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Temozolomide and radiotherapy versus radiotherapy alone in patients with glioblastoma, IDH-wildtype: post-hoc analysis of the EORTC randomized phase 3 CATNON trial

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Contributors

CMST, BGB, TG, PJF, and MJvdB were responsible for the study design. CMST, MS, WW, AAB, PMC, SCE, MAV, AKN, JFB, WPM, HW, OLC, SG, MG, LR, WT, RR, MW, CM, MEvL, KA, RBJ, JMK, PW, AvD, IdH, PNA, HJD, RWWB, WFJvIJ, KJC, VG, BGB, PJF, and MJvdB were responsible for data collection. CMST, IdH, YH, PJF, and MJvdB were responsible for data analysis. CMST, TG, PJF, and MJvdB were responsible for data interpretation. All authors contributed to and approved the final version of the manuscript.

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Abstract

Purpose—In a post-hoc analysis of the CATNON trial (NCT00626990), we explored whether adding temozolomide to radiotherapy improves outcome in patients with *IDH1/2*wt anaplastic astrocytomas with molecular features of glioblastoma (redesignated as glioblastoma, IDH-wildtype in the 2021 WHO classification of CNS tumors).

Experimental Design—From the randomized phase 3 CATNON study examining the addition of adjuvant and concurrent temozolomide to radiotherapy in anaplastic astrocytomas, we selected

a subgroup of *IDH1/2*wt and *H3F3A*wt tumors with presence of *TERT* promoter mutations and/or *EGFR* amplifications and/or combined gain of chromosome 7 and loss of chromosome 10. Molecular abnormalities including *MGMT* promoter methylation status were determined by next-generation sequencing, DNA methylation profiling, and SNaPshot analysis.

Results—Of the 751 patients entered in the CATNON study, 670 had fully molecularly characterized tumors. 159 of these tumors met the WHO 2021 molecular criteria for glioblastoma, IDH-wildtype. Of these patients, 47 received radiotherapy only and 112 received a combination of radiotherapy and temozolomide. There was no added effect of temozolomide on either overall survival (HR 1.19, 95% CI 0.82–1.71) or progression-free survival (HR 0.87, 95% CI 0.61–1.24). *MGMT* promoter methylation was prognostic for overall survival, but was not predictive for outcome to temozolomide treatment either with respect to overall survival or progression-free survival.

Conclusions—In this cohort of patients with glioblastoma, IDH-wildtype temozolomide treatment did not add benefit beyond that observed from radiotherapy, regardless of *MGMT* promoter status. These findings require a new well-powered prospective clinical study to explore the efficacy of temozolomide treatment in this patient population.

Keywords

IDH-wildtype; anaplastic astrocytoma; glioblastoma; temozolomide; *MGMT*; radiotherapy; IDH1; IDH2

Introduction

The benefit of the addition of temozolomide to radiotherapy in people with newly diagnosed glioblastoma was first demonstrated in 2005 in the pivotal EORTC 26981/22981-NCIC CE3 randomized clinical trial.[1] The efficacy of temozolomide in combination with radiotherapy was confirmed in a study on elderly patients with glioblastoma.[2] In both studies, the clinical benefit of temozolomide treatment was largely confined to patients with glioblastomas with a methylated O^6-methylguanine DNA methyltransferase (*MGMT*) promoter.[2,3] In other clinical trials, a survival benefit of single agent treatment with temozolomide was demonstrated in patients with *MGMT*-promoter methylated high-grade gliomas.[4–6] In the CATNON trial, the efficacy of the addition of temozolomide during and after radiotherapy was investigated in patients with grade 3 astrocytoma. In the recently published 2nd interim analysis of the study, the benefit of temozolomide was found to be restricted to patients with astrocytoma grade 3 with isocitrate dehydrogenase 1 and 2 (*IDH1/2*) mutations (mt), and only for adjuvant temozolomide treatment.[7] There was no clinical benefit of temozolomide in patients with *IDH1/2* wildtype (wt) gliomas regardless of *MGMT* promoter status.[7] However, *IDH1/2*wt gliomas are not a single entity, and molecular subtyping of grade 2 and 3 *IDH1/2*wt gliomas has identified prognostically significant patient subgroups.[8–10] In particular a major subgroup of grade 2 and 3 *IDH1/2*wt glioma has emerged with molecular features of glioblastoma. These are characterized by either (i) a mutation of the telomerase reverse transcriptase promoter (p*TERT*), and/or (ii) paired chromosome 7 trisomy and loss of heterozygosity of chromosome 10 (*7+/10−* signature), and/or (iii) amplification of epidermal growth factor receptor (*EGFR*amp).[11–13] With outcomes resembling those

of glioblastoma, the 2021 world health organization (WHO) classification of central nervous system (CNS) tumors now labels these tumors as glioblastoma, IDH-wildtype and consequently most guidelines recommend to treat them with radiotherapy and both concurrent and adjuvant temozolomide.[14] However, the benefit of adding temozolomide to radiation therapy has not been proven in patients with tumors meeting the molecular criteria of glioblastoma, IDH-wildtype but not the histological criteria.

The randomized CATNON trial (NCT00626990) with a control arm of radiotherapy alone allows the retrospective analyses of the effect of adjuvant and concurrent temozolomide in patients with histologically grade 3 astrocytomas with molecular features of glioblastoma (in the WHO 2021 classified as glioblastoma, IDH-wildtype), also in relation to the *MGMT* promoter methylation status.

Materials and Methods

Patient Population

Patients with tumors meeting the molecular criteria for glioblastoma, IDH-wildtype were identified in the European Organization for Research and Treatment of Cancer (EORTC), non-blinded, multicenter, randomized CATNON trial. This trial examined the effect of concurrent and adjuvant temozolomide given in addition to radiotherapy in adult patients with a diagnosis of primary 1p/19q non-codeleted anaplastic glioma (n=751) according to the 2007 WHO classification of CNS tumors.[7] Patient randomization (1:1:1:1) was based on a 2×2 factorial design; after primary surgery patients were treated with radiotherapy (59.4 Gy in 33 fractions of 1.8 Gy) without any temozolomide, or radiotherapy with concurrent temozolomide (75 mg/m^2 daily, max 7 weeks), or radiotherapy with adjuvant temozolomide (12 4-week cycles: 150–200 mg/m^2 on day 1–5), or radiotherapy with concurrent and adjuvant temozolomide. Patients were stratified based on *MGMT* promoter status as determined by quantitative methylation-specific PCR. The collection of formalin-fixed paraffin-embedded (FFPE) tumor material was part of the study design. All institutions obtained ethics approval from their institutional review boards or ethics review committees before enrollment started. All patients gave written informed consent according to local, national, and international guidelines.

Procedures

DNA was isolated from FFPE tumor material.[15] For samples with ≥60 ng DNA available, the DNA methylation and sequencing data were produced and reported in a previous study.[16] In short, *IDH1/2*, and *H3F3A* mutation status were determined by a standard glioma-tailored next-generation sequencing (NGS) panel.[17] Mutation status of p*TERT* was determined with a SNaPshot assay of the two hotspot mutations in gliomas (C228T and C250T).[18] DNA methylation profiles were acquired with the Infinium MethylationEPIC BeadChip (Illumina, San Diego, CA, USA) according to the manufacturer's instructions after using the Infinium FFPE DNA Restoration Kit. Copy number data (presence of *EGFR*amp, and the *7+/10-* signature) were derived and interpreted from the DNA methylation data as previously described.[16] *MGMT* promoter status was assessed from the DNA methylation data with the *MGMT*-STP27 algorithm.[19] For samples with <60 ng

DNA available, DNA methylation profiling and the standard NGS panel could not both be performed. Instead, *IDH1/2*, *H3F3A*, and p*TERT* mutation status, and copy number data were determined by an in-house developed NGS panel requiring less DNA for successful analysis.[20,21] Two dedicated neuropathologists centrally reviewed all tumor samples (JMK: European and Australian samples, KA: North-American samples). Clinical data such as survival data, sex, age at enrollment, use of corticosteroids at enrollment, type of surgery, mini-mental state examination (MMSE) score at enrollment, and treatment regimen were collected from the study entry forms.

Statistical analysis

For the analyses, the temozolomide treatment arms were combined into several larger cohorts. The 'temozolomide and radiotherapy' cohort is comprised of the concurrent arm, the adjuvant arm, and the concurrent/adjuvant arm. The 'adjuvant temozolomide' cohort consists of the adjuvant arm and the concurrent/adjuvant arm. The 'no adjuvant temozolomide' cohort consists of the concurrent arm and the radiotherapy only arm. The 'concurrent temozolomide' cohort consists of the concurrent arm and the concurrent/adjuvant arm. The 'no concurrent temozolomide' cohort consists of the adjuvant arm and the radiotherapy only arm. The primary endpoint of overall survival and the secondary endpoint of progression-free survival were measured from the date of randomization until the date of event (death or death/progression respectively) or censored at the date of last follow-up. Survival curves were created using the Kaplan-Meier technique and compared with the log-rank test. The Cox regression model was used for univariable and multivariable analysis to determine hazard ratios (HR) with 95% confidence intervals (CI). Significance was set at p-values below 0.05 unless otherwise specified. Statistical analysis was performed using R version 3.6.3 and packages minfi, and survival.

Results

Cohort distribution

We identified 202 patients with *IDH1/2*wt and *H3F3A*wt astrocytomas grade 3 from the 751 patients with astrocytomas grade 3 enrolled in the CATNON study (standard NGS panel: n=194, in-house NGS panel: n=8). The tumors of 159 patients fulfilled the molecular characteristics of glioblastoma, IDH-wildtype i.e. presence of *EGFR*amp, and/or p*TERT*mt, and/or the *7+/10-* signature (*EGFR*amp: n=83, p*TERT*mt: n=144, *7+/10-* signature: n=105, Appendix Table A1). Of this patient cohort, 47 (29.6%) patients received radiotherapy alone and 112 (70.4%) patients received radiotherapy with adjuvant and/or concurrent temozolomide. These data are summarized in Figure 1.

Baseline characteristics

Table 1 illustrates the baseline characteristics of the temozolomide and radiotherapy cohort, and the patient cohort treated with radiotherapy only. No significant differences were found between the two cohorts based on age, sex, type surgery, corticosteroid use, WHO performance score, MMSE score, and presence of necrosis and/or microvascular proliferation. There was a trend towards more tumors with unmethylated *MGMT* promoter in the temozolomide and radiotherapy cohort (p=0.066).

Survival analysis

At the time of database lock (May 7th, 2019), 143 out of 159 patients (89.9%) with tumors meeting the criteria of glioblastoma, IDH-wildtype, were deceased, and in 154 patients (96.9%) progression of disease was reported. The median overall survival of this patient cohort was 1.4 years (95% CI 1.3–1.8 years, Appendix Figure A1A) and the median progression-free survival was 0.5 years (95% CI 0.5–0.7 years, Appendix Figure A1B). In this cohort of patients, there was no added effect of temozolomide in relation to radiotherapy alone on either overall survival (HR 1.19, 95% CI 0.82–1.71, Figure 2A), or progression-free survival (HR 0.87, 95% CI 0.61–1.24, Figure 2B). This lack of effect in overall and progression-free survival was not associated with the timing of the temozolomide treatment i.e. concurrent, adjuvant, or both concurrent and adjuvant temozolomide. Neither the adjuvant temozolomide nor the concurrent temozolomide was associated with clinical benefit in this cohort of patients. Moreover, no significant differences in overall survival or progression-free survival were found between the radiotherapy alone treatment arm and the radiotherapy with both concurrent and adjuvant temozolomide treatment arm (Appendix Figure A2).

MGMT promoter methylation status and survival

For 152 of the 159 patients in this cohort, tumor DNA methylation data were available allowing the determination of the *MGMT* promoter methylation status by the *MGMT*-STP27 algorithm. Of these, 53 (34.9%) of tumors were *MGMT*-methylated, and the remaining 99 tumors (65.1%) were *MGMT*-unmethylated. Patients with *MGMT*-methylated tumors had superior overall survival (HR 0.65, 95% CI 0.45–0.92, Figure 3A); the median overall survival for the cohort with *MGMT*-methylated tumors was 1.8 years (95% CI 1.4–2.2 years), and for the cohort with *MGMT*-unmethylated tumors was 1.4 years (95% CI 1.2–1.6 years). *MGMT* promoter methylation was not prognostic for progression-free survival (HR 0.95, 95% CI 0.68–1.34, Appendix Figure A3A) with a median progression-free survival of 0.5 years for both the cohort with *MGMT*-methylated tumors (95% CI 0.4–0.8 years), and the cohort with *MGMT*-unmethylated tumors (95% CI 0.5–0.7 years). No survival benefit was detected for temozolomide in addition to radiotherapy on overall survival in either the cohort with *MGMT*-methylated tumors (HR 1.36, 95% CI 0.75–2.48, Figure 3B), or the cohort with *MGMT*-unmethylated tumors (HR 0.88, 95% CI 0.54–1.42, Figure 3C). Similarly, no predictive effect for temozolomide efficacy was identified on progression-free survival in patients with *MGMT*-methylated and *MGMT*-unmethylated tumors (Appendix Figure A3B–C). The lack of predictive effect of *MGMT* promoter methylation extended to overall survival and progression-free survival and to each temozolomide cohort i.e. in none of the three temozolomide arms a clinical benefit was observed (Appendix Figure A4).

Multivariable analysis

To correct for possible confounding factors, we selected all available factors from univariable analyses with likelihood ratio test p values ≤ 0.10. For overall survival, these factors included age group (<50 years vs. ≥50 years), MMSE score (≤26 vs. 27–30), type of surgery (biopsy vs. resection), use of corticosteroids at randomization (yes vs.

no), and *MGMT* promoter status (methylated vs. unmethylated) (Appendix Table A2). For progression-free survival, the significant factors included age group, type of surgery, and use of corticosteroids at randomization (Appendix Table A3). Lack of clinical benefit of temozolomide was still apparent after correction for these factors in this cohort of patients on overall survival (temozolomide and radiotherapy vs. radiotherapy only: HR 1.03, 95% CI 0.69–1.53, Table 2), and in progression-free survival (HR 0.79, 95% CI 0.55–1.13, Appendix Table A4).

Tumors with *TERT* promoter mutations only

Twenty-nine of the 159 patients with tumors meeting the criteria of glioblastoma, IDH-wildtype (18.2%) had a mutation of p*TERT*, and were negative for *EGFR*amp and the *7+/10-* signature (p*TERT*mt only). Although this cohort is limited in size, we examined this subgroup in more detail. Patients with p*TERT*mt only tumors did not differ from other patients with tumors meeting the criteria of glioblastoma, IDH-wildtype with respect to overall survival (median overall survival p*TERT*mt only 1.4 years vs other glioblastoma, IDH-wildtype 1.4 years, HR 0.78, 95% CI 0.50–1.21, Appendix Figure A5A), or in progression-free survival (median progression-free survival p*TERT*mt only 0.6 years vs other glioblastoma, IDH-wildtype 0.5 years, HR 0.79, 95% CI 0.52–1.19, Appendix Figure A5B). We also failed to identify a beneficial effect of temozolomide in the patient cohort with p*TERT*mt only tumors on either overall survival or progression-free survival, though this analysis is based on few patients (radiotherapy only: n=9, temozolomide and radiotherapy: n=20, Appendix Figure A5C–D).

Histological features

As per study protocol, all samples included in the CATNON trial were diagnosed as an astrocytoma grade 3 by at least one central dedicated neuropathologist according to the 2007 WHO classification of CNS tumors. Therefore, all glioblastoma, IDH-wildtype analyzed in the current study were also diagnosed as such. Despite the strict histological criteria, subtle signs of necrosis and/or microvascular proliferation were reported at central histology review in 28 tumor samples (necrosis only: n=4, microvascular proliferation only: n=14, both necrosis and microvascular proliferation: n=10) which are considered histological features of glioblastoma but did not lead to exclusion from the study. Presence of these histological features of glioblastoma in the patients with molecularly defined glioblastoma, IDH-wildtype was associated with shorter overall survival (HR 1.62, 95% CI 1.06–2.48, Appendix Figure A6A), but no significant difference was found in progression-free survival (HR 1.46, 95% CI 0.96–2.22, Appendix Figure A6B). After adjustment for significant factors from univariable analysis including histological factors for glioblastoma, futility of temozolomide treatment remained for this cohort of patients with glioblastoma, IDH-wildtype in overall survival (HR 0.90, 95% CI 0.60–1.35, Appendix Table A5), and progression-free survival (HR 0.79, 95% CI 0.55–1.14, Appendix Table A6).

Discussion

This is the first dataset investigating temozolomide treatment efficacy in patients with *IDH1/2*wt astrocytomas grade 3 with molecular features of glioblastoma treated in a

randomized clinical trial with a control arm of radiotherapy only. Of 202 *IDH1/2*wt and *H3F3A*wt tumors present in the CATNON trial, 159 tumors fulfilled the WHO 2021 molecular criteria of glioblastoma, IDH-wildtype.[14] We did not observe benefit of the addition of temozolomide to radiotherapy in this cohort of patients, neither for overall nor progression-free survival. Similarly, no benefit of temozolomide was observed in the subgroup of patients with tumors harboring a methylated *MGMT* promoter. Moreover, the timing of the temozolomide treatment (concurrent, adjuvant or both) was not related to survival outcome.

Our data conflict with the results from earlier randomized clinical trials examining the efficacy of temozolomide in combination with radiotherapy in glioblastoma.[1,2] The study by Stupp et al. showed efficacy of concurrent temozolomide followed by 6 cycles of adjuvant temozolomide.[1] However, during enrollment and primary analysis of this trial the role of *IDH1/2* in glioma had not yet been described. The exact percentage of patients with *IDH1/2*mt tumors in that study is unspecified, although in a later subgroup analysis of 160 tumor samples only 8% had an *IDH1* mutation.[22] In the study by Perry et al. on elderly patients with glioblastoma, the percentage of patients with *IDH1/2*mt tumors is described, comprising less than 1% of patients.[2] Intriguingly, there is a possibility that age-based selection could have had an effect on outcome in this study; patients younger than 70 years had no survival benefit of additional temozolomide in combination with radiotherapy, whereas patients older than 70 years did show a prolonged survival due to temozolomide treatment.[2] Thus, the results we find from the CATNON trial might not be as easily comparable to these previous studies due to a younger patient population in our study and a well-documented molecular subtyping of the tumors of the investigated patients.

With the possible exception of 28 samples with subtle signs of necrosis and/or microvascular proliferation, we prognosticated patients solely on molecular data. For patients with an *IDH1/2*wt lower-grade glioma, both *EGFR*amp and the *7+/10-* signature are now indicators of a grade 4 diagnosis on their own.[9,23,24] Conversely, cohorts of patients with p*TERT*mt only tumors have been described with variable patient outcome.[13,23,25] In our cohort, we did not observe a difference in overall survival or progression-free survival between patients with p*TERT*mt only tumors and patients with the typical glioblastoma, IDH-wildtype. However, the number of patients with IDH-wildtype, p*TERT*mt only tumors was limited, and we emphasize the importance of excluding other p*TERT*mt tumor diagnoses (e.g. 1p/19q codeleted tumors, pleomorphic xanthoastrocytomas) when performing similar analyses, or when setting up prospective trials.[12] It is also important to note, that the CATNON trial only included patients with a grade 3 tumor, and it remains to be determined if patients with p*TERT*mt only tumors, grade 2 have a comparable prognosis.[25]

The major limitations of this study are the modest sample size, and the post-hoc design. The CATNON trial was not specifically powered to answer the clinical questions of the present study; the lack of predictive effect in this post-hoc study of a subset of tumors now meeting the criteria for glioblastoma, IDH-wildtype and the lack of impact of *MGMT* promoter methylation on overall survival could be due to the limited small sample size. However, a recent randomized study in 37 patients with grade 2 or 3 IDH-wildtype glioma showing *TERT* promoter mutations did observe a survival benefit of the addition of temozolomide to

radiotherapy.[26] Despite the mentioned limitations of our study, we extracted a 159-patient cohort by clearly defined and now official diagnostic criteria from the entire CATNON dataset without an indication of temozolomide efficacy. At the minimum, our study therefore questions whether the addition of temozolomide treatment to radiotherapy is beneficial for patients with molecularly defined glioblastoma, IDH-wildtype.

In short, we found no effect of adjuvant and concurrent temozolomide treatment in patients with anaplastic astrocytomas now meeting the molecular criteria for glioblastoma, IDH-wildtype, regardless of *MGMT* promoter status. At present, these findings are insufficient to warrant a change in the management of these patients; i.e. given the outcome of other studies we believe these patients should be offered radiotherapy in combination with temozolomide chemotherapy. However, these findings do warrant a well-powered prospective study on the effectiveness of temozolomide when added to radiotherapy in tumors meeting the contemporary WHO 2021 molecular criteria for glioblastoma, IDH-wildtype. The choice for a trial design will depend on whether the trial should demonstrate that adding temozolomide will improve patient outcome as compared to radiotherapy alone, or whether it should demonstrate that temozolomide can safely be left out.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declarations of interest

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Translational relevance

The practice changing randomized phase III CATNON trial has established the role for adjuvant temozolomide in patients with IDH-mutant astrocytoma, grade 3. In this study on the efficacy of temozolomide in anaplastic glioma without 1p/19q codeletion, patients were also included with tumors that are redesignated as IDH-wildtype glioblastomas by the 2021 WHO classification of CNS tumors. In this manuscript, we describe an absence of clinical benefit of temozolomide treatment in the IDH-wildtype glioblastoma patient population. Moreover, this lack of clinical benefit is not related to *MGMT* promoter methylation status, or timing of the temozolomide treatment i.e. concurrent, adjuvant, or both concurrent and adjuvant temozolomide. Our data raise important questions about the current treatment for IDH-wildtype glioblastoma patients. A new well-powered prospective clinical study is required to explore the efficacy of temozolomide treatment in patient with histological anaplastic astrocytoma that meet the molecular criteria for IDH-wildtype glioblastoma.

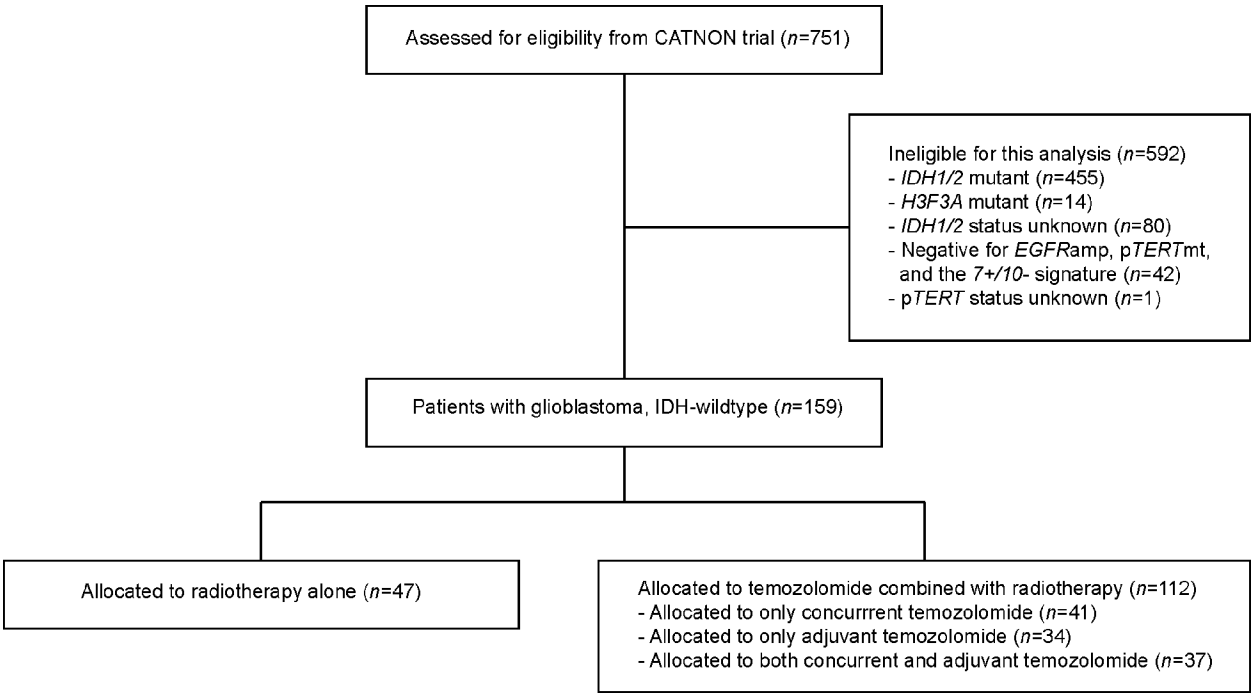
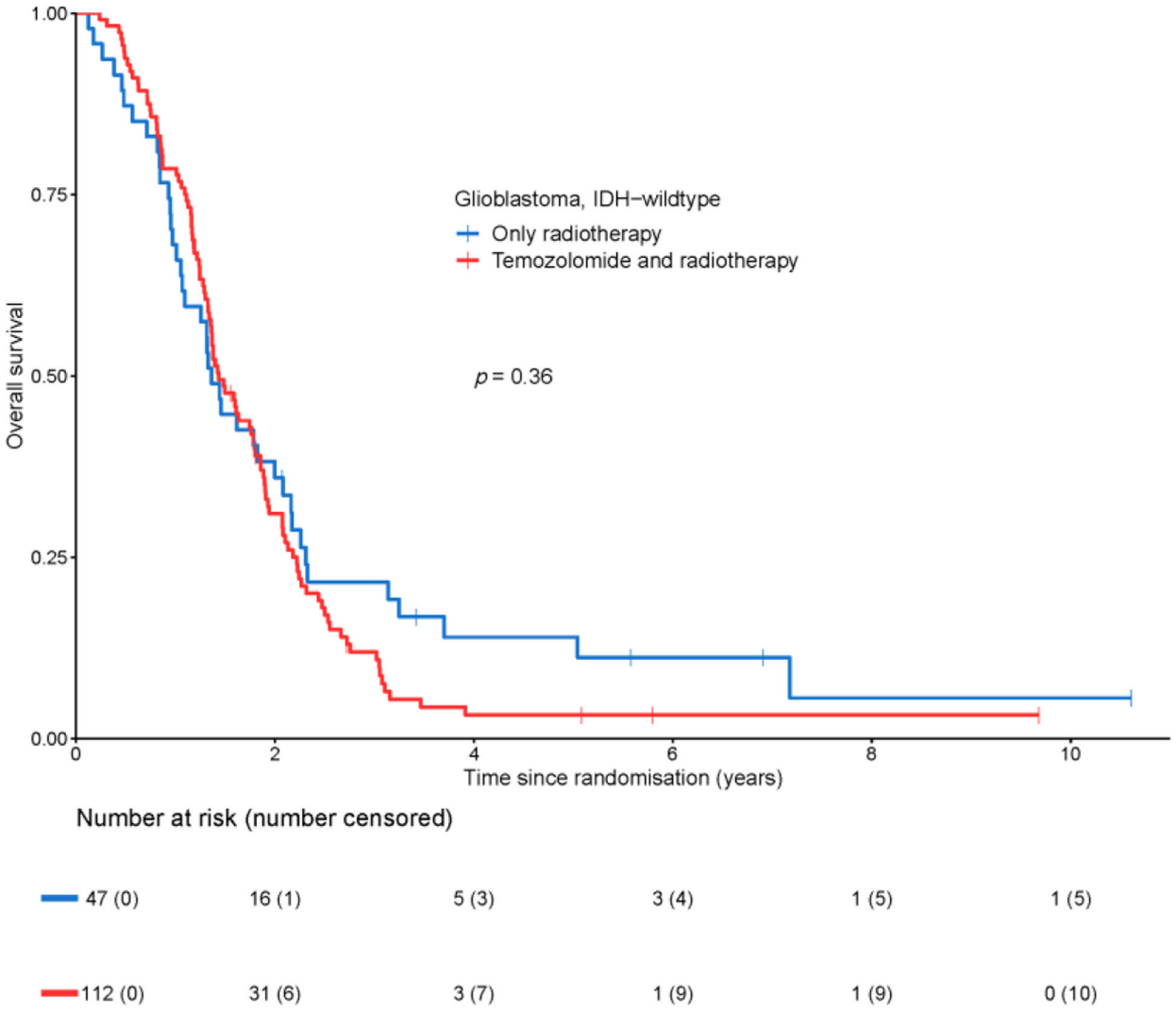


Figure 1.
Consort diagram.

A: Overall survival.



Number at risk (number censored)

Only radiotherapy	47 (0)	16 (1)	5 (3)	3 (4)	1 (5)	1 (5)
Temozolomide and radiotherapy	112 (0)	31 (6)	3 (7)	1 (9)	1 (9)	0 (10)

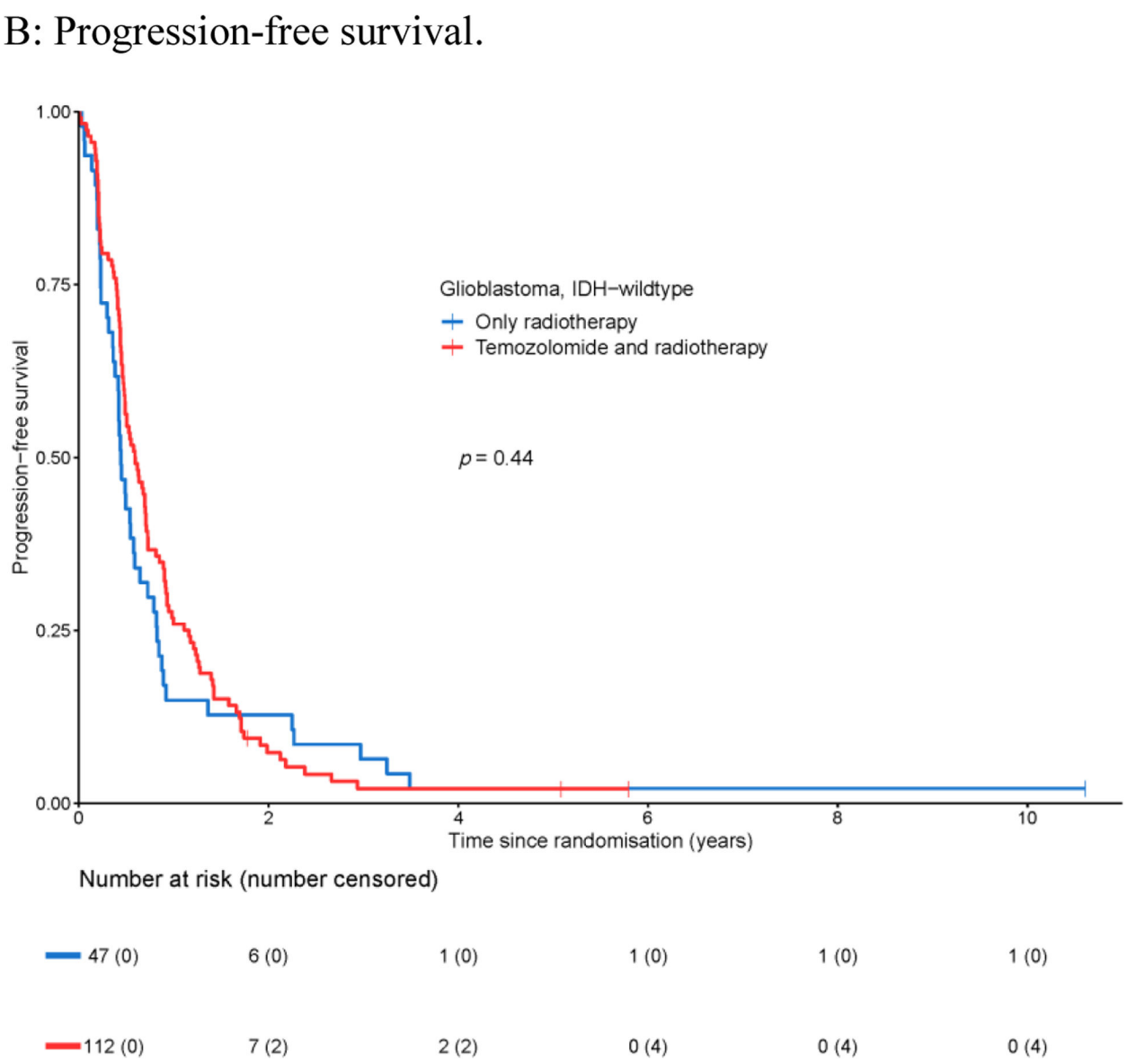
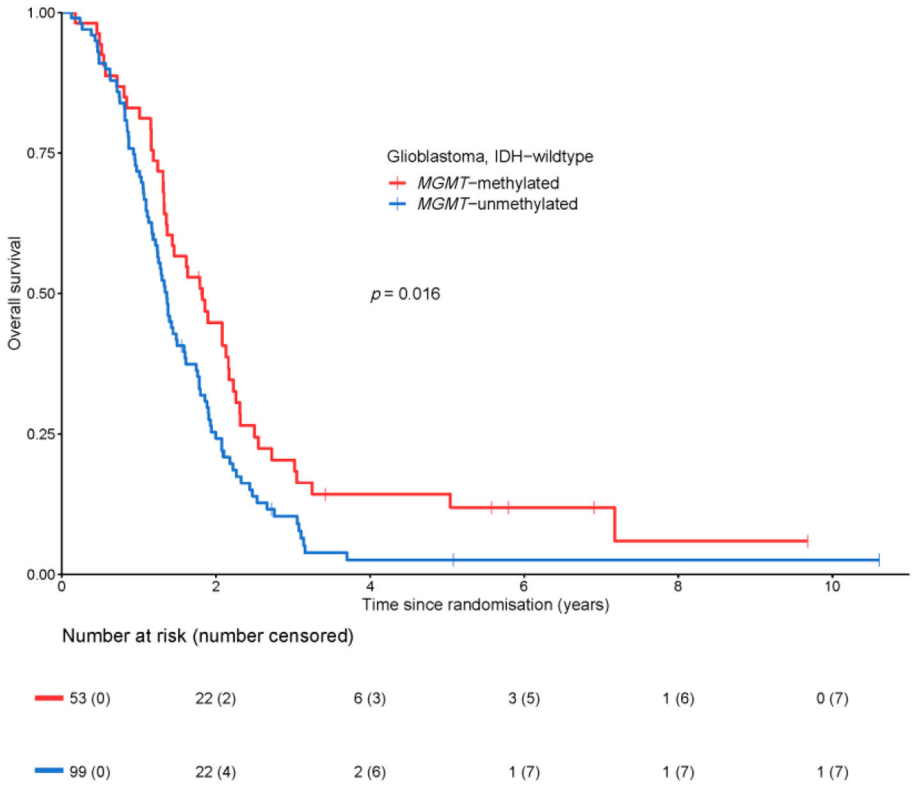
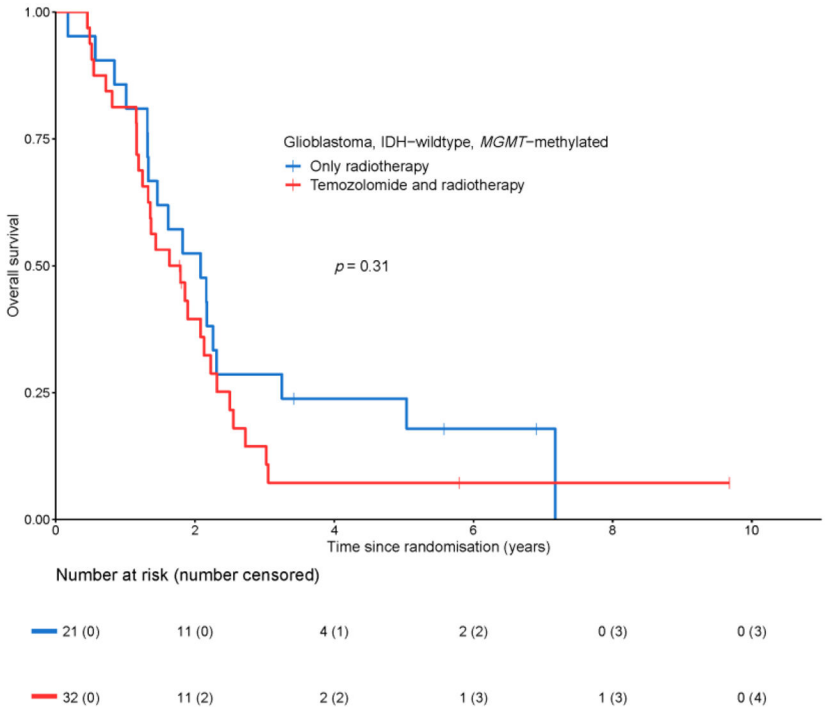


Figure 2.
Survival of patients with glioblastoma, IDH-wildtype with respect to treatment regimen: temozolomide and radiotherapy vs. only radiotherapy.

A: Patients with glioblastoma, IDH-wildtype: *MGMT*-methylated vs. *MGMT*-unmethylated.



B: Patients with glioblastoma, IDH-wildtype, *MGMT*-methylated: temozolomide and radiotherapy vs. only radiotherapy.



C: Patients with glioblastoma, IDH-wildtype, *MGMT*-unmethylated: temozolomide and radiotherapy vs. only radiotherapy.

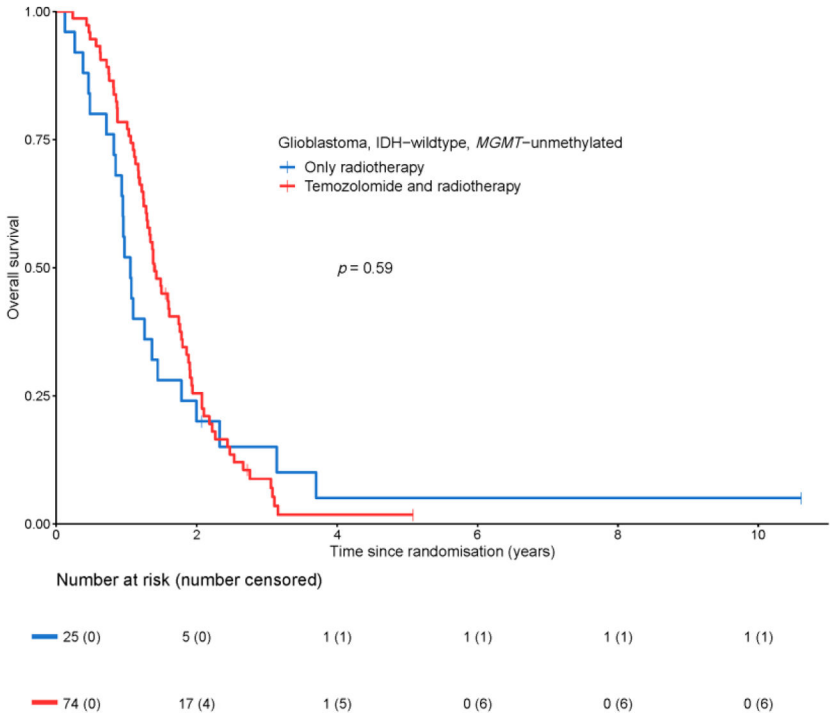


Figure 3.
Overall survival with respect to *MGMT* promoter methylation.

Table 1.

Baseline characteristics of the 159 patients with glioblastoma, IDH-wildtype of the CATNON trial. P values compare patients that received only radiotherapy (*n*=47) with patients that received radiotherapy with concurrent and/or adjuvant temozolomide (*n*=112).

Characteristics	Radiotherapy only (*n*=47)	Temozolomide and radiotherapy (*n*=112)	p value
Age			>0.9[a]
Median	55	55	
IQR	46–67	48–63	
Sex			0.4[b]
Female	19 (40%)	37 (33%)	
Male	28 (60%)	75 (67%)	
WHO performance score			0.2[b]
0	28 (60%)	53 (47%)	
≥1	19 (40%)	59 (53%)	
MMSE score			0.2[b]
27–30	32 (68%)	90 (80%)	
≤26	11 (23%)	17 (15%)	
Unknown	4 (9%)	5 (4%)	
Type of surgery			0.6[b]
Resection	35 (74%)	79 (71%)	
Biopsy	12 (26%)	33 (29%)	
Corticosteroid use			0.6[b]
No use	33 (70%)	74 (66%)	
Stable/decreasing dose	14 (30%)	38 (34%)	
MGMT promoter			0.066[b]
Unmethylated	25 (53%)	74 (66%)	
Methylated	21 (45%)	32 (29%)	
Unknown	1 (2%)	6 (5%)	
Necrosis and/or microvascular proliferation			0.5[b]
Absent	36 (77%)	90 (80%)	
Present	10 (21%)	18 (16%)	
Unknown	1 (2%)	4 (4%)	

[a] Wilcoxon rank sum test.

[b] Pearson's Chi-squared test. IQR = interquartile range. WHO = World Health Organization. MMSE = mini-mental state examination.

Table 2.

Multivariable analysis for overall survival of 143 patients with glioblastoma, IDH-wildtype (16 patients excluded due to missing data) by Cox proportional hazards model. The effect of the treatment regimen is adjusted for significant covariables (univariable analysis p <0.10) excluding histological factors.

Variables	***n***	**HR (95%CI)**	**p value**[a]
Treatment regimen			0.57
Temozolomide and radiotherapy vs. radiotherapy only	101 vs. 42	0.89 (0.60–1.33)	
Age group			0.009
≥50 years vs. <50 years	101 vs. 42	1.75 (1.15–2.67)	
MMSE score			0.22
≤26 vs. 27–30	27 vs. 116	1.33 (0.84–2.38)	
Type of surgery			0.095
Biopsy vs. resection	42 vs. 101	1.40 (0.94–2.07)	
Corticosteroid use			0.019
Stable/decreasing dose vs. no use	47 vs. 96	1.61 (1.08–2.38)	
MGMT promoter			0.14
Methylated vs. unmethylated	50 vs. 93	0.75 (0.52–1.10)	

[a]Wald test. HR = hazard ratio. CI = confidence interval. MMSE = mini-mental state examination.