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Interim results from the CATNON trial (EORTC study 26053-22054) of treatment with concurrent and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma: a phase 3, randomised, open-label intergroup study

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See **Online** for appendix

Contributors

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Declaration of interests

The other authors declare no competing interests.

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Summary

Background—The role of temozolomide chemotherapy in newly diagnosed 1p/19q non-co-deleted anaplastic gliomas, which are associated with lower sensitivity to chemotherapy and worse prognosis than 1p/19q co-deleted tumours, is unclear. We assessed the use of radiotherapy with concurrent and adjuvant temozolomide in adults with non-co-deleted anaplastic gliomas.

Methods—This was a phase 3, randomised, open-label study with a 2 × 2 factorial design. Eligible patients were aged 18 years or older and had newly diagnosed non-co-deleted anaplastic glioma with WHO performance status scores of 0–2. The randomisation schedule was generated with the electronic EORTC web-based ORTA system. Patients were assigned in equal numbers

(1:1:1:1), using the minimisation technique, to receive radiotherapy (59·4 Gy in 33 fractions of 1·8 Gy) alone or with adjuvant temozolomide (12 4-week cycles of 150–200 mg/m^2 temozolomide given on days 1–5); or to receive radiotherapy with concurrent temozolomide 75 mg/m^2 per day, with or without adjuvant temozolomide. The primary endpoint was overall survival adjusted for performance status score, age, 1p loss of heterozygosity, presence of oligodendroglial elements, and *MGMT* promoter methylation status, analysed by intention to treat. We did a planned interim analysis after 219 (41%) deaths had occurred to test the null hypothesis of no efficacy (threshold for rejection p<0·0084). This trial is registered with ClinicalTrials.gov, number NCT00626990.

Findings—At the time of the interim analysis, 745 (99%) of the planned 748 patients had been enrolled. The hazard ratio for overall survival with use of adjuvant temozolomide was 0·65 (99·145% CI 0·45–0·93). Overall survival at 5 years was 55·9% (95% CI 47·2–63·8) with and 44·1% (36·3–51·6) without adjuvant temozolomide. Grade 3–4 adverse events were seen in 8–12% of 549 patients assigned temozolomide, and were mainly haematological and reversible.

Interpretation—Adjuvant temozolomide chemotherapy was associated with a significant survival benefit in patients with newly diagnosed non-co-deleted anaplastic glioma. Further analysis of the role of concurrent temozolomide treatment and molecular factors is needed.

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Introduction

Temozolomide combined with radiotherapy in glioblastoma provided significant and clinically meaningful benefit in a pivotal European Organisation for Research and Treatment of Cancer (EORTC) phase 3 trial.[1] In the same study, *MGMT* gene promoter methylation was found to be a biomarker for increased activity of temozolomide.[2] Two trials done simultaneously with the EORTC study, involving patients with anaplastic oligodendroglioma, investigated the use of procarbazine, lomustine, and vincristine (PCV) chemotherapy adjuvant to radiotherapy.[3,4] No survival benefit was found at the time of the first analyses, but the deletion of both the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q), known as 1p/19q co-deletion, was found to be an important prognostic factor. This co-deletion had previously been associated with increased sensitivity to chemotherapy[5] compared with 1p/19q non-co-deleted tumours.

We investigated whether combined radiotherapy and temozolomide chemotherapy would improve outcomes in patients with non-co-deleted anaplastic gliomas, and whether concurrent or adjuvant use of temozolomide would have any effect on survival benefit. We designed a 2 × 2 factorial, randomised trial to enable assessment of four different regimens: radiotherapy with or without concurrent temozolomide and with or without adjuvant temozolomide. Soon after accrual ended, a planned interim analysis was done. The findings led the independent data monitoring committee to release the data on adjuvant temozolomide immediately, which we present in this Article. This work was also presented in part at the American Society of Clinical Oncology meeting, June 2016, in Chicago, IL, USA.

Methods

Study design and participants

The CATNON intergroup trial was done in 137 institutions in 12 countries in Europe (EORTC, Medical Research Council, and NeuroOnkologische Arbeitsgemeinschaft der Deutschen Krebsgesellschaft), Australia (Cooperative trials Group for Neuro-Oncology), and North America (NRG Oncology, Canadian Clinical Trials Group). The trial was a phase 3, randomised, open-label study with a 2 × 2 factorial design. Eligible patients had newly diagnosed anaplastic glioma without 1p/19q co-deletion, were aged 18 years or older, had WHO performance status scores of 0–2 and adequate haematological, renal, and liver function, and were taking stable or decreasing doses of corticosteroids. Previous surgery for low-grade glioma was allowed if an anaplastic tumour had been histologically confirmed at the time of progression. Treatment with other experimental agents was not allowed. Other exclusion criteria are presented in the study protocol. Radiotherapy had to start within 7 weeks of surgery and within 8 days of randomisation.

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.

Tumour assessment

At enrolment, tumour material was submitted for assessment of 1p/19q co-deletion and *MGMT* promoter methylation statuses and review of pathology. 1p/19q co-deletion status was assessed in two central laboratories, one for North American and one for Europe and Australia. After central review of local 1p/19q testing procedures, dedicated and experienced European centres were allowed to do these assessments and pathology reviews. In Europe and Australia, 1p/19q co-deletion status was assessed locally by microsatellite analysis, whereas in North America fluorescent in-situ hybridisation was used.[6,7] *MGMT* promoter methylation status was assessed in two central laboratories with quantitative PCR, as previously described.[8] If methylation status was not available before patients were randomly assigned to treatment, patients were classified as having indeterminate status. For patients from centres that needed central pathology review, the diagnosis of anaplastic glioma had to be confirmed before assessment.

Randomisation

We stratified patients by institution, performance status score (>0 *vs* 0), age (>50 *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 and indeterminate or invalid *vs* unmethylated). The randomisation schedule was generated centrally with the electronic EORTC web-based ORTA system, which was accessed by study physicians via the Internet. Patients were assigned in equal numbers (1:1:1:1), using the minimisation technique, to radiotherapy alone, radiotherapy and concurrent temozolomide, radiotherapy with adjuvant temozolomide, or radiotherapy and concurrent temozolomide plus adjuvant temozolomide.

Treatment

All patients received radiotherapy of 59·4 Gy given in 33 fractions of 1·8 Gy. Whenever possible, target-volume definition was based on co-registered MRI done before or, ideally, after surgery. From 2011 onwards, centres could use intensity-modulated radiotherapy after quality assurance was verified. The radiotherapy gross tumour volume was the entire region of high signal intensity on T2-weighted or fluid attenuation inversion recovery sequence MRI, plus the regions of enhancement and the tumour resection cavity. A margin of 1·5–2·0 cm (edited for anatomical barriers) was added to the gross tumour volume for microscopic spread, plus an additional 0·5–0·7 cm to allow for daily set-up variability. Planning could be done with either three-dimensional conformal radiotherapy or intensity-modulated radiotherapy, and the plan had to conform to the criteria in International Commission on Radiation Units and Measurements reports 50 and 62 for target volume coverage, dose normalisation, and homogeneity.[9,10] When given concurrently with radiotherapy, temozolomide was given daily, including on non-radiotherapy weekend days, at a dose of 75 mg/m^2 for a maximum of 7 weeks. As adjuvant chemotherapy, temozolomide was started 4 weeks after completion of radiotherapy, for a maximum of 12 4-week cycles. Patients received 150 mg/m^2 temozolomide on days 1–5 of the first cycle and 200 mg/m^2 on days 1–5 of subsequent cycles if no or minor toxicity was seen during the first cycle, and dose modifications could made as described elsewhere.[1]

Treatment after disease progression was left to the discretion of the treating physicians, but use of temozolomide was suggested for patients who had been assigned to receive radiotherapy alone. During concomitant chemoradiotherapy, prophylactic treatment against *Pneumocystis jirovecii* was mandatory.

Assessments

Patients were reviewed weekly during radiotherapy, every 4 weeks during adjuvant temozolomide treatment, and every 3 months after the completion of all treatment. Tumours were assessed with MRI at baseline, 4 weeks after the end of radiotherapy and every 3 months thereafter until disease progression. We used the Macdonald criteria[11] for glioblastoma, including steroid dose, with a description of possible pseudoprogression to assess disease progression. For non-enhancing tumours, progression was defined as a 25% increase in tumour area, defined as the product of the two largest perpendicular diameters. Toxicity was scored with the National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0. We used the EORTC QLQ-C30 and QLQ-BN20 questionnaires to assess health-related quality of life[12] at baseline and at all visits when MRI was done. Cognition was also assessed at these timepoints with the Mini-Mental State Examination questionnaire, and then annually after the start of radiotherapy in dedicated centres with a more comprehensive test battery.[13,14] Data on health-related quality of life and cognitive assessments will be reported separately.

Outcomes

The primary endpoint was overall survival adjusted by all stratification factors except institution. The study was intended to answer two questions: whether concurrent temozolomide chemotherapy was associated with improved overall survival compared with

radiotherapy alone, radiotherapy with adjuvant temozolomide, or concurrent chemoradiotherapy with adjuvant temozolomide; and whether adjuvant temozolomide chemotherapy was associated with improved overall survival compared with radiotherapy alone or concurrent radiotherapy and temozolomide. Overall survival was calculated from the date of randomisation to the date of death from any cause.

Secondary endpoints were univariate analysis of overall survival, progression-free survival adjusted for stratification factors, including univariate 5-year overall and progression-free survival and landmark overall and progress-free survival analyses, health-related quality-of-life outcomes, adverse events, and cognitive effects. Progression-free survival was defined as the time from randomisation to the date of first progression or death, whichever was earlier.

For all time-to-event analyses, patients who were still alive and had not met the endpoint at the last follow-up visit were censored.

Statistical analysis

We assumed that median survival would be 24 months in patients receiving radiotherapy only, and that risk reduction would be 0·775 for patients receiving radiotherapy with concurrent and adjuvant temozolomide (two-sided log-rank test). We set an overall significance level of 5%. Therefore, to achieve 83% power to show this difference between groups, we calculated that we would need to assess 523 deaths and that 748 patients would need to be recruited. One interim analysis for efficacy was planned when 219 (41%) deaths had occurred, in which we considered only the rejection of null hypothesis of no efficacy for both trial questions; the nominal significance level for rejecting the null hypothesis was 0·0084. On the basis of the interim analysis, we calculated that 11 additional events would be needed to maintain power in the final analysis (534 instead of 523).

The primary analysis was 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 univariate estimates to calculate the hazard ratios (HRs) and 95% CIs for overall and progression-free survival. In the analyses of overall and progression-free survival adjusted for stratification factors, a Cox proportional hazards model was fitted with a question indicator for each question the trial was intended to answer. We set the CI for this analysis at 99·145%.

We measured relative dose intensity 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 2011, the study protocol was amended to include a prospective analysis of efficacy in relation to tumour *IDH1* and *IDH2* mutation status and to allow use of intensity-modulated radiotherapy.

We did all analyses with SAS version 9.4. This trial is registered with ClinicalTrials.gov, number NCT00626990.

Role of the funding source

The funder had no role in the study design, data collection, analysis, data interpretation, or writing of the report. The corresponding author had access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between Dec 4, 2007, and Sept 19, 2015, 1407 patients were screened and 748 were randomly assigned to treatment groups. In May, 2015, the required number of deaths for the interim analysis was reached. The database was first locked on Aug 31, 2015, for the report to the IDMC, and again for the study report on May 12, 2016. Data are reported here up to May 31, 2015. At that time, 1400 patients had been screened and 745 assigned to treatment (figure 1). The patients' characteristics were well balanced across treatment groups at baseline (table 1). *MGMT* promoter methylation status results were available for 275 (37%) of 745 patients before randomisation and for 550 (74%) at the time of the interim analysis.

All patients were treated according to the group to which they were assigned. Radiotherapy was completed in all but 16 (2%) of 733 patients in whom it was started. 30 (8%) of 373 patients did not start adjuvant temozolomide (figure 1), nine (5%) of the 185 assigned to radiotherapy with adjuvant temozolomide and 21 (11%) of 188 assigned to radiotherapy with concurrent temozolomide plus adjuvant temozolomide. In patients with sufficient treatment information available, the relative dose intensity of temozolomide was more than 90% in 312 (89%) of 349 patients who received temozolomide concurrent with radiotherapy and 92% in the 156 patients who completed adjuvant temozolomide. In 31 (12%) of 262 patients who completed or stopped taking adjuvant temozolomide before the interim analysis, relative dose intensity was less than 70%. 167 (64%) of these 262 patients had at least one cycle delayed, 74 (28%) due to haematological adverse events, 16 (6%) due to non-haematological adverse events, eight (3%) because of both haematological and non-haematological adverse events, and 123 (47%) for reasons not related to treatment.

Treatment was generally well tolerated. 8–12% of 549 patients who were allocated to receive temozolomide had grade 3–4 toxicity, with the most frequent event being thrombocytopenia (7–9%; appendix). Apart from constitutional and gastrointestinal events, most other non-haematological events were judged to be unrelated to treatment. Grade 3 or 4 increases in aminotransferase concentrations occurred in five (1%) of patients who received temozolomide.

The median follow-up was 27 months (95% CI 25–30). Up to May 31, 2015, 344 (46%) patients of 745 had had disease progression and 221 (30%) had died (129 [35%] of 372 in the groups that did not receive adjuvant temozolomide and 92 [25%] of 373 in the groups that did receive adjuvant temozolomide). The HR for overall survival adjusted for stratification factors among patients who received adjuvant temozolomide was 0·65 (99·145% CI 0·45–0·93, table 2). If *MGMT* promoter methylation status that became known after randomisation was included, the HR was 0·65 (0·45–0·93). Age was a highly significant risk factor for survival (table 2). In the univariate analysis, adjuvant temozolomide was associated with improved overall survival (HR 0·67, 95% CI 0·51–0·88),

as was progression-free survival (HR 0·62, 95% CI 0·50–0·76; figure 2). Median and 5-year overall and progression-free survival are presented in table 3.

In the groups not given adjuvant temozolomide chemotherapy, 200 (54%) of 372 patients had disease progression, compared with 144 (39%) of 373 in those who did receive adjuvant chemotherapy. Details for treatment after disease progression were available for 338 patients (appendix). Of these, 303 (90%) received additional treatment, which was chemotherapy in 143 (73%) patients who had not received adjuvant temozolomide and in 89 (62%) who had. The most frequently used chemotherapy was temozolomide and the next most frequently used regimen was PCV (appendix). Bevacizumab was given the 44 (23%) patients in the non-adjuvant treatment groups and 38 (27%) in the adjuvant treatment groups.

Discussion

The planned interim analysis of the CATNON trial showed significant and clinically meaningful benefits for overall and progression-free survival with adjuvant temozolomide in patients with non-co-deleted anaplastic glioma. These findings mandated immediate release of the results. With adjuvant temozolomide, median progression-free survival increased from 19·0 to 42·8 months and 5-year overall survival increased from 44% to 56%. The data do not necessarily imply that concurrent temozolomide has no beneficial effect, but at the time of the interim analysis the survival values did not cross the predefined boundaries. Of note, with 30% of patients having died and 46% having had disease progression by the time of the interim analysis, follow-up is still immature. Nevertheless, the HRs for adjuvant temozolomide were striking and passed the very strict statistical boundaries of the preplanned interim analysis. The survival curves for adjuvant versus no adjuvant temozolomide diverged further with increasing length of follow-up, which suggests that with time overall survival could improve further.

This trial is noteworthy for several reasons. We used molecular criteria to ensure that only patients with 1p/19q non-co-deletion anaplastic glioma were included. We decided to take this approach because patients with 1p/19q non-co-deleted tumours had worse outcomes than patients with 1p/19q co-deletion tumours in the trials of PCV chemotherapy to treat anaplastic oligodendroglioma.[3,4] The addition of temozolomide to radiotherapy, rather than PCV, is also novel for WHO grade II or III glioma.[15–17] With a better toxicity profile than PCV and single-agent nitrosoureas,[18,19] temozolomide has become widely used, and has almost completely replaced the former. Nevertheless, until this trial there were no data from well designed trials to support the activity of temozolomide in the adjuvant setting for treatment of diffuse grade II or III glioma. The pivotal trial of temozolomide involved patients with glioblastoma, which are molecularly different from anaplastic glioma and only rarely show *IDH1* or *IDH2* mutations.[1] Although the patients in the CATNON trial had 1p/19q non-co-deleted anaplastic glioma, which are less chemotherapy sensitive than 1p/19q co-deleted tumours, temozolomide was clearly beneficial. Thirdly, in trials of adjuvant PCV chemotherapy in low-grade glioma and anaplastic oligodendroglioma, long-term follow-up was needed to show an overall survival benefit—survival curves diverged 4–6 years after randomisation—and negative effects were initially reported.[15–17] Strikingly, with adjuvant

temozolomide we saw divergence of the overall survival curves within 1 year of treatment that was sufficiently large to be detected in the interim analysis.

Since we started the CATNON trial, new molecular insights have been reported for glioma. In 2009, mutations in *IDH1* and *IDH2* were reported to occur in 70–80% of all grade II and III diffuse glioma.[20] These mutations are associated with improved outcomes and are now the cornerstone of the WHO 2016 classification of glioma.[21–25] In 2011, we amended our study protocol to incorporate analyses of mutations in *IDH1* and *IDH2* to investigate their predictive value for temozolomide efficacy, for which the analyses are pending. As there are substantial metabolic differences between tumours with and without these mutations, we suggest that future trials should involve only patients with either mutated or wild-type *IDH1* and *IDH2* grade II and III gliomas.

Results from *MGMT* promoter methylation testing were not available for 63% of patients at the time of randomisation, mainly because testing of 1p/19q co-deletion and *MGMT* methylation status could not always be completed in the limited time beforehand. However, when we included results that became available after randomisation, *MGMT* promoter methylation status remained well balanced across groups. We also noted that the percentage of successfully tested tumours showing *MGMT* promoter methylation (42%) was lower than anticipated in a trial of *IDH*-mutated tumours, and was more in the range expected for glioblastoma. This finding might be explained by the PCR technique used, which was optimised for glioblastoma.[8,26] To overcome this technical issue, we will repeat *MGMT* promoter methylation status testing with a genome-wide methylation platform.[27] The presence of *IDH1* and *IDH2* mutations and *MGMT* promoter methylation have both been proposed as predictive factors for benefit from chemotherapy.[28,29] The results of this study, in which we enrolled patients with *IDH1* and *IDH2* mutant and wild-type gliomas, could show differences in prognosis and sensitivity to chemotherapy and will help to identify the best discriminating molecular factor for benefit.

Our interim analysis showed a similar risk reduction in non-co-deleted anaplastic glioma treated with adjuvant temozolomide (HR 0·65) to that achieved with adjuvant PCV in low-grade gliomas (overall HR 0·59 and 0·73 in patients with astrocytoma, which are less likely to have 1p/19q co-deletion).[17] WHO grade II and III diffuse gliomas have similar molecular abnormalities that diverge gradually, making distinction difficult and often judged subjectively. It seems reasonable, therefore, to consider adjuvant temozolomide also for all patients classified as having grade II non-co-deleted diffuse gliomas. Furthermore, four trials have shown clear clinical benefits from adding chemotherapy to radiotherapy (two studies of PCV in anaplastic oligodendroglioma, one of PCV in low-grade glioma, and one of temozolomide in non-co-deleted anaplastic glioma),[15–17] whereas two trials in grade II and III glioma (one of temozolomide *vs* radiotherapy in low-grade glioma and one of PCV or temozolomide *vs* radiotherapy in anaplastic glioma) showed no improved outcome with initial chemotherapy alone compared with initial radiotherapy alone.[30,31] The available data suggest, therefore, that treatment with chemotherapy alone will yield worse overall survival than radiotherapy with adjuvant chemotherapy.

We used 12 cycles of adjuvant temozolomide in this trial, whereas for glioblastoma six cycles of adjuvant temozolomide are recommended.[32] We decided to use 12 cycles to ensure that patients assigned to receive adjuvant chemotherapy without preceding concurrent chemoradiotherapy would have sufficient exposure to temozolomide. The role of concurrent temozolomide remains to be clarified. Concurrent radiotherapy and temozolomide improves outcomes in glioblastoma, but it remains unknown whether both concurrent and adjuvant temozolomide are needed for the improvement of outcomes in this disease.[1] The risk of late neurotoxic effects might be increased by concurrent administration of temozolomide and radiotherapy, which will be especially relevant in patients with favourable prognoses.

In the CATNON trial, 12 cycles of adjuvant temozolomide after radiotherapy significantly improved overall survival in patients with 1p/19q non-co-deleted anaplastic glioma, and should now constitute the standard care for this group of patients. Further follow-up and tissue studies are needed to establish the efficacy of concurrent temozolomide chemotherapy and the effects of molecular signatures on outcome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in context

Evidence before this study

At the time the study started, patients with anaplastic oligodendrogliomas, which were assumed to be responsive to chemotherapy, had no survival benefit when treated with procarbazine, lomustine, and vincristine chemotherapy given after radiotherapy. Additionally, prognosis was much worse in patients with 1p/19q non-co-deleted tumours than in those with 1p/19q co-deleted tumours. In patients with glioblastoma, which was thought to be at least partly chemotherapy resistant, radiotherapy combined with concurrent and adjuvant temozolomide improved outcomes. In these patients, *MGMT* promoter methylation was predictive of benefit with temozolomide, but whether the timing of temozolomide was relevant to improved outcomes remained unclear. We did a randomised, open-label, phase 3 trial to investigate the use of radiotherapy with concurrent and adjuvant temozolomide chemotherapy in adults with non-co-deleted anaplastic glioma.

Added value of this study

In a preplanned interim analysis, we found that radiotherapy plus 12 4-week cycles of adjuvant temozolomide (150–200 mg/m^2 given on days 1–5) improved overall and progression-free survival in patients with 1p/19 non-co-deleted anaplastic glioma.

Implications of all the available evidence

The standard of care for 1p/19q non-co-deleted anaplastic glioma should be surgery followed by radiotherapy and 12 4-week cycles of temozolomide given on days 1–5. Ongoing molecular research within this trial will show whether *IDH1* and *IDH2* mutational status and *MGMT* promoter methylation can be used to identify the patients who will benefit most from temozolomide chemotherapy. Further follow-up will be necessary to understand whether temozolomide given concurrently with radiotherapy also improves survival.

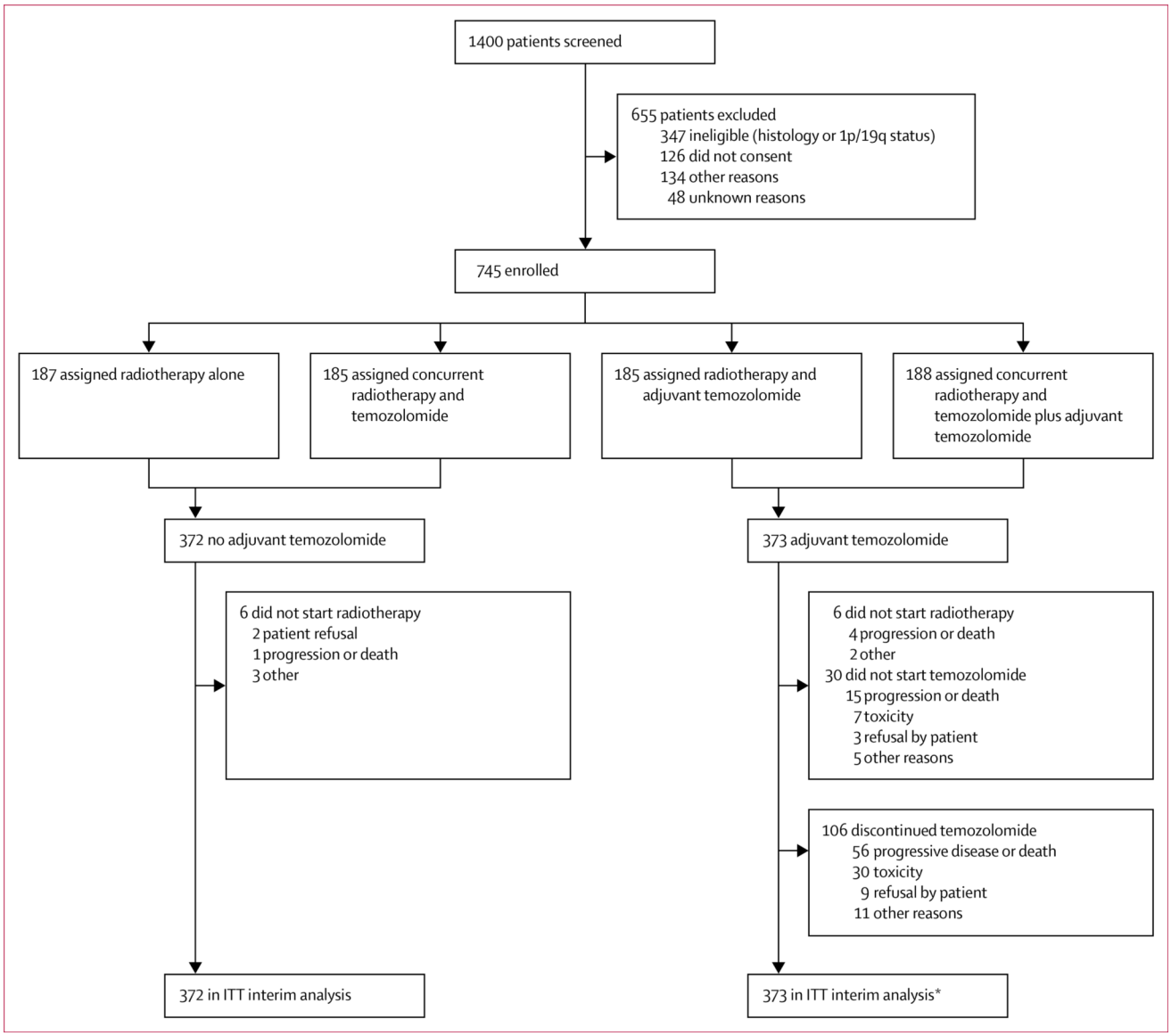

Figure 1. Trial profile for patients included in the interim analysis

TT=intention-to-treat. *51 patients were still receiving temozolomide and 24 had missing data.

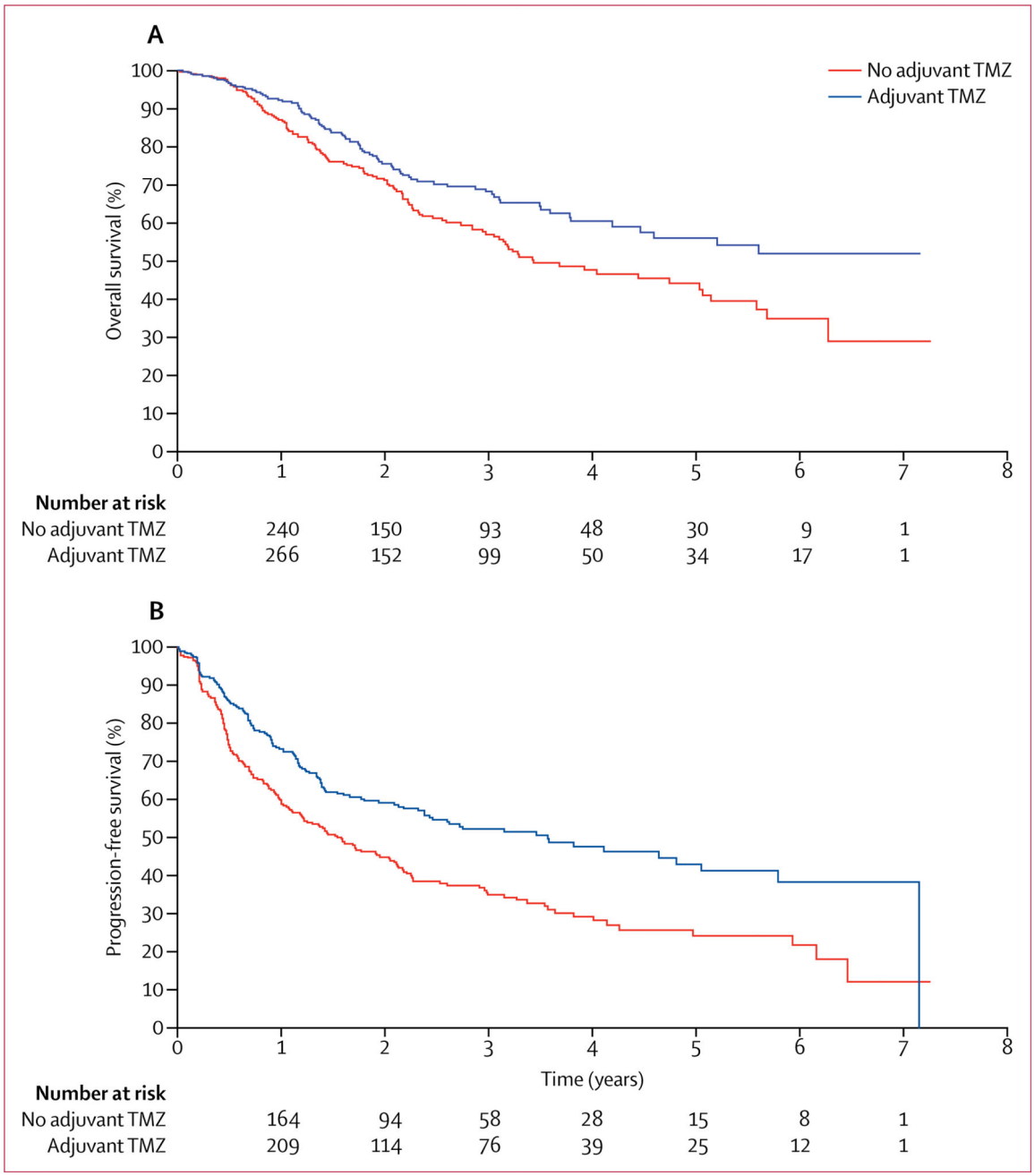

Figure 2. Survival in patients treated with or without adjuvant temozolomide

(A) Overall survival. (B) Progression-free survival. TMZ=temozolomide.

Table 1

Baseline characteristics

	Radiotherapy alone (n=187)	Concurrent radiotherapy and temozolomide (n=185)	Radiotherapy with adjuvant temozolomide (n=185)	Concurrent radiotherapy and temozolomide plus adjuvant temozolomide (n=188)	All patients (n=745)
Age (years)					
Median (range)	42·2 (19·0–81·2)	43·2 (20·1–77·1)	39·9 (20·0–82·3)	42·8 (18·3–80·1)	42·2 (18·3–82·3)
≤50	132 (71%)	124 (67%)	129 (70%)	129 (69%)	514 (69%)
>50	55 (29%)	61 (33%)	56 (30%)	59 (31%)	231 (31%)
Sex					
Male	107 (57%)	116 (63%)	102 (55%)	102 (54%)	427 (57%)
Female	74 (40%)	65 (35%)	79 (43%)	79 (42%)	297 (40%)
Missing	6 (3%)	4 (2%)	4 (2%)	7 (4%)	21 (3%)
Presence of oligodendroglial elements					
Yes	43 (23%)	44 (24%)	42 (23%)	44 (23%)	173 (23%)
No	144 (77%)	141 (76%)	143 (77%)	144 (77%)	572 (77%)
WHO performance status score					
0	110 (59%)	109 (59%)	108 (58%)	112 (60%)	439 (59%)
>0	77 (41%)	76 (41%)	77 (42%)	76 (40%)	306 (41%)
1p loss of heterozygosity					
Yes	14 (8%)	12 (7%)	14 (8%)	13 (7%)	53 (7%)
No	173 (93%)	173 (94%)	171 (92%)	175 (93%)	692 (93%)
MGMT promoter methylation status					
Available before randomization					
Methylated	29 (16%)	27 (15%)	29 (16%)	29 (15%)	114 (15%)
Unmethylated	40 (21%)	40 (22%)	40 (22%)	41 (22%)	161 (22%)
Indeterminate or invalid	118 (63%)	118 (64%)	116 (63%)	118 (63%)	470 (63%)
Available after randomisation					
Methylated	60 (32%)	53 (29%)	66 (36%)	54 (29%)	233 (31%)

	Radiotherapy alone (n=187)	Concurrent radiotherapy and temozolomide (n=185)	Radiotherapy with adjuvant temozolomide (n=185)	Concurrent radiotherapy and temozolomide plus adjuvant temozolomide (n=188)	All patients (n=745)
Unmethylated	80 (43%)	76 (41%)	76 (41%)	85 (45%)	317 (43%)
Indeterminate or invalid	47 (25%)	56 (30%)	43 (23%)	49 (26%)	195 (26%)
Mini-Mental State Examination score					
Median (range)	29 (18–30)	30 (19–30)	30 (5–30)	29 (9–30)	29 (5–30)
<27	25 (13%)	21 (11%)	21 (11%)	24 (13%)	91 (12%)
≥27	138 (74%)	150 (81%)	145 (78%)	146 (78%)	579 (78%)
Missing	24 (13%)	14 (8%)	19 (10%)	18 (10%)	75 (10%)
Taking corticosteroids at study entry					
Yes	49 (26%)	54 (29%)	52 (28%)	58 (31%)	213 (29%)
No	131 (70%)	128 (69%)	128 (69%)	122 (65%)	509 (68%)
Unknown	7 (4%)	3 (2%)	5 (3%)	8 (4%)	23 (3%)
Previous surgery for low-grade tumour					
No	158 (85%)	161 (87%)	160 (87%)	154 (82%)	633 (85%)
Yes	23 (12%)	20 (11%)	21 (11%)	27 (14%)	91 (12%)
Unknown	6 (3%)	4 (2%)	4 (2.2%)	7 (4%)	21 (3%)
Type of surgery					
Biopsy	33 (18%)	41 (22%)	35 (19%)	40 (21%)	149 (20%)
Partial tumour removal	100 (54%)	86 (47%)	89 (48%)	72 (38%)	347 (47%)
Total tumour removal	48 (26%)	54 (29%)	57 (31%)	69 (37%)	228 (31%)

Table 2

Cox proportional hazards model of overall survival in patients receiving adjuvant temozolomide, adjusted by baseline stratification factors

	Hazard ratio (99·145% CI)	p value
Adjuvant temozolomide	0·65 (0·45–0·93)	0·0014
Age (>50 years *vs* ≤50 years)	4·04 (2·78–5·87)	<0·0001
WHO performance status score (>0 *vs* 0)	1·36 (0·94–1·96)	0·0273
1p loss of heterozygosity (yes *vs* no)	1·56 (0·84–2·88)	0·0572
Presence of oligodendroglial elements (yes *vs* no)	1·20 (0·81–1·76)	0·2230
MGMT promotor methylation before randomisation		
Methylated *vs* unmethylated	0·49 (0·26–0·93)	0·0031
Indeterminate or invalid *vs* unmethylated	0·81 (0·54–1·21)	0·1606

Table 3

Median and 5-year overall and progression-free survival

	Overall survival			Progression-free survival		
	Number of deaths	Median (95% CI) survival (months)	5-year survival (95% CI)	Number of patients with disease progression	Median (95% CI) survival (months)	5-year survival (95% CI)
Received adjuvant temozolomide	92	Not reached	55·9% (47·2–63·8)	144	42·8 (28·6–60·6)	43·1% (35·0–50·9)
Did not receive adjuvant temozolomide	129	41·1 (36·6–60·7)	44·1% (36·3–51·6)	200	19·0 (14·4–24·6)	24·3% (17·7–31·6)