Adjuvant and concurrent temozolomide for 1p/19q non-co-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): second interim analysis of a randomised, open-label, phase 3 study

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Summary

Background The CATNON trial investigated the addition of concurrent, adjuvant, and both current and adjuvant temozolomide to radiotherapy in adults with newly diagnosed 1p/19q non-co-deleted anaplastic gliomas. The benefit of concurrent temozolomide chemotherapy and relevance of mutations in the *IDH1* and *IDH2* genes remain unclear.

Methods This randomised, open-label, phase 3 study done in 137 institutions across Australia, Europe, and North America included patients aged 18 years or older with newly diagnosed 1p/19q non-co-deleted anaplastic gliomas and a WHO performance status of 0–2. Patients were randomly assigned (1:1:1:1) centrally using a minimisation technique to radiotherapy alone (59·4 Gy in 33 fractions; three-dimensional conformal radiotherapy or intensity-modulated radiotherapy), radiotherapy with concurrent oral temozolomide (75 mg/m² per day), radiotherapy with adjuvant oral temozolomide (12 4-week cycles of 150–200 mg/m² temozolomide given on days 1–5), or radiotherapy with both concurrent and adjuvant temozolomide. Patients were stratified by institution, WHO performance status score, age, 1p loss of heterozygosity, the presence of oligodendroglial elements on microscopy, and *MGMT* promoter methylation status. The primary endpoint was overall survival adjusted by stratification factors at randomisation in the intention-to-treat population. A second interim analysis requested by the independent data monitoring committee was planned when two-thirds of total required events were observed to test superiority or futility of concurrent temozolomide. This study is registered with ClinicalTrials.gov, NCT00626990.

Findings Between Dec 4, 2007, and Sept 11, 2015, 751 patients were randomly assigned (189 to radiotherapy alone, 188 to radiotherapy with concurrent temozolomide, 186 to radiotherapy and adjuvant temozolomide, and 188 to radiotherapy with concurrent and adjuvant temozolomide). Median follow-up was 55·7 months (IQR 41·0–77·3). The second interim analysis declared futility of concurrent temozolomide (median overall survival was 66·9 months [95% CI 45·7–82·3] with concurrent temozolomide *vs* 60·4 months [45·7–71·5] without concurrent temozolomide; hazard ratio [HR] 0·97 [99·1% CI 0·73–1·28], p=0·76). By contrast, adjuvant temozolomide improved overall survival compared with no adjuvant temozolomide (median overall survival 82·3 months [95% CI 67·2–116·6] *vs* 46·9 months [37·9–56·9]; HR 0·64 [95% CI 0·52–0·79], p<0·0001). The most frequent grade 3 and 4 toxicities were haematological, occurring in no patients in the radiotherapy only group, 16 (9%) of 185 patients in the concurrent temozolomide group, and 55 (15%) of 368 patients in both groups with adjuvant temozolomide. No treatment-related deaths were reported.

Interpretation Adjuvant temozolomide chemotherapy, but not concurrent temozolomide chemotherapy, was associated with a survival benefit in patients with 1p/19q non-co-deleted anaplastic glioma. Clinical benefit was dependent on *IDH1* and *IDH2* mutational status.

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Introduction

In 2005, a randomised controlled trial reported improved survival for patients with glioblastoma treated with concurrent and adjuvant temozolomide in addition to radiotherapy.[1] However, at that time, no survival improvement was seen in patients with anaplastic oligodendroglioma treated with adjuvant procarbazine, lomustine, and vincristine chemotherapy after radiotherapy.[2,3] Additionally, patients with anaplastic glioma without combined 1p/19q loss (1p/19q non-co-deleted) had worse outcomes than those with 1p/19q co-deleted tumours. In response to these results, the CATNON

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Research in context

Evidence before this study

When this study was planned, anaplastic oligodendrogliomas were considered to be responsive to chemotherapy. However, patients with these tumours had no survival benefit when treated with adjuvant procarbazine, lomustine, and vincristine chemotherapy following radiotherapy. Additionally, patients with 1p/19q non-co-deleted tumours had a much worse prognosis than those with 1p/19q co-deleted tumours. In patients with glioblastoma, a tumour thought to be relatively chemotherapy resistant, radiotherapy combined with concurrent and adjuvant temozolomide improved outcomes. No further systematic literature review was done. In the randomised, open-label, phase 3 CATNON trial, we aimed to investigate the addition of concurrent and adjuvant temozolomide chemotherapy to standard adjuvant radiotherapy in adults with 1p/19q non-co-deleted anaplastic glioma. The first planned interim analysis of CATNON (published in 2017) showed that the addition of 12 cycles of adjuvant temozolomide chemotherapy after radiotherapy improved overall survival. At that time, the question of the value of temozolomide given concurrently with radiotherapy could not be answered. Furthermore, no data were yet available on the association of the mutational status of *IDH1* and *IDH2* with outcome. These driver mutations are present in a large subset of anaplastic astrocytoma and are now diagnostic markers in the WHO 2016 brain tumour classification.

Added value of this study

In a second preplanned interim analysis, we found that temozolomide given simultaneously with radiotherapy does not improve overall survival compared with not giving temozolomide. Even more importantly, we found that the clinical benefit of adding adjuvant temozolomide to radiotherapy is limited to patients with *IDH1* or *IDH2* mutant tumours.

Implications of all the available evidence

For patients with *IDH1* or *IDH2* mutant anaplastic astrocytoma, the standard of care consists of 59·4 Gy radiotherapy in 33 fractions followed by 12 cycles of adjuvant temozolomide chemotherapy. Further molecular analysis will be required to establish the role of *MGMT* promoter methylation in *IDH1* and *IDH2* wild-type tumours. Further clinical follow-up is needed to fully evaluate the role of concurrent temozolomide in *IDH1* or *IDH2* mutant tumours, if any.

intergroup study was initiated to determine whether temozolomide given concurrently with radiotherapy or temozolomide given adjuvant to radiotherapy would improve survival. An interim analysis done shortly before the end of enrolment showed superior overall survival in patients receiving 12 cycles of adjuvant temozolomide following 59·4 Gy of radiotherapy compared with those not receiving 12 cycles of adjuvant temozolomide.[4] At that time, no signal of efficacy or futility was observed for the concurrent temozolomide comparison.

Mutations in *IDH1* and *IDH2* were first identified in 2008 and subsequently reported to represent early events in gliomagenesis, occurring in up to 70–80% of all diffuse WHO grade II and III gliomas.[5–7] The presence of *IDH1* and *IDH2* mutations was found to have a major prognostic effect on overall survival of patients with diffuse glioma and has been related to therapy response.[8–10] The 2016 revision of the WHO classification of CNS tumours classified diffuse glioma according to *IDH1* and *IDH2* mutation status, with anaplastic astrocytoma now being classified as either *IDH1* and *IDH2* mutant or wild-type.[11]

A second interim analysis of CATNON was planned to report on the efficacy or futility of concurrent temozolomide compared with not receiving concurrent temozolomide. We report the results of this second interim analysis and an analysis based on *IDH1* and *IDH2* mutation status, which aligns with the updated WHO 2016 brain tumour classification. We also present analyses by *MGMT* promoter methylation status in *IDH1* and *IDH2* wild-type tumours.[12]

Methods

Study design and participants

The study design has previously been reported in detail.[4] In short, this randomised, open-label, phase 3 study with a two-by-two factorial design was done in 137 institutions across Australia, Europe, and North America (appendix pp 3–7). Patients with newly diagnosed anaplastic glioma without 1p/19q co-deletion, aged 18 years or older, with a WHO performance status of 0–2, with adequate haematological, renal, and liver function, and without known HIV, chronic hepatitis B or hepatitis C virus infection were eligible. Central confirmation of pathology and assessment of 1p/19q status and *MGMT* promoter methylation were required before randomisation, but dedicated centres with confirmed testing procedures were allowed to enrol patients based on local histological diagnosis and 1p/19q assessment.

All institutions obtained ethics approval from their institutional review boards or ethics review committees before enrolment started. All patients gave written informed consent according to local, national, and international guidelines before study enrolment. The latest (13th) version of the protocol can be accessed online.

Randomisation and masking

The randomisation schedule was generated centrally via the European Organization of Research and Treatment of Cancer (EORTC) web-based ORTA system, which was accessed by local investigators. Patients were stratified by institution, WHO performance status score (>0 *vs* 0),

age (>50 years *vs* ≤50 years), 1p loss of heterozygosity (yes *vs* no), the presence of oligodendroglial elements on microscopy (yes *vs* no), and *MGMT* promoter methylation status (methylated *vs* unmethylated *vs* undetermined or invalid). Patients were assigned (1:1:1:1) using the minimisation technique, to radiotherapy alone, radiotherapy with concurrent temozolomide, radiotherapy with adjuvant temozolomide, or radiotherapy with both concurrent and adjuvant temozolomide. Patients and investigators were not masked to treatment.

Procedures

Radiotherapy (three-dimensional conformal radiotherapy or intensity-modulated radiotherapy), given to patients in all groups, consisted of 59·4 Gy given in 33 fractions to involved fields. Patients assigned to concurrent temozolomide treatment received daily 75 mg/m² oral temozolomide during the entire radiotherapy period. Patients assigned to adjuvant temozolomide chemotherapy commenced treatment 4 weeks after the end of radiotherapy. 12 cycles of temozolomide were given on days 1–5 every 28 days; for the first cycle 150 mg/m² was given orally per day and, in case of no or minimal toxicity in cycle one, the dose was escalated to 200 mg/m² daily in subsequent cycles. Dose reductions and delays were per protocol as previously described.[1,4] Patients were followed up during concurrent temozolomide with weekly assessment of haematology, and during radiotherapy and adjuvant temozolomide treatment every 4 weeks, with assessment of haematology, liver, and renal function, and electrolytes. Adverse events were monitored using the International Common Terminology Criteria for Adverse Events (CTCAE; version 3.0). After the end of treatment, follow-up including MRI and neurological examination was obtained every 3 months until progression. Progression-free survival was assessed locally using Macdonald criteria;[13] the protocol gave guidelines for handling of suspected pseudoprogression.

For biomarker analysis, 5–10 µm thick tissue sections were macrodissected for areas with highest tumour content (marked by a dedicated neuropathologist [JMK] on a consecutive haematoxylin and eosin-stained section). DNA was then isolated using the formalin-fixed paraffin embedded (FFPE) Allprep DNA/RNA FFPE kit (Qiagen, Venlo, Netherlands).[14] Mutations in *IDH1* and *IDH2* were assessed with a glioma-dedicated capture-based next-generation sequencing panel (Agilent sureselect, Agilent, Santa Clara, CA, USA; ThermoFisher Scientific, Waltham, MA, USA).[15,16] For patients with insufficient tumour material available, a second smaller glioma-dedicated sequencing panel that requires less material was used.[16,17] *MGMT* promoter methylation analysis was done following bisulphite treatment: before randomisation using methylation-specific PCR (MS-PCR) and at the time of biomarker analysis using the Infinium MethylationEPIC BeadChip Kit (EPIC arrays; Illumina, San Diego, CA, USA) and the MGMT-STP27 algorithm.[18–20] For the molecular analysis, 1p/19q status was confirmed using the copy number alterations extracted from the methylation data.[21]

Outcomes

The primary endpoint was overall survival adjusted for stratification factors at randomisation. Secondary endpoints were progression-free survival, neurological deterioration-free survival, quality of life, safety, and development of cognitive deterioration. Overall survival was defined as time from randomisation to death from any cause, and progression-free survival was defined as time from randomisation to disease progression or death from any cause. Analyses of quality of life, neurological deterioration-free survival, and development of cognitive deterioration are subject to further analysis and results are not yet available.

Statistical analysis

Two questions were addressed in this study: comparison of patients receiving radiotherapy alone or radiotherapy and adjuvant temozolomide with those receiving radiotherapy and concurrent temozolomide or radiotherapy and concurrent temozolomide followed by adjuvant temozolomide; and comparison of patients receiving radiotherapy alone and radiotherapy and concurrent temozolomide with those receiving radiotherapy alone followed by adjuvant temozolomide or radiotherapy and concurrent temozolomide followed by adjuvant temozolomide. For both questions, a hazard ratio (HR) of 0·775 (ie, a death risk reduction of 22·5%) was assumed based on a two-sided log-rank test at an overall significance level of 5% (median overall survival of 24 months in patients receiving radiotherapy only, 31 months in patients treated with concurrent temozolomide or adjuvant temozolomide, and 40 months in patients treated with concurrent and adjuvant temozolomide). To achieve 83% power to show the targeted difference for the two questions, 534 overall survival events were needed for the final analysis, and 748 patients had to be recruited.[22] The first interim analysis for efficacy based on the ρ family (ρ=2) stopping boundaries was initially planned when 41% of the overall survival events had been observed. This analysis was done when a slightly larger number of overall survival events was observed at modified significance level 0·00855 (instead of 0·0084). The analyses were significant for the adjuvant temozolomide question, but not for the concurrent temozolomide one.[4] Further to the recommendation of the independent data monitoring committee (IDMC), the protocol was amended (version 13) on June 28, 2017, to include a second interim analysis to assess the concurrent temozolomide question with more mature data and to provide more details on the testing for *IDH1* and *IDH2* and other biological correlates, including *MGMT*.

The second interim analysis presented here proposed to stop either for futility (reject H1) or efficacy (reject H0)

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See **Online** for appendix

For the **protocol (version 13)** see https://www.eortc.be/services/doc/protocols/26053-22054-version5.0.pdf

For the **ORTA system** see http://www.eortc.be/random

after two-thirds of total planned events were observed (356 of 534) using an efficacy stopping boundary from the ρ family (ρ=2) and an O'Brien-Fleming futility stopping boundary.[23] Futility for the concurrent temozolomide question would be declared if the observed HR was higher than 0·882 and efficacy if less than 0·778 (p<0·009). The HR 0·882 corresponds to an overall survival rate at 2 years of 71·9% in the control group versus 74·7% in the experimental group (difference <3%). The final analysis after 534 deaths would be done at a significance level of 0·044.

All efficacy (progression-free survival and overall survival) analyses were done in the intention-to-treat population, which was defined as all patients randomly assigned to a treatment group. We used the Kaplan-Meier technique for the univariable estimates to calculate the HRs and 95% CIs for overall survival and progression-free survival. For patients alive at the time of analysis, overall survival was censored at last follow-up visit date. For patients alive and without progression at the time of analysis, progression-free survival was censored at the last follow-up visit date. In the primary analyses of overall survival and progression-free survival adjusted for stratification factors (WHO performance status, age, the presence of 1p loss of heterozygosity only, the presence of oligodendroglial elements, and *MGMT* promoter methylation status at time of randomisation), a Cox proportional-hazards model was fitted with a question indicator for each question the trial was intended to answer. We did supportive analyses using Cox models with both questions adjusted by the stratification factors and *MGMT* methylation status after randomisation. The analysis of the adjuvant temozolomide question was repeated at retrospective 5% significance.

For both overall survival and progression-free survival, Cox analyses proportional-hazards assumptions were checked with a Kolmogorov-type supremum test based on the ASSESS statement of SAS PHREG procedure at a conservative 1% significance level. The tests were computed with all variables in the models (treatment, age, WHO performance status, presence of 1p loss only, presence of oligodendroglioma components, and *MGMT* methylation status at randomisation). If the proportional-hazards assumptions for a variable were violated, the variable was removed from the models (eg, linear predictors) and used as a stratification factor in the Cox models. These analyses were considered as sensitivity analyses.

In response to emerging molecular data, the CATNON study protocol was amended (version 8) on June 27, 2011, to include analyses based on the mutation status of *IDH1* and *IDH2* genes. This amendment also allowed intensity modulated radiotherapy. For the analysis of the *IDH1* and *IDH2* mutation status, we did univariate (prognostic) and interaction (predictive) exploratory approach analyses of overall survival and progression-free survival (with Cox models including marker by treatment interaction terms).

Agreement between results of different *MGMT* assays was assessed using concordance percentage and κ statistics with 95% CI. We measured relative dose intensity of temozolomide in patients with sufficient treatment information. Values were calculated as the sum of doses delivered per administration divided by the total planned dose for the total planned time of delivery. In the exploratory analyses, p values of less than 0·05 were considered to be significant (appendix p 30).

All clinical study data were captured locally on study specific case record forms and submitted to the EORTC Data Center, where they were entered in a central study database. We used SAS (version 9.4) for all analyses.

This study is registered with ClinicalTrials.gov, NCT00626990.

Role of the funding source

The funder had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Dec 4, 2007, and Sept 11, 2015, 1407 patients were registered and 751 patients were randomly assigned to radiotherapy alone (n=189), radiotherapy with concurrent temozolomide (n=188), radiotherapy and adjuvant temozolomide (n=186), and radiotherapy with concurrent temozolomide and adjuvant temozolomide (n=188). The second interim analysis includes all data up to Feb 3, 2018 (second clinical cutoff date). All subsequent entries were censored at that date. The database was locked on Aug 2, 2018. At that date, the median follow-up was 55·7 months (IQR 41·0–77·3), 395 (53%) patients were still alive, and 267 (36%) patients were alive without progression. Figure 1 provides the CONSORT diagram of patients per study group and the *IDH1* and *IDH2* mutation status per study group. For the planned analyses of the prognostic and predictive value of *IDH1* and *IDH2* mutations, the clinical data were updated up to Feb 3, 2019, with another database lock on May 7, 2019. At that date, median follow-up was 66·7 months (IQR 50·1–88·6) and 384 (51%) patients were still alive. With an additional six patients enrolled after the first IDMC report (Oct 6, 2015), the treatment groups remained well balanced for baseline clinical characteristics (appendix p 8). The table provides the randomisation outcome, treatment details and temozolomide treatment intensity, reasons for stopping treatment, and survival status at the time of analysis.

Futility of concurrent temozolomide was declared (median overall survival was 66·9 months [95% CI 45·7–82·3] with concurrent temozolomide *vs* 60·4 months [45·7–71·5] without concurrent temozolomide; HR 0·97 [99·1% CI 0·73–1·28], p=0·76), and the IDMC therefore recommended release of the study results (appendix p 11).

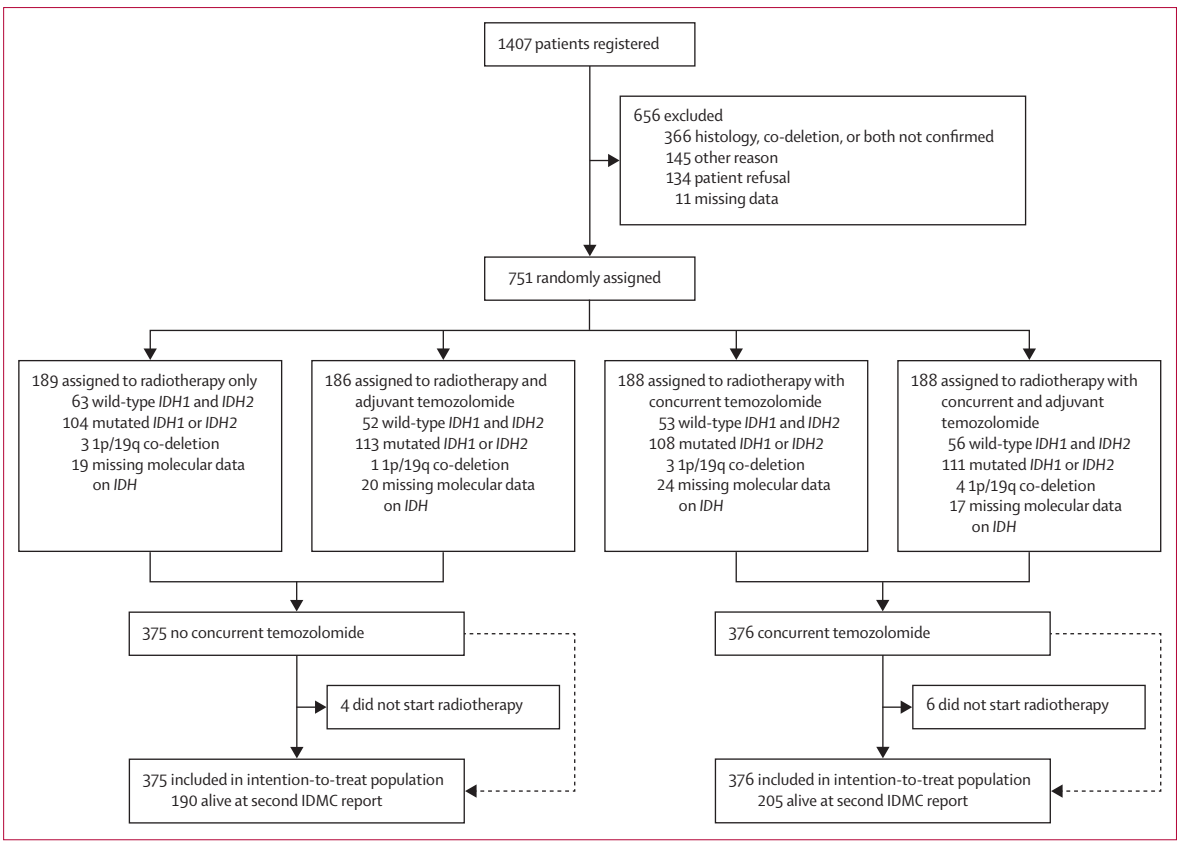

Figure 1: **Trial profile**
IDMC=independent data monitoring committee.

The analysis for adjuvant temozolomide question remained significant (median overall survival 82·3 months [95% CI 67·2–116·6] with adjuvant temozolomide *vs* 46·9 months [37·9–56·9] without adjuvant temozolomide; HR 0·64 [95% CI 0·52–0·79], p<0·0001; appendix p 11). The supportive univariable analyses provided similar conclusions (figure 2A, 2B; appendix p 12). With 356 patients having died (table), overall survival was not significantly different with versus without concurrent temozolomide (5-year overall survival 52·7% [95% CI 46·9–58·1] *vs* 50·2% [44·4–55·7]; HR 0·93 [95% CI 0·75–1·14], p=0·46; figure 2A; appendix p 12). Overall survival was, however, significantly different with versus without adjuvant temozolomide (5-year overall survival 58·5% [95% CI 52·8–63·8] *vs* 44·3% [38·6–49·9; HR 0·67 [95% CI 0·55–0·83], p<0·0001; figure 2B; appendix p 12). With 484 patients having progressed or died (appendix p 13), progression-free survival was not significantly different with versus without concurrent temozolomide (appendix p 12). Progression-free survival was significantly improved after adjuvant temozolomide versus without adjuvant temozolomide (appendix p 12). Tests for interaction between the concurrent part of the treatment and the adjuvant part of the treatment remained negative (p=0·71; appendix p 27). For all Cox analyses, the proportional-hazards assumptions were violated for age. The results of the sensitivity analyses with age as a stratification factor in the Cox models are presented in the appendix (pp 31–62). Sensitivity analyses confirmed the results of the primary analyses for progression-free survival and overall survival for the two therapeutic questions.

The number of progression-free survival events per group and treatments given at progression are shown in the appendix (p 13). In the group of patients assigned to radiotherapy only, 118 (81%) of 145 patients who progressed had received some type of further treatment. This treatment was chemotherapy in 111 (77%) of 145 patients, 97 (67%) of whom received temozolomide.

Grade 3 and 4 adverse events were rare, except for haematological adverse events (appendix pp 16–21). 55 (15%) of 368 patients in both adjuvant temozolomide groups and 16 (9%) of 185 patients in the concurrent temozolomide group had grade 3 or 4 haematological adverse events, in particular thrombocytopenia (36 [10%] of 368 patients in the adjuvant temozolomide groups and 14 [8%] of 185 patients in the concurrent temozolomide group) and neutropenia (24 [7%] and five [3%]). Treatment was stopped for adverse events in seven (4%) of 188 patients receiving concurrent temozolomide, 14 (8%)

	Radiotherapy alone group (n=189)	Radiotherapy with concurrent temozolomide group (n=188)	Radiotherapy and adjuvant temozolomide group (n=186)	Radiotherapy with concurrent temozolomide and adjuvant temozolomide group (n=188)
Treatment never started	3 (2%)	3 (2%)	3 (2%)	3 (2%)
Completed treatment	175 (93%)	163 (87%)	107 (58%)	89 (47%)
Exposure to radiotherapy				
Missing information	1 (1%)	1 (1%)	0	1 (1%)
Total dose given, Gy	59·4 (10·8–61·2)	59·4 (1·8–64·9)	59·4 (52·2–60·9)	59·4 (7·2–60·2)
Clinical target volume, mL	230 (2–698)	242 (7–684)	225 (3–1736)	225 (6–730)
Exposure to concurrent temozolomide				
Missing information	..	2 (1%)	..	0
Relative dose intensity				
≤70%	..	5 (3%)	..	2 (1%)
71–90%	..	19 (10%)	..	11 (6%)
91–110%	..	158 (85%)	..	171 (92%)
111–120%	..	1 (1%)	..	1 (1%)
Exposure to adjuvant temozolomide				
Started adjuvant temozolomide	..	..	172 (92%)	163 (87%)
Number of cycles	..	..	12 (6–12)	12 (6–12)
Received more than six cycles	..	..	124/172 (72%)	118/163 (72%)
Completed 12 cycles	..	..	108/172 (63%)	90/163 (55%)
Reason for treatment discontinuation				
Progressive disease or death due to progressive disease	6 (3%)	7 (4%)	49 (26%)	40 (21%)
Toxicity	1 (1%)	7 (4%)	14 (8%)	28 (15%)
Refusal	3 (2%)	1 (1%)	5 (3%)	11 (6%)
Major protocol violation	0	1 (1%)	3 (2%)	4 (2%)
Other	2 (1%)	7 (4%)	7 (4%)	13 (7%)
Missing	2 (1%)	2 (1%)	1 (1%)	3 (2%)
Status at the time of second IDMC recommendation				
Alive	82 (43%)	91 (48%)	108 (58%)	114 (61%)
Alive without progression	44 (23%)	62 (33%)	74 (39%)	87 (46%)

Data are n (%) or median (IQR). IDMC=independent data monitoring committee.

Table: **Overview of patients per group, number of events at the time of the second IDMC report, and treatment**

of 186 patients receiving adjuvant temozolomide, and 28 (15%) of 188 patients receiving concurrent and adjuvant temozolomide (table; appendix p 9). No treatment-related deaths were reported; 329 (92%) of the 356 deceased patients died because of tumour progression, four patients died from other causes (pneumonia, acute respiratory failure, cardiovascular, and other cancer) and in 23 (6%) the cause of death remained unknown. The number of serious adverse events per study group are provided in the appendix (p 22). Two patients died due to serious adverse events: one patient in the radiotherapy alone group died from aspiration pneumonia, and one patient in the radiotherapy with concurrent temozolomide group died from CNS haemorrhage.

Sufficient FFPE tumour tissue was available to determine *IDH1* and *IDH2* mutation status in 671 patients. 11 *IDH1* or *IDH2* mutant tumours were found to be 1p/19q co-deleted after copy number analysis of EPIC array data, and were subsequently excluded from this analysis (three in the radiotherapy only group, three in the concurrent temozolomide group, one in the adjuvant temozolomide group, and four in the concurrent and adjuvant temozolomide group). In the 740 patients with 1p/19q intact, the numbers of patients with a *IDH1* or *IDH2* mutant tumour were well balanced between the four groups and varied between 107 (58%) of 186 patients in the radiotherapy only group and 113 (61%) of 184 patients in the radiotherapy with concurrent and adjuvant temozolomide group (appendix p 14). The *IDH1* and *IDH2* mutation status was available in a total of 660 anaplastic astrocytoma tumours: 216 (33%) were wild-type *IDH1* and *IDH2* and 444 (67%) were mutant *IDH1* or *IDH2*. At the time of analysis, 32 (15%) of the 216 patients with *IDH1* and *IDH2* wild-type tumours and 292 (66%) of the 444 patients with *IDH1* or *IDH2* mutant tumours were still alive.

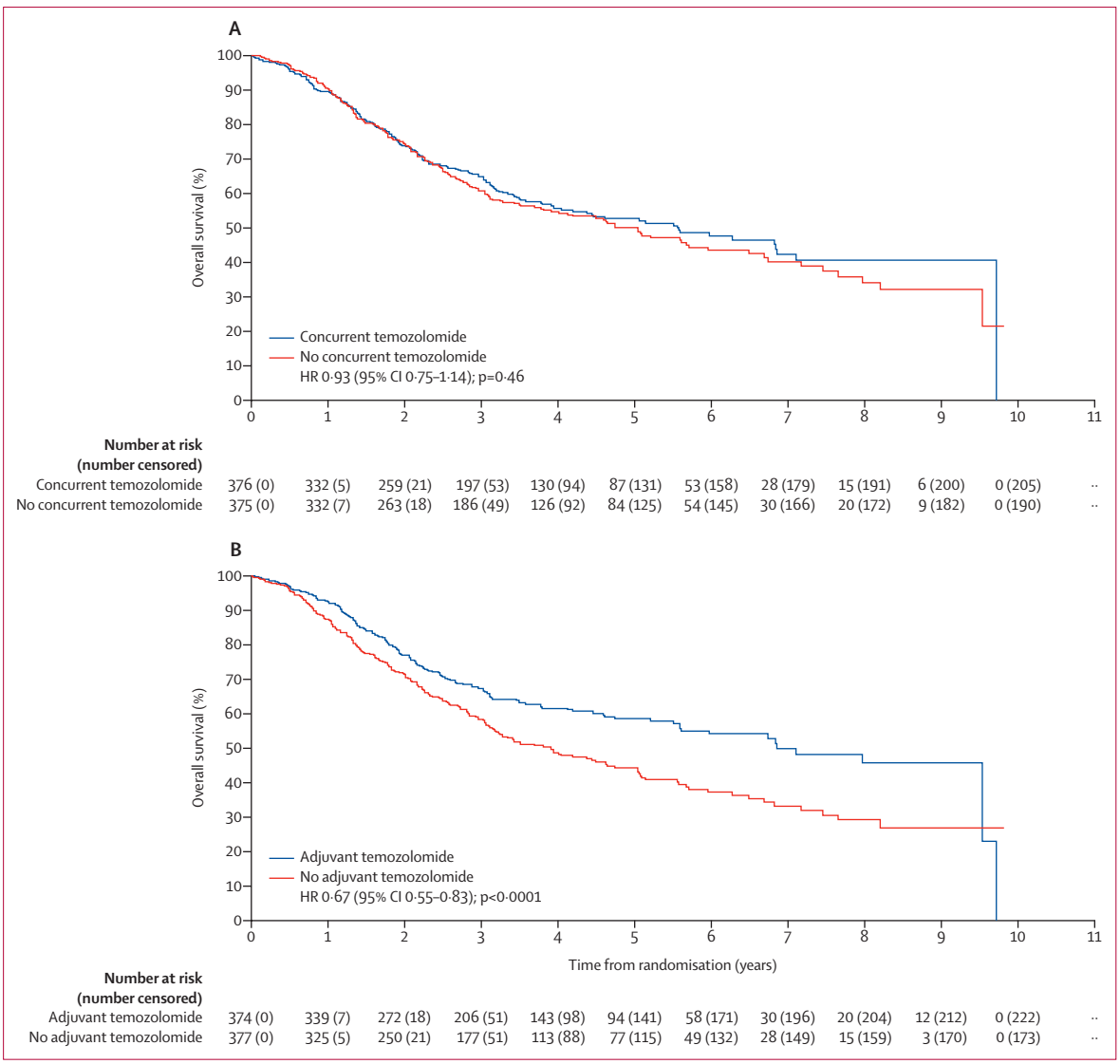

Figure 2: **Univariable analysis of overall survival in all patients regardless of *IDH1* and *IDH2* mutational status**
(A) Patients who received concurrent temozolomide versus those who did not. (B) Patients who received adjuvant temozolomide versus those who did not.

Median overall survival was 19·9 months (95% CI 16·8–22·7) for patients with *IDH1* and *IDH2* wild-type tumours and 98·4 months (85·2–116·6) for patients with *IDH1* or *IDH2* mutant tumours (HR 0·14 [95% CI 0·12–0·18], p<0·0001; appendix p 25). In patients with *IDH1* and *IDH2* wild-type tumours, neither concurrent nor adjuvant temozolomide improved overall survival compared with radiotherapy alone (86 patients who received concurrent temozolomide and 98 patients who did not receive concurrent temozolomide died; 91 people who received adjuvant temozolomide and 93 patients who did not receive adjuvant temozolomide died; figure 3). In patients with *IDH1* or *IDH2* mutant tumours, adjuvant temozolomide improved overall survival compared with no adjuvant temozolomide, but no overall survival benefit was observed after concurrent temozolomide compared with no concurrent temozolomide (85 patients who received concurrent temozolomide and 67 patients who did not receive concurrent temozolomide died; 59 people who received adjuvant temozolomide and 93 patients who did not receive adjuvant temozolomide died; figure 4). With tests for interaction, *IDH1* and *IDH2* mutation status was highly significant for benefit to adjuvant temozolomide (p=0·001), but not concurrent temozolomide (p=0·29). When considering *IDH1* or *IDH2* mutant tumours treated with adjuvant temozolomide, the addition of concurrent temozolomide did not improve overall survival (HR 0·82 [95% CI 0·49–1·36], p=0·44; appendix p 24); 5-year survival was 80·5% (95% CI 71·3–87·0) in patients who did not receive concurrent temozolomide versus 82·8% (73·7–89·0) in patients

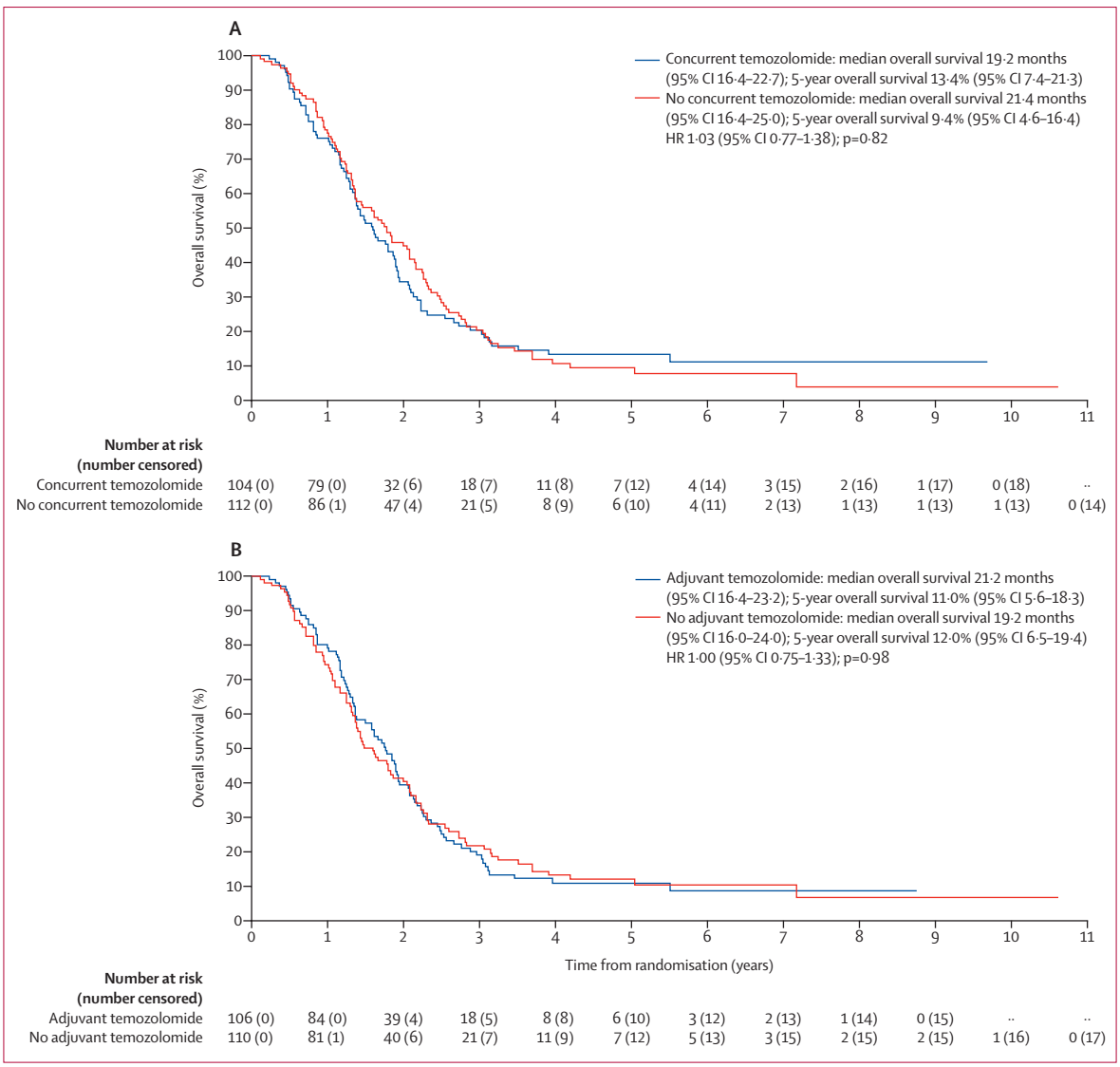

Figure 3: **Univariable analysis of overall survival in patients with *IDH1* and *IDH2* wild-type tumours**
(A) Patients who received concurrent temozolomide versus those who did not. (B) Patients who received adjuvant temozolomide versus those who did not.

who received concurrent temozolomide. Conversely, when considering *IDH1* or *IDH2* mutant tumours treated with concurrent temozolomide, adjuvant temozolomide improved overall survival (HR 0·49 [95% CI 0·30–0·81], p=0·0050); 5-year survival was 64·8% (95% CI 54·3–73·5) *vs* 82·8% (73·7–89·0; appendix p 24). In *IDH1* or *IDH2* mutant tumours, the median overall survival in the 337 patients with any temozolomide as part of initial treatment was 114·4 months (95% CI 90·3–not reached) versus 68·2 months (55·7–91·8) in the 107 patients initially treated with radiotherapy alone (HR 0·53 [95% CI 0·38–0·74], p<0·0001; appendix p 25). In patients with *IDH1* or *IDH2* mutations, median progression-free survival in patients treated with any temozolomide was 77·0 months (95% CI 60·3–86·7) versus 34·2 months (19·9–42·8) in patients treated with radiotherapy only (HR 0·48 [95% CI 0·37–0·63], p<0·0001; appendix p 26).

In the 740 patients without 1p/19q co-deletion, *MGMT* promoter methylation status could be assessed in 663 (90%) patients using the MGMT-STP27 algorithm. Originally, 185 (25%) patients could not have their *MGMT* status assessed by the MS-PCR method, so we used the MGMT-STP27 algorithm. Of the *IDH1* and *IDH2* wild-type tumours, 133 (62%) of 216 had unmethylated *MGMT* and 78 (36%) had methylated *MGMT*; no results were obtained in five tumours. In the *IDH1* and *IDH2* wild-type tumours, *MGMT* status as determined with MS-PCR correlated moderately with the MGMT-STP27 algorithm (percentage concordance 85%, κ statistics 0·67 [95% CI 0·55–0·80]). 117 (88%) of the 133 patients with unmethylated *MGMT* tumours and 63 (81%) of the

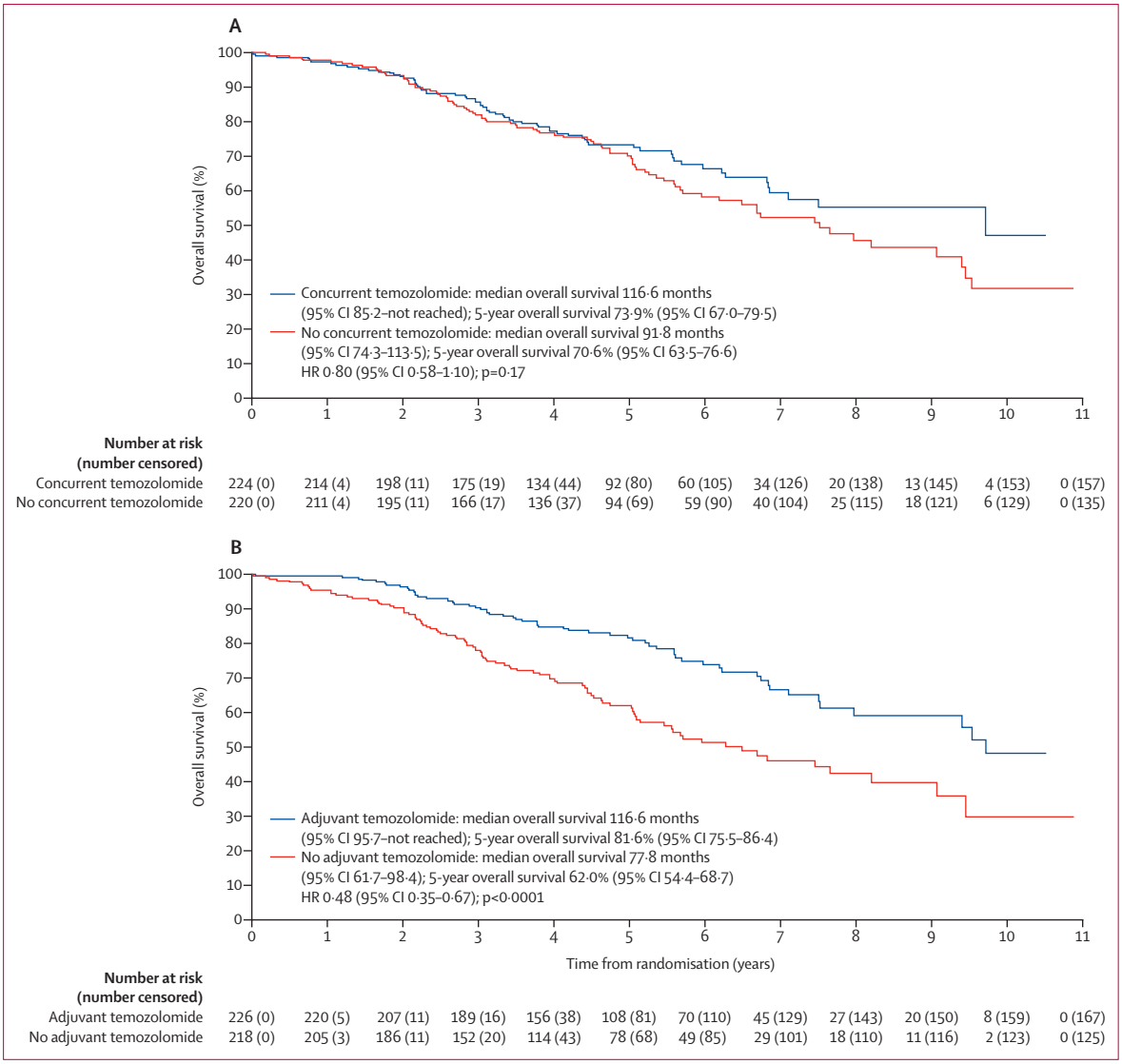

Figure 4: **Univariable analysis of overall survival in patients with *IDH1* or *IDH2* mutant tumours**
(A) Patients who received concurrent temozolomide versus those who did not. (B) Patients who received adjuvant temozolomide versus those who did not.

78 patients with methylated *MGMT* tumours had died at the time of the analysis. Survival of these patients according to treatment is presented in the appendix (p 14). Overall survival by *MGMT* methylation status with and without concurrent temozolomide, with and without adjuvant temozolomide, and with and without any temozolomide are shown in the appendix (pp 28–29).

Discussion

The initial report on the CATNON trial on newly diagnosed anaplastic astrocytoma without 1p/19q co-deletion showed a benefit from the addition of 12 cycles of adjuvant temozolomide and defined the new standard of care in this disease.[4] In this second interim analysis, we show no benefit from giving daily temozolomide concurrently with radiotherapy. Importantly, we are now able to report the study incorporating the *IDH1* and *IDH2* mutation status, according to the revised WHO 2016 brain tumour classification.[11] This analysis reveals lack of clinical benefit from either concurrent or adjuvant temozolomide in the *IDH1* and *IDH2* wild-type tumours, and clinical benefit from the adjuvant temozolomide only in patients with *IDH1* or *IDH2* mutant tumours. With the current number of events analysed, there is no clinically relevant benefit of temozolomide given concurrently with radiotherapy to patients with *IDH1* or *IDH2* mutant anaplastic astrocytoma. The lack of a clear effect is further emphasised if one considers patients who were treated with adjuvant temozolomide. However, in the subgroup of patients with *IDH1* or *IDH2* mutant tumours who did receive temozolomide concurrently with radiotherapy, adding adjuvant temozolomide still significantly improved overall

survival. Taken together, the CATNON trial shows that the benefit from temozolomide is derived from the adjuvant phase and is limited to patients with *IDH1* or *IDH2* mutant anaplastic astrocytoma.

Previous trials examining adjuvant procarbazine, lomustine, and vincristine in anaplastic oligodendroglioma and low-grade glioma identified either *IDH1* and *IDH2* mutation status or *MGMT* promoter methylation as predictive factors for benefit from alkylating chemotherapy.[10,20,24] At the time that this study was initiated, it was well established that *MGMT* promoter methylation was a predictor of sensitivity to alkylating chemotherapy. Subsequent studies found that the vast majority (85–90%) of *IDH1* or *IDH2* mutant tumours also had a methylated *MGMT* promoter.[12] In this trial, we used two methodologies to determine the *MGMT* status: MS-PCR and genome-wide methylation analysis. In the prespecified multivariable analysis of the primary endpoint, *MGMT* status as determined by MS-PCR was of independent significance, but this potentially also reflects its relation to *IDH1* and *IDH2* mutation status; moreover, methylation status could not be determined in about a quarter of patients. We explored the association of *MGMT* promoter methylation status with outcome in the group of 216 patients with *IDH1* and *IDH2* wild-type tumours, and found no evidence of clinical benefit after concurrent temozolomide or after adjuvant temozolomide in patients with *MGMT* methylated, *IDH1* and *IDH2* wild-type tumours. This lack of efficacy is unexpected in view of the significant benefit of the addition of temozolomide to radiotherapy in patients with glioblastomas with *MGMT* promoter methylation, which are predominantly wild-type for *IDH1* and *IDH2*.[25,26] One potential explanation for this might be the limited number of patients with *IDH1* and *IDH2* wild-type tumours in this study. Additionally, *IDH1* and *IDH2* wild-type astrocytomas are not a single entity, and only a subgroup of such tumours show a molecular background reflecting glioblastoma.[27,28] A further report on the CATNON study will detail the association of *MGMT* status with outcome in the *IDH1* and *IDH2* wild-type tumours, including the subgroup of anaplastic glioma with molecular features of glioblastoma.

The most relevant limitation of these analyses is that the study was powered to ask the concurrent and adjuvant temozolomide question in a two-by-two factorial design trial, and not for further subgroup analysis. A second limitation is the thus-far short follow-up and the low number of survival events in patients with *IDH1* or *IDH2* mutant tumours. This limited follow-up might mask more subtle beneficial effects of concurrent temozolomide treatment in the *IDH1* or *IDH2* mutant tumours. Given the slight separation of the survival curves after concurrent temozolomide in *IDH1* or *IDH2* mutant tumours, with longer follow-up, an overall survival signal might emerge similar to observations in studies on low-grade glioma and on anaplastic oligodendroglioma.[24,29] Hence, a longer-term analysis is required, with the required number of survival events needed for the final analysis anticipated to occur in 2024–25. Nevertheless, the current data convincingly show that the adjuvant administration of temozolomide has a greater effect on overall survival than concurrent administration. There are two toxicity concerns with concurrent temozolomide (although admittedly data are scarce): first, concurrent temozolomide and radiotherapy might potentiate delayed neurotoxicity, and second, pseudoprogression occurs more often if radiotherapy is combined with chemotherapy.[30] In this context, currently, our results argue for treating *IDH1* or *IDH2* mutant anaplastic astrocytoma with only 12 cycles of adjuvant temozolomide.

To conclude, the present analysis shows that the benefit from temozolomide in anaplastic astrocytoma is derived from the adjuvant phase of the treatment and is observed only in patients with *IDH1* or *IDH2* mutant tumours. Longer follow-up is needed, especially in *IDH1* or *IDH2* mutant tumours, as the increase in progression free survival could in time translate into an overall survival benefit. Further studies are ongoing to assess molecular factors associated with prognosis.

For the **data sharing policy** see http://www.eortc.org/app/uploads/2017/03/pol008.pdf

Contributors

MvdB, WW, MW, MAV, and WPM did the literature search. MvdB, WW, MW, MAV, WPM, TG, PF, and BGB designed the study. MvdB, CMST, WW, MS, AAB, PMC, SE, MAV, AKN, JFB, WPM, HW, OLC, SG, MG, LR, WT, RR, MW, CM, JR, RHE, FC, TL, SC, AG, EL, UH, PH, FD, IdH, KA, RBJ, HJD, JMK, PW, SN, VG, TG, PF, and BGB collected data. MvdB, CMST, TG, and PF analysed the data. MvdB, CMST, TG, and PF interpreted the data. All authors wrote and approved the final version of the report. MvdB, TG, and CMST verified all the data. All authors had access to all data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

MJvdB reports grants from the Dutch Cancer Foundation, Brain Tumor Charity, Strijd van Salland, and Merck Sharp & Dohme (formerly Schering Plough), during the conduct of the study; and personal fees from Carthera, Nerviano, Bayer, Cellgene, Agios, AbbVie, Karyopharm, Boston Pharmaceuticals, and Genenta, outside the submitted work. PMC reports personal fees from Bristol Meyers Squibb, AbbVie, Merck Serono, Merck Sharp & Dohme, Vifor Pharma, DaNchi Sankyo, LEO Pharma, AstraZeneca, and Takeda, outside the submitted work. MAV reports grants from the US National Cancer Institute, during the conduct of the study, and personal fees from Tocagen and Celgene, outside the submitted work. AKN reports grants and personal fees from AstraZeneca, and Douglas Pharmaceuticals, and personal fees from Bayer Pharmaceuticals, Roche Pharmaceuticals, Boehringer Ingelheim, Merck Sharp & Dohme, Pharmabcine, Atara Biotherapeutics, and Trizell, outside the submitted work. MW reports grants and personal fees from AbbVie, Merck Sharp & Dohme, Merck (EMD); grants from Adastra, Novocure; and personal fees from Basilea, Bristol Myer Squibbs, Celgene, Nerviano, Orbus, Roche, and Tocagen, outside the submitted work. UH reports non-financial support from Medac, and personal fees from Novartis, Daiichi-Sankyo, Noxxon, AbbVie, Bayer, Janssen, and Karyopharm, outside the submitted work. HJD reports personal fees from AbbVie, outside the submitted work. BGB reports personal fees and non-financial support from Roche, outside the submitted work. All other authors declare no competing interests.

Data sharing

Clinical data will be shared upon full completion of the protocol.

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