Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study

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Summary

Background Outcome of low-grade glioma (WHO grade II) is highly variable, reflecting molecular heterogeneity of the disease. We compared two different, single-modality treatment strategies of standard radiotherapy versus primary temozolomide chemotherapy in patients with low-grade glioma, and assessed progression-free survival outcomes and identified predictive molecular factors.

Methods For this randomised, open-label, phase 3 intergroup study (EORTC 22033-26033), undertaken in 78 clinical centres in 19 countries, we included patients aged 18 years or older who had a low-grade (WHO grade II) glioma (astrocytoma, oligoastrocytoma, or oligodendroglioma) with at least one high-risk feature (aged >40 years, progressive disease, tumour size >5 cm, tumour crossing the midline, or neurological symptoms), and without known HIV infection, chronic hepatitis B or C virus infection, or any condition that could interfere with oral drug administration. Eligible patients were randomly assigned (1:1) to receive either conformal radiotherapy (up to 50·4 Gy; 28 doses of 1·8 Gy once daily, 5 days per week for up to 6·5 weeks) or dose-dense oral temozolomide (75 mg/m² once daily for 21 days, repeated every 28 days [one cycle], for a maximum of 12 cycles). Random treatment allocation was done online by a minimisation technique with prospective stratification by institution, 1p deletion (absent *vs* present *vs* undetermined), contrast enhancement (yes *vs* no), age (<40 *vs* ≥40 years), and WHO performance status (0 *vs* ≥1). Patients, treating physicians, and researchers were aware of the assigned intervention. A planned analysis was done after 216 progression events occurred. Our primary clinical endpoint was progression-free survival, analysed by intention-to-treat; secondary outcomes were overall survival, adverse events, neurocognitive function (will be reported separately), health-related quality of life and neurological function (reported separately), and correlative analyses of progression-free survival by molecular markers (1p/19q co-deletion, *MGMT* promoter methylation status, and *IDH1/IDH2* mutations). This trial is closed to accrual but continuing for follow-up, and is registered at the European Trials Registry, EudraCT 2004-002714-11, and at ClinicalTrials.gov, NCT00182819.

Findings Between Sept 23, 2005, and March 26, 2010, 707 patients were registered for the study. Between Dec 6, 2005, and Dec 21, 2012, we randomly assigned 477 patients to receive either radiotherapy (n=240) or temozolomide chemotherapy (n=237). At a median follow-up of 48 months (IQR 31–56), median progression-free survival was 39 months (95% CI 35–44) in the temozolomide group and 46 months (40–56) in the radiotherapy group (unadjusted hazard ratio [HR] 1·16, 95% CI 0·9–1·5, p=0·22). Median overall survival has not been reached. Exploratory analyses in 318 molecularly-defined patients confirmed the significantly different prognosis for progression-free survival in the three recently defined molecular low-grade glioma subgroups (*IDH*mt, with or without 1p/19q co-deletion [*IDH*mt/codel], or *IDH* wild type [*IDH*wt]; p=0·013). Patients with *IDH*mt/non-codel tumours treated with radiotherapy had a longer progression-free survival than those treated with temozolomide (HR 1·86 [95% CI 1·21–2·87], log-rank p=0·0043), whereas there were no significant treatment-dependent differences in progression-free survival for patients with *IDH*mt/codel and *IDH*wt tumours. Grade 3–4 haematological adverse events occurred in 32 (14%) of 236 patients treated with temozolomide and in one (<1%) of 228 patients treated with radiotherapy, and grade 3–4 infections occurred in eight (3%) of 236 patients treated with temozolomide and in two (1%) of 228 patients treated with radiotherapy. Moderate to severe fatigue was recorded in eight (3%) patients in the radiotherapy group (grade 2) and 16 (7%) in the temozolomide group. 119 (25%) of all 477 patients had died at database lock. Four patients died due to treatment-related causes: two in the temozolomide group and two in the radiotherapy group.

Interpretation Overall, there was no significant difference in progression-free survival in patients with low-grade glioma when treated with either radiotherapy alone or temozolomide chemotherapy alone. Further data maturation is needed for overall survival analyses and evaluation of the full predictive effects of different molecular subtypes for future individualised treatment choices.

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Introduction

Low-grade glioma encompasses a diverse group of diffusely infiltrative, slowly growing, glial brain tumours that most frequently affect adults in their third or fourth decade of life. The natural history of these tumours varies greatly and optimum management remains controversial. Treatment options include watchful waiting, radical surgery, radiotherapy, chemotherapy, or a combination thereof.[1] Individual management decisions depend on clinical and molecular prognostic factors, extent of neurological symptoms, estimated risk of malignant transformation, and risk of acute and late treatment-associated toxicity.[2] We previously derived a prognostic score with estimated median survival times varying from 3·2 years (95% CI 3·0–4·0) to 7·8 years (6·8–8·9).[3] Age 40 years or older, astrocytic histology, tumour size of 6 cm or larger, tumours crossing the midline of the brain, and the presence of neurological deficits were all associated with a shortened life expectancy.[3] In the past 10 years, molecular characteristics, especially co-deletion of chromosomal arms 1p and 19q, which are associated with oligodendroglial histology and mutations of isocitrate dehydrogenase genes 1 (*IDH1*) and 2 (*IDH2*), have been associated with a more favourable prognosis and better response to both chemotherapy and radiotherapy compared with people without these alterations.[4,5]

Radiotherapy has been the standard treatment for progressive and inoperable low-grade glioma for more than three decades, established at a time when neither modern imaging technology nor alternative treatment modalities were available.[3,6–9] Temozolomide (Merck & Co, White House Station, NJ, USA), an alkylating drug, was specifically developed to have chemical properties that allow it to cross the blood–brain barrier and in 1999 was the first drug to be approved by the US Food and Drug Administration for the treatment of recurrent anaplastic astrocytoma.[10] High sensitivity to chemotherapy had been shown for oligodendroglioma with 1p/19q co-deletion, and uncontrolled trials[11–14] suggested that temozolomide also had activity against low-grade glioma. Dose-dense regimens allowing for increased doses and prolonged exposure were viewed as conceptually attractive, especially for slow-proliferating tumours such as low-grade glioma.[15–17]

Research in context

Evidence before this study

The optimum treatment modality and sequence of patients with low-grade glioma is highly controversial, aiming to balance a favourable effect on progression-free survival versus long-term toxicity in this overall young patient population (median <45 years). We searched PubMed between June 1, 1993, and April 30, 2016, using the search terms "randomized", "low grade glioma", "chemotherapy", and "radiotherapy". We identified only four conclusive trials (EORTC 22844, EORTC 22845/MRC BR04, NCCTG/RTOG/ECOG, and RTOG 9802), including reports on delaying treatment initiation, or the optimal dose of radiotherapy. The latest report of RTOG 9802 shows an impressive 5·5-year improvement in median overall survival with radiotherapy followed by up to six cycles of adjuvant procarbazine, lomustine, and vincristine chemotherapy, compared with standard radiotherapy alone. However, no data are available for the prognostically highly relevant molecular subtype displaying 1p/19q co-deletion. The absence of this molecular information and the availability of less toxic drugs hinder the translation of molecularly stratified treatment into clinical practice.

Added value of this study

Our study aimed to use data after central histological confirmation and molecular characterisation, and an additional stratification by molecular subtype before randomisation. We therefore had tumour tissue available for most patients, allowing us to confirm the prognostic value of identified molecular subgroups that are now an integral part of the 2016 revised WHO classification of low-grade glioma. To our knowledge, our study is the largest trial of prospectively treated patients with low-grade glioma, allowing for molecular tumour characterisation and analysis of its association with outcome. Although overall no significant difference in progression-free survival was shown between the two treatment groups, our results show the value of molecular characterisation and subgrouping of the disease. Patients with an *IDH* mutation without 1p/19q co-deletion had a significantly longer progression-free survival when treated with radiotherapy versus chemotherapy, whereas those with wild-type *IDH* mutation belonged to different categories of glioma often with a much more aggressive course.

Implications of all the available evidence

In future clinical trials, treatment strategies should be adapted to the risk of tumour progression or recurrence based on molecular subgroups of low-grade gliomas. Ultimately this change in strategy should lead to individually-adapted and risk-adapted treatments. Ongoing exploratory analyses might allow for identification of putative predictive molecular markers for further refinement of the prognostic value of the molecular subtyping, and, importantly, might identify novel therapeutic targets in low-grade glioma.

In this European Organisation for Research and Treatment of Cancer (EORTC) 22033-26033 intergroup study, we investigated whether initial temozolomide chemotherapy confers an advantage in patient survival, toxicity, and quality-of-life outcomes compared with standard radiotherapy. We report the survival outcomes and toxicity findings in this paper. Neurocognitive outcomes and quality-of-life results are reported separately.[18]

Methods

Study design and participants

The EORTC–National Cancer Institute of Cancer (NCIC)–Canadian Cancer Trials Group (CTG)–Trans Tasman Radiation Oncology Group (TROG)–Medical Research Council (MRC)–Clinical Trials Unit intergroup study (EORTC 22033–26033) was a prospective, randomised, phase 3 study done in 78 academic centres and larger hospitals in 19 countries (appendix pp 8–10). Our trial consisted of two steps: first, an initial registration step at any time after initial diagnosis of low-grade glioma, allowing for tissue collection and molecular analyses required for stratification; and second, a randomisation step at the timepoint when treatment was judged to be clinically indicated.

At registration, adult patients (aged ≥18 years) with histologically confirmed, supratentorial, diffusely infiltrating low-grade gliomas (astrocytoma, oligoastrocytoma, or oligodendroglioma; grade II classified according to the WHO classification)[19] who did not have a known HIV infection or chronic hepatitis B or C infection, and were free from any medical condition that could interfere with oral medication intake were eligible for the study. Availability of paraffin-embedded tumour tissue, and a blood sample was required for central pathological review and molecular testing for 1p deletion. The *IDH1* and *IDH2* mutations in glioma were only discovered and published[20] in 2009 and were included subsequently in our trial as an exploratory subgroup analysis.[5] For patients with a substantial interval between initial tissue diagnosis and start of treatment, confirmation of the histology by repeat biopsy was recommended in the protocol.

Patients whose tumour had transformed into a higher grade before randomisation, according to WHO's grading system, were excluded. To be eligible for randomisation (second step), patients also had to require active treatment other than surgery (ie, were not candidates for exclusively surgical treatment), defined by at least one of the following criteria: being aged 40 years or older, having radiological tumour progression, new or worsening neurological symptoms, or refractory seizures. The time period between registration and randomisation varied. Other eligibility criteria for randomisation included WHO performance status of 2 or lower; a Radiation Therapy Oncology Group (RTOG) neurological function score of 0–3; adequate haematological, renal, and hepatic function (absolute neutrophil count ≥1500 cells/μL; platelet count ≥100 000 cells/μL; serum creatinine concentration ≤1·5×the upper limit of normal [ULN]; total serum bilirubin concentration ≤1·5×ULN; and liver function values [alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase] ≤2·5×ULN); and had results of genetic testing available. Patients who had received previous chemotherapy or radiotherapy were excluded.

The protocol was approved by the ethics committees and authorities of all participating centres and countries. We completed the trial according to the Declaration of Helsinki. All patients gave written informed consent for pathology review, molecular testing, and participation in the trial at registration and provided a separate written informed consent before randomisation.

Randomisation and masking

Before randomisation, eligible patients were stratified according to WHO performance status (0–1 *vs* 2), age (<40 years *vs* ≥40 years), presence versus absence of contrast enhancement on MRI, 1p status (deleted *vs* non-deleted *vs* indeterminate), and by the medical institution at which they received treatment. Patients were then assigned 1:1 to receive either temozolomide chemotherapy or standard radiotherapy. The EORTC did the random assignment of patients online using a minimisation technique. Patients had to begin their assigned treatment within 6 weeks of randomisation. Given the nature of the intervention, the trial was open-label and patients, treating physicians, and researchers were all aware of the assigned intervention.

Procedures

Patients in the radiotherapy group received standard radiotherapy treatment, which consisted of three-dimensional conformal radiotherapy up to 50·4 Gy (28×1·8 Gy once daily, 5 days per week, over 5–6 weeks, and up to a maximum treatment period of 6·5 weeks). Intensity-modulated and stereotactically guided radiotherapy was allowed if the same dose prescription as that for non-stereotactic radiotherapy was used. Radiotherapy treatment volumes were defined based on T2 or fluid-attenuated inversion recovery (FLAIR) MRI. In case of tumour resection, postoperative imaging was used. All participating sites had to comply with an extensive quality assurance programme including dosimetry, dummy run, and review of individual patient plans for radiotherapy (level III of quality assurance of radiation therapy, as defined by the EORTC Radiation-Oncology Group).[21–23] No dose adjustments were allowed, irrespective of the length of any treatment interruptions. Interruptions were generally not allowed, but were occasionally unavoidable (eg, holidays and technical failures).

Patients randomly assigned to the temozolomide group received oral temozolomide in a dose-dense schedule of 75 mg/m² per day for 21 days, repeated every

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For the **protocol** see http://www.eortc.be/services/doc/protocols/22033-26033-version2.2.pdf

See **Online** for appendix

28 days (one cycle) for up to 12 cycles or until disease progression or unacceptable toxicity (defined as repeated grade 4 haematological toxicity or grade 3–4 non-haematological toxicity [except for alopecia, nausea, and vomiting]). Antibiotic prophylaxis against opportunistic *Pneumocystis jirovecii* infections was recommended for patients with lymphocyte counts lower than 500 cells per µL. Anti-emetic prophylaxis was administered at the local investigators' discretion. However, if vomiting occurred during treatment, no re-dosing was allowed before the next scheduled dose. In the case of an absolute neutrophil count (ANC) lower than $1{\cdot}0\times10^9$ cells per L (≥grade 3), platelet count lower than 75×10^9 cells per L (≥grade 2), or non-haematological toxicity of grade 2 or worse (except alopecia, nausea, and vomiting), temozolomide treatment had to be withheld until recovery to toxicity of grade 1 or less. For subsequent treatment cycles a lower dose of 60 mg/m² was recommended. Patients who met criteria for unacceptable toxicity immediately and definitively had to discontinue temozolomide treatment.

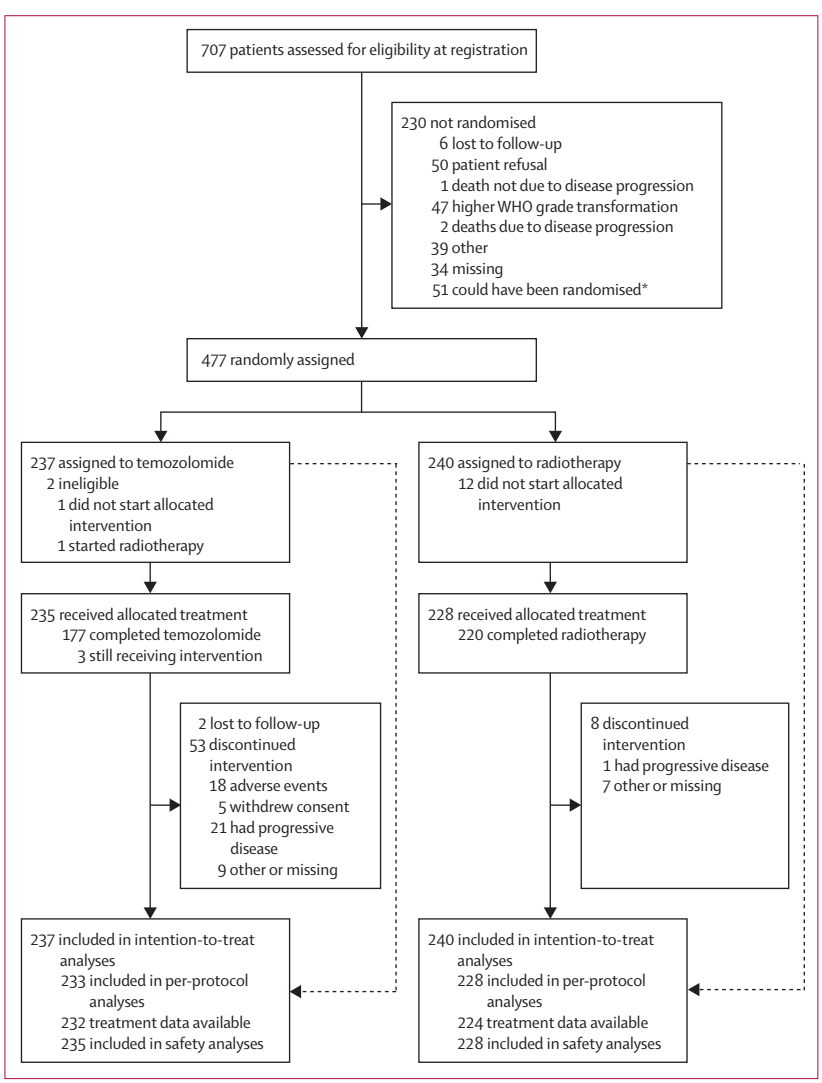

Figure 1: **Trial profile**
*At the date of database lock, 51 registered patients had not progressed or required anti-tumour therapy, and were thus not randomised.

The baseline evaluation (within 6 weeks of randomisation) included MRI, a health-related quality-of-life questionnaire (EORTC QLQ-30, version 3, and the Brain Cancer Module QLQ-BN-20), full clinical and neurological evaluation including assessment of seizure frequency (if applicable), and complete blood counts and blood chemistry. The extent of tumour resection was assessed by the neurosurgeon according to local practice based on postoperative MRI. All patients were evaluated clinically and neurologically every 3 months until progression, including with quality-of-life questionnaires, and tumour assessment with MRI was completed every 6 months after treatment initiation until progression. Radiological progression was defined as an increase of 25% in bi-dimensional perpendicular product of signal hyperintensity on MRI T2-weighted images, or appearance of an area of new contrast enhancement, or a 25% increase in contrast enhancement on T1-weighted MRI with or without an increase in the area of T2-weighted signal hyperintensity. Clinical progression was defined as deterioration due to worsening neurological signs or symptoms with no other explanation or deterioration of WHO performance status or RTOG neurological function. Quality-of-life questionnaire results are reported separately.

Pathological review and molecular testing were done centrally at the EORTC reference laboratory for all non-Canadian centres by AvD, CH, DC, SK, and JMK, and for Canadian centres by JPR. Deletion of chromosomal arms 1p and 19q was tested by microsatellite markers or by use of fluorescence in-situ hybridisation (FISH), as described elsewhere.[24,25] In a post-hoc analysis, we established the mutation status of *IDH1* and *IDH2* by using immunohistochemistry for the most common mutant IDH1R132H, complemented by DNA sequencing of negative cases.[26] We tested the *MGMT* promoter methylation status using the MGMT-STP27 model.[27,28]

Outcomes

The primary endpoint was investigator-assessed progression-free survival, defined as the time between the date of randomisation and the date of clinical or radiological progression or death (whichever occurred first) in the intention-to-treat population, which was defined as all patients assigned to a treatment. Secondary and translational endpoints were overall survival, quality of life, neurological function, adverse events, neurocognitive function (assessed using Mini-Mental State Examination), and the association of molecular markers with outcome. Results for secondary outcomes of quality of life and neurocognitive function are published elsewhere,[18] and neurological function results will be reported elsewhere. Safety was assessed in the

	Radiotherapy (n=240)	Temozolomide (n=237)
Age (years)	43 (36–52)	45 (37–53)
<40	92 (38%)	85 (36%)
≥40	148 (62%)	152 (64%)
Sex		
Men	138 (58%)	137 (58%)
Women	102 (43%)	100 (42%)
WHO performance status		
0	151 (63%)	143 (60%)
I	79 (33%)	86 (36%)
II	10 (4%)	8 (3%)
RTOG neurological function status		
0	126 (53%)	127 (54%)
1	90 (38%)	82 (35%)
2	17 (7%)	22 (9%)
3	7 (3%)	6 (3%)
Contrast enhancement on MRI		
No	119 (50%)	119 (50%)
Yes	121 (50%)	118 (50%)
Initial resection status (by investigator)		
Biopsy	96 (40%)	93 (39%)
Partial removal	106 (44%)	100 (42%)
Total removal	37 (15%)	44 (19%)
Missing	1 (<1%)	0
Time between last biopsy or surgery and treatment initiation (months)*	4·8 (2·9–18·3)	4·8 (2·6–26·4)
Time between first histological diagnosis and treatment start (months)*	5·1 (2·9–25·7)	6·0 (2·7–30·0)
Reason for treatment†		
Refractory seizures‡		
No	212 (88%)	203 (86%)
Yes	28 (12%)	34 (14%)
Radiological progression		
No	90 (38%)	83 (35%)
Yes	150 (63%)	154 (65%)
New or worsening symptoms other than seizures		
No	185 (77%)	189 (80%)
Yes	55 (23%)	48 (20%)
Tumour involving midline		
No	173 (72%)	186 (78%)
Midline shift	29 (12%)	23 (10%)
Midline infiltration	24 (10%)	20 (8%)
Both	10 (4%)	8 (3%)
Unknown	4 (2%)	0
(Continued from previous column)		
Histology (local pathology)		
Astrocytoma WHO grade II	88 (37%)	79 (33%)
Oligoastrocytoma WHO grade II	58 (24%)	60 (25%)
Oligodendroglioma WHO grade II	94 (39%)	98 (41%)
Histology (central review)		
Low-grade glioma confirmed§	227 (95%)	211 (89%)
Low-grade glioma not confirmed¶	8 (3%)	12 (5%)
Missing review	5 (2%)	14 (6%)
Molecular markers		
1p status		
1p deleted	98 (41%)	97 (41%)
1p non-deleted	107 (45%)	106 (45%)
Missing	35 (15%)	34 (14%)
1p/19q status‖		
1p/19q co-deleted	55 (23%)	62 (26%)
1p/19q non-co-deleted	125 (52%)	115 (49%)
Missing	60 (25%)	60 (25%)
IDH1 or *IDH2* mutation status		
IDH1 or *IDH2* mutated	164 (68%)	163 (69%)
IDH1 or *IDH2* wild type	35 (15%)	30 (13%)
Undetermined	41 (17%)	44 (19%)
MGMT promoter methylation status		
MGMT unmethylated	6 (3%)	9 (4%)
MGMT methylated	72 (30%)	63 (27%)
Missing	162 (68%)	165 (70%)

Data are median (IQR) or n (%). RTOG=Radiation Therapy Oncology Group. *For patients who did not start randomised treatment, date of randomisation was used. †Start of treatment was for multiple and non-exclusive reasons: age, refractory seizures, radiological progression, new or worsening symptoms other than seizures. ‡Refractory seizures defined as suffering from persistent seizures, defined as having both persistent seizures interfering with everyday life activities other than driving a car and three lines of anti-epileptic drug regimen had not worked, including at least one combination regimen. §Agreement with at least one of the central reviewers. ¶Discordance, mainly glioma grade 3. ‖Not considered as part of stratification, was prospectively analysed.

Table 1: **Baseline characteristics**

safety population (ie, all patients randomly assigned to a group who started their allocated treatment). Markers prespecified in the protocol were 1p deletion and, following a protocol amendment (version 2.2) on Oct 10, 2007, 19q deletion status (for determination of 1p/19q co-deletion status) and *MGMT* promoter methylation status. This version has been approved by the EORTC and its cooperating international groups.

Statistical analysis

We calculated that 216 observed progression-free survival events in the 466 randomly assigned patients were needed to provide 80% power and a significance level of 5% (two-sided log-rank test) to detect a 13% increase in 5-year progression-free survival (ie, from 45% in the radiotherapy group to 58% in the temozolomide group), corresponding to a treatment hazard ratio (HR) for progression of 0·68. Estimated progression-free survival was calculated using the Kaplan-Meier method from the date of randomisation to an event (progression or death);

for comparison between groups we used a two-sided log-rank test at 5% significance. All analyses, except safety, were done on an intention-to-treat basis, defined as all patients assigned to a treatment. A Cox model with the treatment as the only variable was fitted to measure the unadjusted treatment effect (HR). For sensitivity analysis, HR was also computed and adjusted by the stratification factors (1p deleted *vs* 1p non-deleted *vs* undeterminable; contrast enhancement [presence *vs* absence of contrast enhancement on MRI]; age [<40 *vs* ≥40 years]; and WHO performance status [0–1 *vs* 2]) and other possible confounding factors: tumour crossing the brain midline (no *vs* yes), and baseline RTOG neurological function score (0 *vs* 1 *vs* 2 *vs* 3 *vs* 4). The predictive effect of a marker was assessed by a log-rank interaction test. The prognostic value of each marker was assessed by Kaplan-Meier, log-rank test, and Cox models (to measure HR), stratified by treatment. We did these exploratory analyses at the 5% significance level. No proportionality of hazards assumptions check was planned in the protocol. The association between mutations in *IDH1* or *IDH2* (*IDH*mt) and the extent of primary resection (biopsy *vs* partial resection *vs* total resection) was tested with the Cochran-Armitage trend test. The baseline characteristics were compared between the molecular subgroup with the Kruskal-Wallis non-parametric test. Because treatment duration differed between the two groups, adverse effects are reported separately for the duration of temozolomide chemotherapy (over 1 year) and for the duration of radiotherapy (defined as day 1 of radiotherapy until 28 days after the last administration of radiotherapy). We used SAS version 9.4 for all statistical analyses. For this analysis, a clinical cutoff date of Jan 17, 2013, was used and the database was locked on Aug 7, 2013.

This study is registered at the European Trials Registry, EudraCT number 2004-002714-11, and at ClinicalTrials.gov, number NCT00182819. The trial completed its enrolment, and patients continue to be followed up, as per protocol, until data are mature enough for overall survival analysis (secondary endpoint).

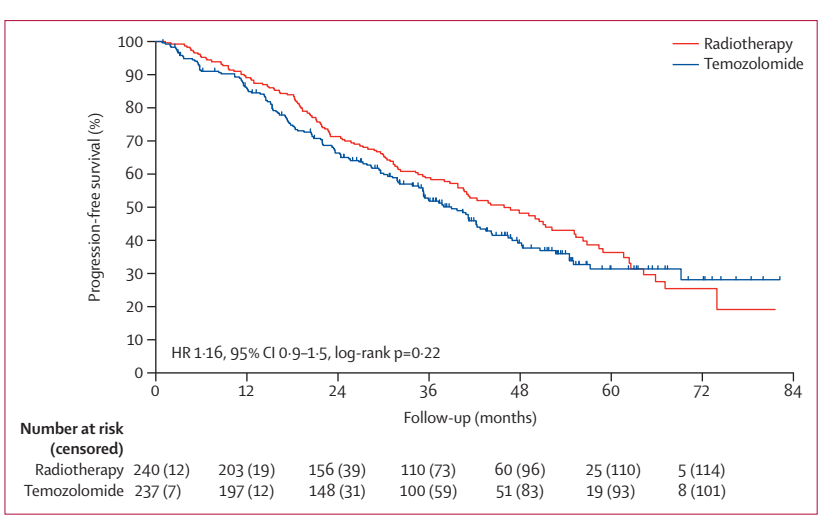

***Figure 2*: Progression-free survival**
HR=hazard ratio.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author (BGB), MEH, and RS had full access to all the data and had final responsibility to submit for publication.

Results

Between Sept 23, 2005, and March 26, 2010, 707 patients from 78 clinical centres in 19 countries were registered. Subsequently, between Dec 6, 2005, and Dec 21, 2012, we randomly assigned 477 of these patients. Reasons for non-randomisation are in figure 1. 240 (50%) patients were assigned to receive radiotherapy, and 237 (50%) to receive temozolomide chemotherapy (figure 1). About half of the patients who were randomly assigned were treated at 12 institutions (appendix pp 8–10). The patient characteristics were well balanced between the groups, with a median age of 45 years (IQR 36–53), 189 (40%) of 477 participants had undergone a diagnostic biopsy only, 206 (43%) participants had a partial tumour debulking, and in 81 (17%) participants the surgeon considered the resection to be complete (table 1). The institutional diagnosis of a WHO grade II glioma was confirmed centrally in 438 (92%) of 477 tumours (table 1). The diagnosis of the histological subtypes, astrocytoma, oligodendroglioma, or oligoastrocytoma, and tumour grade indicated poor inter-observer agreement between the local pathology and central review, as well as the two central pathologists, with κ values between 0·3 and 0·4, respectively (appendix p 1). There was a wide time range between first histological diagnosis and treatment initiation (0·7–151·5 months; median 5·6 months)

At time of database lock, progression events had occurred in 262 (55%) of 477 patients (126 [53%] of 240 in the radiotherapy group and 136 [57%] of 237 in the temozolomide group; see appendix p 3 for type of progression). The median progression-free survival was 46 months (95% CI 40–56) with radiotherapy and 39 months (35–44) with temozolomide (unadjusted HR 1·16 [95% CI 0·9–1·5], log-rank p=0·22; figure 2). Adjusted HRs were computed and provided the same conclusions, showing no significant differences between groups (appendix p 4). At database lock for the present analysis, with only 119 (25%) of all 477 randomised patients having died so far (63 [26%] in the radiotherapy group *vs* 56 [24%] in the temozolomide group), no meaningful analyses of overall survival were possible. A follow-up report will be published that includes overall survival analyses.

Secondary outcomes of quality-of-life results and neurocognitive evaluation by Mini-Mental State

Examination are reported separately.[18] Secondary outcome of neurological function will be reported separately.

Treatment was administered in both groups at the planned intensity and without undue major interruptions or delays in most patients. 219 (91%) of 240 patients completed radiotherapy as planned, and 177 (75%) of 237 completed 12 cycles (range 1–14) of temozolomide chemotherapy. In the 21 (9%) patients who did not receive radiotherapy as planned, 12 did not start radiotherapy (six refused treatment; four progressed to a higher histological tumour grade, one tumour was too large for radiotherapy, and for one patient eligibility criteria were not met). 34 (15%) of 234 patients in the temozolomide group had at least one dose reduction, which was due to haematological toxicity in 19 (8%) patients, non-haematological toxicity in nine (4%) patients, and for other reasons in 11 (5%) patients (some of these patients had a dose reduction for several reasons).

Overall, grade 3–4 haematological toxicity was recorded in 22 (9%) of 235 patients in the safety population who received temozolomide, compared with one (<1%) of 228 patients in the safety population in the radiotherapy group (table 2). Grade 3 or worse infections were reported in two (1%) patients during radiotherapy, and in eight (3%) patients during temozolomide therapy, including two patients with *Pneumocystis jirovecii* pneumonia (one in each treatment group). The most common non-haematological adverse events were neurological (ie, sensory deficits, mood alteration, ischaemia, seizures, and neurocognitive disturbances), which occurred in both groups and were probably related to the underlying brain disease. Moderate to severe fatigue was recorded in eight (4%) patients in the radiotherapy group (grade 2) and 16 (7%) in the temozolomide group (one reported as grade 4; table 2). Thromboembolic events were reported in three (1%) patients (two in the radiotherapy group and one in the temozolomide group). Four patients died during therapy: two patients in the radiotherapy group died of progressive disease 8 days after the last dose of treatment, and two patients in the temozolomide group died; one from progressive disease 5 days after last dose of treatment, and one due to unknown reasons 2 days after last treatment dose (appendix p 2).

In 408 (85%) of 477 patients who were randomly assigned, sufficient tumour tissue was available to assess 1p status (which was a stratification factor). Molecular data of 1p status were missing in 69 (17%) patients (35 in radiotherapy group, 34 in temozolomide group), especially in those who underwent a stereotactic biopsy only (17 patients in radiotherapy, 23 patients in temozolomide group). 1p/19q co-deletion was identified in 117 (33%) of 357 tumours (data were missing for 120 patients, 60 in radiotherapy group and 60 in temozolomide group) and the *MGMT* promoter was methylated in 135 (90%) of 150 tumours (data were missing for 327 patients, 162 in radiotherapy group and 165 in temozolomide group). In an exploratory subgroup analysis, *IDH1* or *IDH2* mutations were detected in 327 (83%) of 392 tumours (table 1), of which 30 (9%) had *IDH1* mutations other than the common *IDH1-R132H* mutation, and nine (3%) were identified in *IDH2*. The associations between distribution of molecular markers and histological glioma subtype (as classified by the local pathologist or the two reference pathologists) are shown in the appendix (pp 7–8). In a representative subgroup of 318 patients in whom both *IDH* and 1p/19q alterations could be assessed (see appendix p 5 for characteristics), the *IDH* mutation status and 1p/19q co-deletion (*IDH*mt/codel) status were available: 269 (85%) patients had *IDH*mt, of whom 104 (39%) were *IDH*mt/codel and

	Radiotherapy (n=228)			Temozolomide (n=235)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Haematological adverse events						
Leucopenia	12 (5%)	0	0	120 (51%)	8 (3%)	1 (<1%)
Neutropenia	6 (3%)	1 (<1%)	0	80 (34%)	6 (3%)	4 (2%)
Thrombocytopenia	0	0	0	8 (3%)	4 (2%)	7 (3%)
Anaemia	7 (3%)	0	0	58 (25%)	1 (<1%)	1 (<1%)
Non-haematological adverse events						
Allergy or immunology	3 (1%)	0	0	11 (5%)	1 (<1%)	0
Auditory or ear	37 (16%)	4 (2%)	0	35 (15%)	1 (<1%)	0
Cardiac (general)	10 (4%)	0	0	11 (5%)	2 (1%)	0
Constitutional symptoms	141 (62%)	8 (4%)	0	159 (68%)	15 (6%)	1 (<1%)
Dermatology or skin	112 (49%)	0	0	73 (31%)	4 (2%)	0
Endocrine	9 (4%)	0	0	12 (5%)	0	0
Gastrointestinal	66 (29%)	4 (2%)	0	158 (67%)	10 (4%)	0
Haemorrhage or bleeding	0	0	0	8 (3%)	0	0
Hepatobiliary or pancreas	0	2 (1%)	0	0	0	0
Infection	23 (10%)	2 (1%)	0	66 (28%)	7 (3%)	1 (<1%)
Lymphatics	1 (<1%)	1 (<1%)	0	9 (4%)	0	0
Metabolic or laboratory	1 (<1%)	2 (1%)	0	4 (2%)	0	0
Musculoskeletal or soft tissue	20 (9%)	2 (1%)	0	21 (9%)	2 (1%)	0
Neurology	134 (59%)	25 (11%)	3 (1%)	125 (53%)	36 (15%)	5 (2%)
Ocular or visual	36 (16%)	0	0	46 (20%)	0	0
Pain	107 (47%)	6 (3%)	0	121 (51%)	7 (3%)	0
Pulmonary or upper respiratory	13 (6%)	1 (<1%)	0	42 (18%)	1 (<1%)	0
Renal or genitourinary	4 (2%)	2 (1%)	0	16 (7%)	0	0
Secondary malignancy	0	1 (<1%)	0	0	1 (<1%)	4 (2%)
Sexual or reproductive function	7 (3%)	0	0	11 (5%)	4 (2%)	0
Surgery or intra-operative injury	2 (1%)	0	0	0	0	0
Syndromes (eg, flu-like or somnolence)	3 (1%)	0	0	12 (5%)	0	0
Vascular	2 (1%)	1 (<1%)	0	1 (<1%)	1 (<1%)	0

These categorial data are treatment-emergent adverse events occurring during treatment and up to 30 days after the end of therapy. An individual patient might have had diverse and several toxicities; therefore the number of patients affected by toxicity is lower than the total number in each treatment group. No patients died from treatment-related causes during treatment or within 30 days after the end of therapy.

Table 2: **Adverse events, in the safety population**

	Total (n=318)*	*IDH*mt/codel (n=104)	*IDH*mt/non-codel (n=165)	*IDH*wt (n=49)	p value
Age (years)					
Median age at diagnosis (range)	45 (36–54)	47 (40–55)	41 (33–49)	52 (42–60)	0·0001
<40 years	115 (36%)	25 (24%)	80 (48%)	10 (20%)	0·0001
≥40 years	203 (64%)	79 (76%)	85 (52%)	39 (80%)	
Median time between last biopsy or surgery and treatment initiation (months [IQR])†	4·5 (2·7–20·8)	4·4 (2·6–23·3)	5·6 (2·9–22·6)	3·6 (2·2–9·6)	0·07
Median time between first histological diagnosis and treatment initiation (months [IQR])†	5·6 (2·8–26·2)	5·6 (2·7–31·2)	8·9 (3·0–27·1)	3·6 (2·1–7·8)	0·0057
Extent of resection					<0·0001
Biopsy	113 (36%)	37 (36%)	44 (27%)	32 (65%)	
Partial removal	148 (47%)	51 (49%)	86 (52%)	11 (22%)	
Total removal	56 (18%)	16 (15%)	34 (21%)	6 (12%)	
Missing	1 (<1%)	0	1 (<1%)	0	
Sex					0·50
Women	134 (42%)	39 (37%)	74 (45%)	21 (43%)	
Men	184 (58%)	65 (63%)	91 (55%)	28 (57%)	
MGMT methylation status‡					0·0003
Unmethylated	14/126 (11%)	0/45 (0%)	10/72 (14%)	4/9 (44%)	
Methylated	112/126 (89%)	45/45 (100%)	62/72 (86%)	5/9 (56%)	
Median progression-free survival (months [95% CI])					Interaction test p=0·013
Temozolomide	40·48 (35·25–46·95)	55·03 (37·95–NR)	36·01 (28·42–46·95)	23·69 (5·55–42·25)	
Radiotherapy	50·99 (39·79–61·63)	61·63 (42·32–NR)	55·36 (47·87–65·87)	19·09 (11·27–25·69)	
Progression-free survival at 5 years (% [95% CI])					Interaction test p=0·013
Temozolomide	28·92% (19·78–38·69)	47·39% (30·71–62·35)	19·43% (8·87–33·00)	17·78% (3·69–40·48)	
Radiotherapy	40·18% (29·94–50·19)	58·49% (39·43–73·41)	42·50% (27·38–56·83)	0% (0·00–0·00)	
Hazard ratio for overall progression-free survival of temozolomide *vs* radiotherapy (95% CI; p value)	1·18 (0·87–1·60; p=0·30)	1·04 (0·56–1·93; p=0·91)	1·86 (1·21–2·87; p=0·004)	0·67 (0·34–1·32; p=0·24)	..

Data are n (%), unless otherwise stated. We used Kruskal-Wallis non-parametric test for p values to test for overall heterogeneity between three molecular subtypes. The log-rank interaction test was presented to assess the difference of treatment effect (temozolomide *vs* radiotherapy) between the molecular subgroups. *IDH*mt=*IDH* mutated. *IDH*mt/codel=*IDH* mutated and 1p/19q co-deletion. *IDH*mt/non-codel=*IDH* mutated and 1p/19q non-co-deletion. *IDH*wt=*IDH* wild type. NR=not reached. *Subgroup representative of the overall population with respect to baseline characteristics (except for the more frequent debulking surgery in this group than in the overall population) and overall outcome of progression-free survival. †For patients who did not start their randomly assigned treatment, we used date of randomisation. ‡Test only available for a subgroup.

Table 3: **Clinical parameters and outcomes of different molecular subtypes**

49 (15%) were *IDH* wild type (*IDH*wt; table 3). These three molecular subgroups differed significantly in clinical characteristics (table 3), which is in line with reports in the past 2 years of several WHO grade II and III glioma datasets.[5,29–31] Time from initial surgery or histology to treatment was longer in patients with *IDH*mt/non-codel than in those with *IDH*mt/codel or *IDH*wt (table 3). The *MGMT* promoter status was methylated in all patients with *IDH*mt/codel, in most of those with *IDH*mt/non-codel, and in just over half of those with *IDH*wt (table 3).

The interaction test showed a significant predictive value of the molecular subtypes for progression-free survival in the subgroup of 318 patients who were molecularly characterised (p=0·013; table 3). Pairwise analyses showed a median progression-free survival of 62 months (95% CI 41–not reached) for *IDH*mt/codel patients, 48 months (41–55) for *IDH*mt/non-codel patients, and 20 months (12–26) for *IDH*wt patients (figure 3A). Patients with *IDH*mt/non-codel tumours had longer progression-free survival if treated with radiotherapy than with temozolomide (table 3, figure 3B; appendix p 6). However, no treatment-related differences were recorded for patients in the other two molecular subgroups (table 3; figure 3C, D; appendix p 6).

Discussion

The results of this study show that overall there was no significant difference in progression-free survival in patients with low-grade glioma treated with temozolomide chemotherapy or radiotherapy. To the best of our knowledge, this is the first randomised trial to assess the use of chemotherapy alone as initial treatment for low-grade glioma and the first prospective randomised trial in this disease to molecularly stratify tumour subgroups before randomisation. The study was designed more than 15 years ago on the basis of the insights available at that time. However, our analysis also included recently defined molecular markers and subgroups for their prognostic and predictive value.

Although we did not establish an overall preferred treatment modality, our results showed the high variability of the individual disease course. Although some patients recurred after only a few months, other patients were symptom-free and without detectable disease progression for many years. This result underlines the need to individualise treatment strategies based on molecular characteristics, in addition to tumour size and location, and patient characteristics.

For low-grade glioma, an expectative approach with watchful waiting or surgery if feasible, and risk-adapted adjuvant treatment are often the initial management.[1] Treatment is initiated on the basis of clinical symptoms, patient's age at presentation, tumour size, radiological characteristics, and tumour growth rate. These criteria lead to a variable timepoint of treatment initiation depending on local practice and physician judgment, histological tumour characteristics, and grade, and could have changed over time, creating additional heterogeneity in this patient population. In our trial, the wide time range from initial histological diagnosis to initiation of treatment is indicative of both variation in local practice and the heterogeneous natural history of the disease. To account for this variability between local practice and investigators, we stratified patients before randomisation according to the treating institution.

Since the past 4–5 years, lower grade gliomas (WHO grade II or III) can now readily be subclassified into prognostic molecular subgroups with the use of an integrative diagnostic approach,[26] which is now an integral part of routine diagnostics since the fourth revised version of WHO's 2016 classication of tumours of the CNS.[32] *IDH* mutations, which were discovered after we started this trial, are characteristic of low-grade glioma and are present in more than 80% of these tumours.[5,20] In our post-hoc analysis in this trial, patients with *IDH*wt tumours had the worst prognosis independent of treatment, whereas patients with *IDH*mt/codel tumours had the best prognosis independent of treatment, which is consistent with other published datasets of lower grade gliomas.[5,29–31]

According to the latest understanding, *IDH*wt tumours might actually belong, molecularly, to other tumour entities—mostly different subtypes of glioblastoma, such as underdiagnosed glioblastoma or *H3 K27M* mutant glioblastoma, but also indolent tumours such as ganglioglioma or pilocytic astrocytoma.[29,33] Retrospective reports[5,29,31,34] published in the past 2 years suggest that in *IDH*mt gliomas, molecular characterisation might be a stronger predictor for outcome than histological tumour grade and other prognostic markers. However, the initial

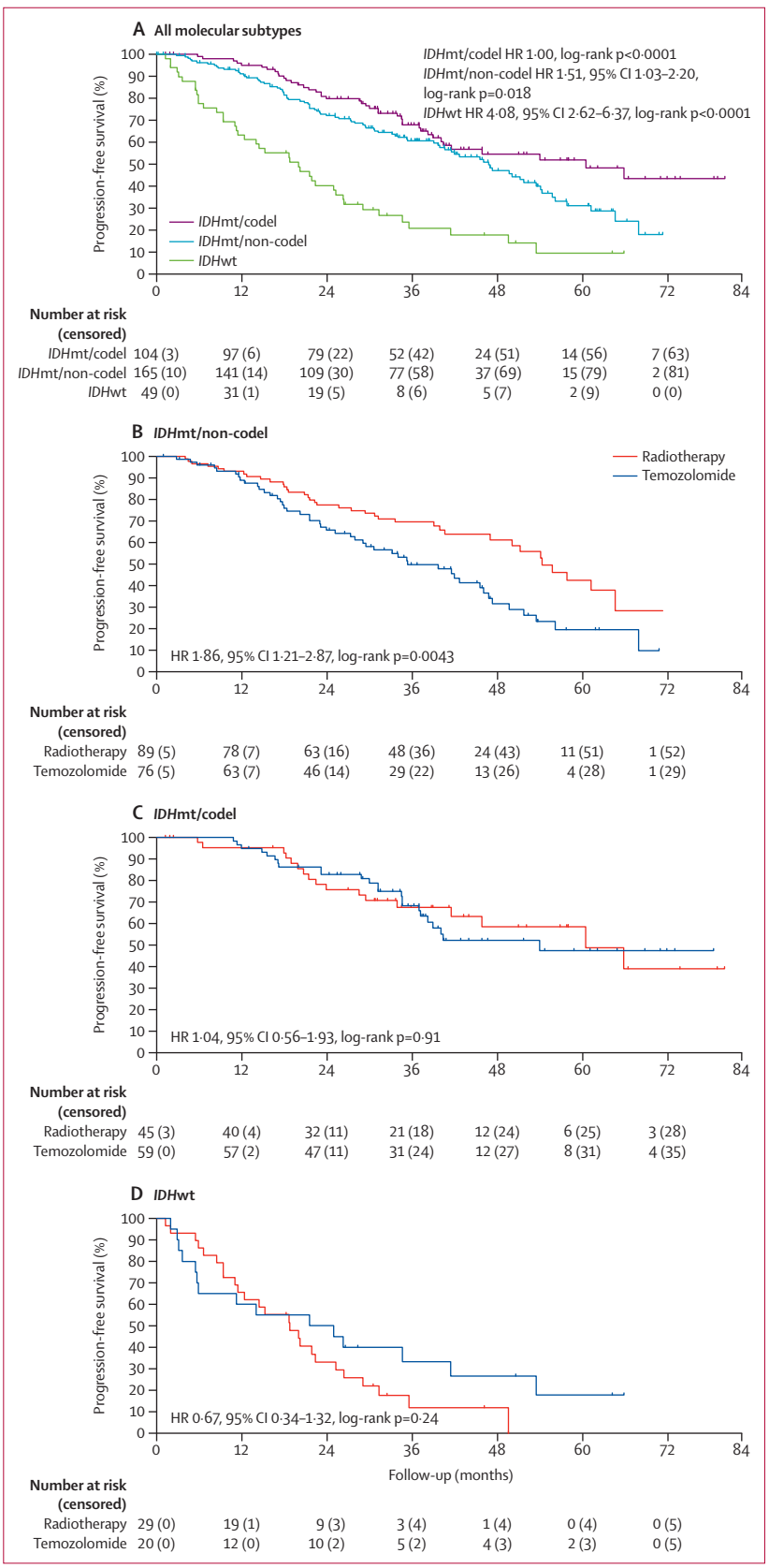

***Figure 3*: Progression-free survival for all molecular subgroups, and by treatment**
Progression-free survival for all molecular subtypes (A), and pairwise comparisons of the two treatment groups by molecular subtype: *IDH*mt/non-codel (B), *IDH*mt/codel (C), and *IDH*wt (D). HR=hazard ratio. *IDH*mt/codel=*IDH* mutated and 1p/19q co-deleted. *IDH*mt/non-codel=*IDH* mutated and 1p/19q non-co-deleted. *IDH*wt=*IDH* wild type.

treatment concept varied in these studies and was affected by the tumour grade—eg, in the prospective German Glioma Network registry,[31] less than 10% of patients with WHO grade II gliomas received adjuvant radiotherapy or chemotherapy after initial surgery, by contrast with more than 90% of the WHO grade III glioma population. Furthermore, the criteria and indication for treatment have probably changed over time and between institutions.

Notably, our study was not powered for the molecular subgroup analyses. All analyses were done for hypotheses generation at 5% significance. Our analyses suggest in patients with *IDH*mt/non-codel tumours that treatment with primary chemotherapy might be deleterious; patients in this subgroup treated with temozolomide had a significantly shorter progression-free survival than those who received radiotherapy. Conversely, progression-free survival was similar between patients treated with radiotherapy and temozolomide in both subgroups of patients with *IDH*mt/codel and *IDH*wt tumours. However, the *IDH*wt subgroup was small (n=49), potentially heterogeneous, as this glioma subtype is molecularly insufficiently defined.

All *IDH*mt/codel and most of the *IDH*mt/non-codel tumours characterised in this study had a methylated *MGMT* promoter, implying that the clinical effect of this biomarker cannot be differentiated from the *IDH* mutation alone, or from its associated CpG island methylator phenotype[35] because of the nested dependency of these changes.[27] Thus, *MGMT* testing does not provide additional prognostic or predictive value in the *IDH*mt subgroup. In *IDH*wt tumours, *MGMT* promoter methylation status might be of predictive value; however, the rarity of this constellation in our cohort did not allow us to do formal statistical testing. Nevertheless, previous reports by our group and others in *IDH*wt grade III gliomas strongly suggest a predictive effect for benefit from chemotherapy for patients with a methylated *MGMT* status.[36,37]

Accurate molecular prognostication is of particular importance in a disease such as glioma, where the individual outcome is highly variable. Although intensive therapy is warranted for rapidly progressive tumours, acute and long-term toxicity and deficits might impair quality of life and neurological function in patients with indolent tumours.[2,38,39] The quality-of-life and Mini-Mental State Examination findings from this trial are reported separately.[18] The median progression-free survival with radiotherapy alone in our trial is 46 months, which is similar to the 48 months reported for the radiotherapy-only group of the randomised RTOG98–02 trial,[9] in which patients were randomly assigned between radiotherapy alone or radiotherapy followed by adjuvant procarbazine–lomustine–vincristine chemotherapy. After long-term follow-up (12 years), the trial results showed a survival benefit favouring adjuvant chemotherapy,[9] almost exclusively in patients with oligodendroglioma (the subtype that often has the 1p/19q co-deletion). However, the RTOG98–02 trial[9] and our trial are not readily comparable. The median age in RTOG98–02 was 4 years younger than our trial (median 40–41 years in their treatment groups *vs* 44–45 years in our trial), the distribution of the histological subtypes was different, and molecular subgroup analyses for 1p/19q co-deletion are not available in the RTOG98–02 trial.[9] The high inter-observer difference even between expert neuropathologists that occurred in our study and in others precludes reliable comparisons at present. The question of whether or not combined modality therapy should be used for the initial treatment of low-grade glioma was not addressed in our trial because we were aiming to minimise the potential risk of late toxicity by postponing radiotherapy(if temozolomide could be used instead) in a patient population who might live for more than 10–20 years.[2]

Association of molecular tumour characterisation with outcome and subsequent rational treatment decisions will be of great benefit for the individualised and standardised management of patients with low-grade glioma. In the molecular subgroups of patients with a poor prognosis identified in our trial (*IDH*wt or *IDH*mt/non-codel tumours), novel or more intensive treatment strategies are warranted even at the cost of some toxicity, whereas the optimal treatment strategy for patients with *IDH*mt/codel tumours and a more favourable prognosis remains controversial. Our results did not show improvement of progression-free survival with upfront treatment of patients with chemotherapy alone, but substitution of irradiation by equally effective temozolomide chemotherapy might prevent or delay long-term radiation-induced side-effects. In the German NOA-04 trial[40] in patients with anaplastic glioma, the treatment sequence (chemotherapy first then radiotherapy at progression, or vice versa) did not affect overall survival. Long-term follow-up of EORTC and RTOG trials on anaplastic (WHO grade III) glioma suggests an improved outcome for patients with 1p/19q co-deleted tumours treated with radiotherapy and early adjuvant chemotherapy.[41,42]

In this trial, we set out to evaluate a well tolerated and, at the time of trial initiation, novel, alkylating agent as the primary treatment for low-grade glioma. However, our study has some inherent limitations. The primary endpoint is progression-free survival, and therefore depends on imaging technique, method of tumour assessment, and the frequency of imaging.[43] Observer experience and potential imaging changes induced by radiotherapy that would be absent in the chemotherapy group might be further confounding factors. In the most favourable subgroups, patients in either group might not yet have experienced tumour progression, and data are therefore still immature. Nonetheless, the striking differences in outcome for the distinct molecular subgroups underline the need for integration of the molecular markers into tumour diagnosis for future

treatment stratification. On the basis of our results, the search for *IDH* mutation and 1p/19q co-deletion should be part of the initial diagnostic work-up for all patients with low-grade glioma as now implemented in the updated WHO classification 2016,[32] whereas the *MGMT* promoter methylation status might have an added value only in *IDH*wt tumours. Our trial contributes to molecularly defining the individual therapeutic strategy, with intensive treatments for poor-prognosis patients while avoiding overtreatment in indolent disease. Although recent mature results and subgroup analyses from a randomised trial done in the 1990s shows a superior outcome for radiotherapy followed by chemotherapy than for radiotherapy alone both in grade II and grade III glioma, our results might support the option of initial chemotherapy alone in good-prognosis *IDH*mt and 1p/19q co-deleted tumours.[9,44] Only very long-term follow-up will establish the role of single modality chemotherapy in patients with chemotherapy-sensitive disease.

Contributors

BGB, MEH, and RS designed the trial concept and protocol, with contributions from MJvdB, AvD, TG, GR, DL, and WPM. BGB, MEH, and RS acted as principal investigators for the trial coordination (BGB for radiation oncology, RS for medical oncology, and MEH for molecular and translational research coordination), and all reviewed the data and data quality. Quality assurance for radiotherapy was completed with the guidance of BGB. MEH coordinated tissue collection, translational research, and molecular analyses. AvD, CH, DC, JMK, and JPR did pathological reviews. AvD, CH, SK, and MEH did molecular analyses. MJBT and JR and were responsible for the quality-of-life and neurocognitive component of the trial. GR, WPM, and JR were responsible for setting up of the trial and getting ethical approval in their national organisations of Tasman Radiation Oncology Group, National Cancer Institute of Canada, and the UK Medical Research Council. TG did the statistical analyses. The trial was coordinated by the EORTC headquarters staff, under the responsibility of ND and DL. All authors provided administrative support and contributed to trial activation, patient inclusion, patient care, patient treatment, and follow-up (patient-related activities were done by only clinicians), data collection, data interpretation, manuscript writing or reviewing and commenting, and approval of the final version of the manuscript.

Declaration of interests

BGB reports personal fees from Merck Sharp & Dohme (MSD), outside the submitted work. MEH reports grants from Swiss Bridge Award and Swiss Cancer League, during the conduct of the study; and reports other from MSD and MDxHealth, outside the submitted work. MJvdB reports grants from Roche and Abbvie, and personal fees from Roche, Abbvie, Merck AG, Novocure, Cavion, Bristol-Myers Squibb, Novartis, and Actelion, outside the submitted work. AvD reports a patent (US 8,367,347 B2: "Methods for the diagnosis and prognosis of a brain tumor") with royalties paid to Dianova GmbH (Hamburg, Germany). MJBT reports personal fees from Hoffmann La Roche, outside the submitted work. CH has a patent (*IDH*1 R132H specific antibody) with royalties paid to Company Dianova. DC reports a patent (US 8,367,347 B2: "Methods for the diagnosis and prognosis of a brain tumor") with royalties paid to Dianova GmbH (Hamburg, Germany). WW reports grants from MSD, Roche, Boehringer Ingelheim, Apogenix, and Vaximm, and personal fees from MSD and Roche, outside the submitted work. WW has a patent IDH1 R132H specific antibody with royalties paid to Company Dianova. MR reports grants from Celgene, Novartis, and Pharmamar, and reports personal fees from Celgene, Boehringer, Genentech, Lilly, and Merck-Serono, outside the submitted work. BT acknowledges financial support from NCIC-CTG, during the conduct of the study. OC reports grants, personal fees and non-financial support from Roche, and personal fees from Ipsen and AstraZeneca, outside the submitted work. JB-M acknowledges support from EORTC during the conduct of the study. PMC reports grants from MSD, outside the submitted work. RS has served on advisory boards for Abbvie, Merck KGaA, Merck & Co/MSD (outside the submitted work), Novartis, Novocure, Pfizer and Roche, fees (when applicable) to institution. TG, KH-X, AAB, GK, MBH, GR, JMK, SK, RE, FD, JEB, LF, JCR, JMMG, JPR, ND, CB, CM, TT-S, RAN, JR, DL, and WPM declare no competing interests.

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