at room temperature.

TROG sites will not be undertaking collection of tissues for later translational research.

2. Fixation of brain tumour tissues

Very good results for histological and molecular analyses are achieved with the following procedure:

1) Larger brain tumor samples should be cut into slices of 4 to 5 mm thickness.
   Penetration of formaldehyde is approximately 0.5 mm per hour from each side.

2) Tissues should be placed in 20 volumes or more of 10% buffered Formalin. This corresponds to 4% buffered Formaldehyde.
   Fixation with Bouin solution (0.9% picric acid, 9.5% formaldehyde, 4.8% ascetic acid) is to be strictly avoided. Bouin fixation is not compatible with retrieval of sufficient DNA for molecular analysis.
   Concentrated Formalin corresponds to a stock solution of approximately 37% formaldehyde including roughly 10% methanol in order to inhibit oxidation to formic acid. A 1 in 10 dilution of concentrated formalin yields 4% formaldehyde.

3) Fixation time should be between 6 and 24 hours.
   Longer fixation times result in the material becoming hard and brittle and in difficulties with DNA extraction.
   If longer fixation times cannot be avoided (weekend etc.), fixation should be performed at 4°C.

4) Paraffin embedding is followed by histological and molecular analyses. Materials can be stored for long periods.

3. Storage of blood for molecular analysis

Very good results for molecular analyses are achieved with the following procedure:

1) 20 ml of citrated blood best taken before surgery.
   Citrated blood is preferred to Heparin blood. Heparin chelates Mg++ ions. Traces of Heparin in DNA extractions require adjustments of Mg++ ion concentration in some buffers used at PCR amplification. However, Heparin blood will do, too.

2) Blood samples should not be frozen, as they will then not be suitable for shipping at room temperature.
Appendix S: Medical Research Council - NCRI Brain Tumour Clinical Studies Group

MRC BR13 Group Specific Appendix Version 0.4 - 22/06/2006
Appendix:

Medical Research Council
NCRI Brain Tumour Clinical Studies Group

Specific Appendix to the EORTC 22033 trial

MRC BR13 Trial

This trial is supported in the UK by the NCRI Brain Tumour Clinical Studies Group. The MRC Clinical Trials Unit will coordinate UK participation in this trial.

1 Administrative Responsibilities

1.1 The National Coordinators

The MRC/NCRI Brain Tumour Clinical Studies Group national coordinators will be responsible for presenting the protocol to the group and discussing it with the investigators of the group who will participate in the protocol. The Study National Coordinator’s responsibility is to work with the MRC CTU to encourage accrual and ensure that high quality data are collected and used in accordance with the group’s policy.

National Coordinator:

1.2 MRC Clinical Trials Unit

The MRC Clinical Trials Unit is responsible for handling investigator authorisation procedures and will act as a "mailbox" in this trial (see chapter on forms and procedures for data collection in protocol). All methodological questions should be addressed to the MRC Clinical Trials Unit who will forward them to the appropriate person in EORTC.
1.3 Medical Research Council/ NCRI Brain Tumour Clinical Studies Group

MRC NCRI Brain Tumour Clinical Studies Group is responsible as a group to guarantee the general compliance of their members with procedures described in this appendix.

2 Investigator Authorisation Procedures

Investigators will be authorised to randomise patients in this trial only when they have returned the following documents to the MRC Clinical Trials Unit:

♦ Confirmation of Local Research Ethics Committee (site-specific assessment) and R&D approval

♦ Copy of the most recent version of the patient information sheet and consent form on local headed paper

♦ Completed commitment statement/study acknowledgment (signed by the institution PI) and copy of PI’s CV

♦ Completed signature log (signature list and delegation of responsibilities)

♦ Full contact details for all site personnel
3 Patient Randomisation Procedures

MRC/NCRI investigators will only be able to randomise into the trial after they have been added to the EORTC authorisation list.

Step 1: Registration

MRC/NCRI investigators should use the EORTC registration/randomisation system as described in chapter 14 of the protocol. After having validated the eligibility criteria of the patient, MRC/NCRI investigators can register patients directly on the EORTC online randomisation system (ORTA).

**Internet process:** A patient can be registered after verification of eligibility directly on the Internet through the EORTC Data Centre Computer, 24 hours a day, 7 days a week, via the website: www.eortc.be/random

To access the interactive randomisation program, the investigator needs a username and a password (that can be interactively requested via the same website as above)

In the event of problems connecting to the EORTC website investigators should call the MRC registration/randomisation line on:

020 7670 4777

*(available Monday-Friday, 9am to 5pm)*

Notification of registration will be emailed to the investigator and the MRC CTU.

Step 2: Molecular/Genetic Testing

Following registration biological samples need to be sent to Heidelberg for central testing to identify the 1p19q status of the patient. Full details of this process and the sample requirements are described in appendix K of the protocol.

The results of these tests are required before a patient can be randomised. The MRC CTU will be informed of the results; these will then be forwarded to the PI and first point of contact at the registering site.
Step 3: Randomisation

Randomisation can be completed using the system described in ‘Step1: Registration’.

The patient will have to be selected from 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, chart number and date of birth will automatically be inserted in the identification screen. After this the additional information must be added including actual values of the eligibility parameters where applicable.

The EORTC Data Centre will inform the MRC Clinical Trials Unit and the PI of the randomisation by e-mail.

4 Forms and Procedures for Collecting Data

Investigators participating on behalf of Medical Research Council/NCRI Brain Cancer Clinical Studies Group should send all forms directly to:

BR13 Trial
Cancer Group
MRC Clinical Trials Unit
222 Euston Road
LONDON
NW1 2DA
United Kingdom

Fax: +44 (0) 20 7670 4818

Please do not send forms to the EORTC Data Centre.

For detailed procedures on CRF completion and the schedule for completion please refer to chapter 15 of the protocol.

If an investigator (or an authorised staff member) needs to modify a CRF after the original form has been returned, he/she should notify the MRC Clinical Trials Unit by using the Data Correction Form and a copy should be kept with the other CRF copies.

Extensive data consistency checks on the CRFs will be carried out at the EORTC Data Centre. EORTC Data Centre will issue query forms in the case of inconsistent data. MRC Clinical Trials Unit will forward the query forms to the centres and they must be answered and signed by the investigator (or an authorised staff member). The original must be returned to the MRC Clinical Trials Unit and a copy must be appended to the investigator’s copy of the CRFs.

The investigator's CRF copies must not be modified unless modifications are reported on a Query Form or a Data Correction Form.

5 Guidelines for Sample Management

Please do not send any samples to the MRC Clinical Trials Unit in the UK.

Once a patient has been registered on to the trial samples are to be sent for pre-randomisation genetic testing. At this time samples will be tested for the loss of 1p and 19q. These samples are to be sent to

Full descriptions of sample handling and shipment are located in appendix K of the protocol.
Translational Study
Separate informed consent is required for the translational study and patient participation is optional. Currently no procedures are in place for this part of the study, however those centres entering patients into this aspect of the trial must store:

♦ Fresh frozen tumour tissue
♦ Fresh frozen serum
♦ Fresh frozen lymphocytes

These will be collected at a later time.

6 Safety Reporting
Definitions of terms on safety reporting and detailed guidelines on serious adverse events/reaction reporting can be found in chapter 16 of the protocol.

Remark: In this study death due to progression of disease will be exempted as an SAE and must therefore not be reported as an SAE.

Please fax the Serious Adverse Event Reporting form (form 89) within 24 hours of the initial observation of the event to:

MRC CTU
Fax: 020 7670 4818

To enable Schering-Plough to comply with regulatory reporting requirements completed documentation of any reported serious adverse events or serious adverse drug reactions must be returned within 10 calendar days of the initial report to:

MRC CTU
Fax: 020 7670 4818

7 Quality Assurance

7.1 Data
MRC Clinical Trials Unit will follow standard policies and procedures in accordance with ICH GCP guidelines regarding quality assurance. MRC Clinical Trials Unit risk assessment will be performed to establish the level of monitoring required for this trial. Based on the assessment, site monitoring may be conducted at active participating centres. Collaborating institutions should be aware that direct access to patient data by the MRC Clinical Trials Unit, EORTC Data Centre staff and regulatory authorities may be required for trial-related monitoring or audit.

EORTC Data Centre will perform a data timeliness request every three months for overdue data. MRC Clinical Trials Unit will forward the request to the investigator, who should return the requested data within 6 weeks.

7.2 Radiotherapy
The quality assurance team will review the irradiation technique. 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.
7.2.1 The dummy run procedure (see section 17.5 in the protocol for full details)

Please note that the deadline for successfully completing the dummy run procedure is before randomisation of the 5th patient in your institute and/or one year from the activation of your centre (whichever comes first). If your 4th patient has been randomised the dummy run procedure has not been performed, your centre will not be able to enter patients into the study until the dummy run has been done or problems are solved. In any case, you shall be notified beforehand.

The centre specific applicable list of required documents will be included in the protocol activation package, with adequate instructions as required for the questionnaires and dummy run procedure.

8 Ethical Considerations

The Local Research Ethics Committee (LREC) must approve each institution before patients are entered at that institution (Site Specific Assessment SSA).

The patient’s consent to participate in the trial must be obtained after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment, and the manner of treatment allocation. The patient should be given sufficient time after being given the patient information sheet to consider and discuss participation in the trial with friends and family. A contact number should be given to the patient should they wish to discuss any aspect of the trial. The patient must sign a consent form before joining the trial. One copy should be given to the patient, one copy should be kept with patient’s hospital notes and one copy should be kept in the local investigator’s file. The right of a patient to refuse to participate without giving reasons must be respected. After the patient has entered the trial the clinician must remain free to give alternative treatment to that specified in the protocol at any stage if he/she feels it to be in the patients best interest. But the reason for doing so should be recorded and the patient will need to be remained within the trial for the purposes of follow-up and data analysis according to the treatment option to which he/she had been allocated. Similarly the patient must remain free to withdraw at any time from protocol treatment without giving reasons and without prejudicing his/her further treatment.

The full name of the patient will neither be asked for nor recorded at the allocated data centre. A sequential identification number (seqID) 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 initials (maximum of 4 letters), date of birth and local hospital number (if available) will also be reported on the case report forms and all related documents.

A statement on MRC policy on ethical considerations in the clinical study of cancer therapy is available from the MRC Head Office website (http://www.mrc.ac.uk). This may be used to give guidance to participating investigators and to accompany LREC applications.

9 Trial Sponsorship And Funding

EORTC is a sponsor for all investigators participating on behalf of the MRC/NCRI Brain Cancer Clinical Studies Group. For each patient randomised (not only registered) in to the trial your centre will receive 1442 Euros from the EORTC as part of an educational grant. This will be paid one year following randomisation on receipt of adequate baseline data.

10 Trial Insurance

All participants from EU countries are covered by the EORTC insurance.