

# Concurrent and Adjuvant Temozolomide for Newly Diagnosed Grade III Gliomas without 1p/19q Co-deletion: A Randomized, Open-Label, Phase 2 Study (KNOG-1101 Study)

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## Purpose

We investigated the efficacy of temozolomide during and after radiotherapy in Korean adults with anaplastic gliomas without 1p/19q co-deletion.

## Materials and Methods

This was a randomized, open-label, phase 2 study and notably the first multicenter trial for Korean grade III glioma patients. Eligible patients were aged 18 years or older and had newly diagnosed non-co-deleted anaplastic glioma with an Eastern Cooperative Oncology Group performance status of 0-2. Patients were randomized 1:1 to receive radiotherapy alone (60 Gy in 30 fractions of 2 Gy) (control group, n=44) or to receive radiotherapy with concurrent temozolomide (75 mg/m<sup>2</sup>/day) followed by adjuvant temozolomide (150-200 mg/m<sup>2</sup>/day for 5 days during six 28-day cycles) (treatment group, n=40). The primary endpoint was 2-year progression-free survival (PFS). Seventy patients (83.3%) were available for the analysis of the isocitrate dehydrogenase 1 gene (*IDH1*) mutation status.

## Results

The two-year PFS was 42.2% in the treatment group and 37.2% in the control group. Overall survival (OS) did not reach to significant difference between the groups. In multivariable analysis, age was a significant risk factor for PFS (hazard ratio [HR], 2.08; 95% confidence interval [CI], 1.04 to 4.16). The *IDH1* mutation was the only significant prognostic factor for PFS (HR, 0.28; 95% CI, 0.13 to 0.59) and OS (HR, 0.19; 95% CI, 0.07 to 0.50). Adverse events over grade 3 were seen in 16 patients (40.0%) in the treatment group and were reversible.

## Conclusion

Concurrent and adjuvant temozolomide in Korean adults with newly diagnosed non-co-deleted anaplastic gliomas showed improved 2-year PFS. The survival benefit of this regimen needs further analysis with long-term follow-up at least more than 10 years.

## Key words

Anaplastic glioma, 1p/19q co-deletion, Temozolomide, Chemotherapy, Adjuvant treatment

## Introduction

Anaplastic (i.e., World Health Organization [WHO] grade III) gliomas account for approximately 20% of adult gliomas [1]. While surgery and radiotherapy may prolong life, prognosis remains dismal, with a median survival of 2-5 years [2-4]. To date, despite inconclusive data, there has been growing evidence of improved survival that the addition of nitrosourea-based chemotherapy to radiotherapy could be beneficial for patients with WHO grade III gliomas [5]. In particular, adjuvant chemotherapy may be effective in 1p/19q co-deleted anaplastic oligodendrogliomas [6,7]. Two large randomized phase III trials of radiotherapy with or without adjuvant procarbazine, lomustine, and vincristine (PCV) demonstrated significant improvement in the progression-free survival (PFS) and near doubling of the overall survival (OS) to greater than 14 years in 1p/19q co-deleted tumors treated with adjuvant radiotherapy and PCV [6,7]. However, patients with 1p/19q non-co-deleted tumors may experience worse prognosis and faster tumor growth, requiring further attention. Although some studies suggested that 1p/19q non-co-deleted tumors benefited from early chemotherapy, optimal indications, dosing regimens, or survival analyses remain controversial [1]. Therefore, we focused on these conditions and analyses and on how the CATNON trial was distinguishable from other studies [8].

Separately, the role of chemotherapy for gliomas has been reappraised with the development of temozolomide, and clear benefits were found when temozolomide was added to radiotherapy to treat newly diagnosed glioblastomas [9]. Further investigation is now being directed toward unveiling its optimal indications, leading researchers to explore whether radiation plus temozolomide would benefit patients with anaplastic gliomas. Some of our authors have investigated the potential survival benefit and safety of concurrent chemoradiotherapy (CCRT) with temozolomide followed by adjuvant temozolomide for WHO grade III gliomas [10,11]. In these studies, however, the role of molecular markers, such as chromosome 1p/19q co-deletion or O<sup>6</sup>-methylguanine-DNA methyltransferase (MGMT) promoter methylation, could not be determined because of the small sample size. These results prompted the authors to conduct a multi-institutional trial.

We investigated the efficacy of temozolomide during and after radiotherapy in Korean adult patients with newly diagnosed WHO grade III gliomas without the 1p/19q co-deletion. In this study, the authors studied the role of temozolomide in patients who were expected to have worse prognoses according to the status of chromosome 1p/19q, i.e., 1p/19q non-co-deleted tumors. The treatment group (surgery plus CCRT with temozolomide followed by six cycles

of adjuvant temozolomide) was compared to the control group (surgery plus radiotherapy alone) in terms of the efficacy and safety of temozolomide.

## Materials and Methods

### 1. Study design and patients

The KOREANA study was a multicenter study performed by the Korean Neuro-Oncology Group of Korean Society for Neuro-Oncology (KSNO). The trial was a randomized, open-label, phase 2 study to evaluate the efficacy between only radiotherapy versus combination therapy with radiotherapy and temozolomide in Korean adult patients with newly diagnosed supratentorial grade III gliomas without the 1p/19q co-deletion. The protocol was registered at clinicaltrials.gov (NCT01534845).

Patients with newly diagnosed, histologically proven supratentorial anaplastic gliomas, i.e., WHO grade III glioma without the 1p/19q co-deletion was eligible to participate in this study. The inclusion criteria were as follows: diagnosis of anaplastic gliomas according to the 2007 WHO criteria; age  $\geq$  18 years; Eastern Cooperative Oncology Group performance status of 0 or 1; stable or decreasing dose of steroids for  $\geq$  5 days prior to randomization; recursive partitioning analysis classification of III, IV, or V; and adequate hematologic, renal, and hepatic functions, including an absolute neutrophil count  $>$  1,500/ $\mu$ L, platelet count  $\geq$  100,000/ $\mu$ L, serum creatinine  $<$  1.7 mg/dL, bilirubin level  $\leq$  2.0 mg/dL, and aspartate aminotransferase/alanine aminotransferase  $\leq$  2.5 $\times$ the upper limit of the normal range of each institution.

The exclusion criteria consisted of having prior chemotherapy within the last 5 years, having prior radiotherapy of the head and neck area, receiving concurrent investigational agents or having received an investigational agent within 30 days prior to randomization, having planned surgery for other diseases, having a history of malignancy with the exception of cervical carcinoma *in situ* or basal cell carcinoma of the skin, being pregnant or lactating, refusing to use effective contraception, having concurrent illness that would interfere with the prescribed treatment, and being unable to undergo gadolinium-based magnetic resonance imaging (MRI).

### 2. Treatment schema

At enrollment, the diagnosis of anaplastic glioma had to be confirmed at each institution. In addition, the tumor material was submitted for assessment of the 1p/19q co-dele-

tion status and review of pathology by pathologist (G.C.) at the central laboratory. The 1p/19q co-deletion status was assessed by fluorescent *in situ* hybridization [12]. After identifying the status of the 1p/19q co-deletion, patients were screened for inclusion and then assigned in equal numbers to receive CCRT with temozolomide followed by adjuvant temozolomide (treatment group [arm A]) or to receive radiotherapy alone (control group [arm B]). The clinical data were collected and validated with a web-based clinical research management platform (Velos Inc., Fremont, CA).

All patients received fractionated focal irradiation in daily fractions of 2 Gy given 5 days per week for 6 weeks, for a total of 60 Gy. When given concurrently with radiotherapy, temozolomide was given daily from the first to the last day of radiotherapy, including on non-radiotherapy weekend days, at a dose of 75 mg/m<sup>2</sup> for a maximum of 6 weeks. As adjuvant chemotherapy, temozolomide was started 4 weeks after completion of radiotherapy for a maximum of six cycles. Patients received 150 mg/m<sup>2</sup> temozolomide on days 1-5 of the first cycle and 200 mg/m<sup>2</sup> on days 1-5 of subsequent cycles if no or minor toxicity was seen during the first cycle, and dose modifications could be made as described elsewhere [9]. Treatment after disease progression, the rescue regimen will be administered: the use of temozolomide was suggested for patients who had been assigned to receive radiotherapy alone.

### 3. Response assessment

Patients were followed up weekly during radiotherapy, every 2 weeks during adjuvant temozolomide treatment, and every 3 or 4 months after the completion of all treatment. Tumors were assessed with MRI and steroid dose. MRI was performed 4 weeks after the end of radiotherapy and every 3 months until the second year and every 6 months thereafter until disease progression. Radiographic response is determined in comparison to the tumor measurement obtained at pretreatment baseline measurements as a reference and is categorized into four groups using new criteria proposed by the Response Assessment in Neuro-Oncology working group [13]. Patients with possible pseudoprogression were kept on current treatment and re-evaluated 4 weeks thereafter to clarify the response. Steroid dose was reviewed at every outpatient visit. Clinical evaluation with adverse events was scored with the National Cancer Institute Common Toxicity Criteria for Adverse Event ver. 4.0.

The evaluation of health-related quality of life was assessed using the European Organization for Research and Treatment of Cancer quality-of-life questionnaire (QLQ-C30) and brain module (QLQ-BN20). Questionnaires were completed on paper at baseline (prior to randomization) and subsequently at all visits when MRI was performed. Data on

health-related quality of life will be reported separately.

### 4. Outcomes

The primary endpoint was 2-year PFS. Landmark PFS was also analyzed. PFS was calculated from the date of randomization to the date of first tumor progression or death whichever was earlier, with censoring of patients who were lost to follow-up. Two-year PFS was defined as the survival rate at the second year from randomization.

The second endpoints were overall PFS and OS adjusted for stratification factors, health-related quality of life outcomes, and adverse events. OS was defined as the time from randomization to the date of death from any cause.

### 5. Statistical analysis

Baseline characteristics, details of treatments and adverse events were expressed as the mean with standard deviation for continuous variables and the frequency with percentage for categorical variables. The comparisons between arm A and arm B were carried out using Student's t test, Pearson's chi-square or Fisher exact test, as appropriate. The survival curves were estimated using the Kaplan-Meier method, and the difference between survival curves was evaluated using the log-rank test. The Kaplan-Meier estimates at fixed time points (3, 6, 12, 18, and 24 months for PFS and 12, 24, and 60 months for OS) were compared based on the Z test. The Z test statistics used variance estimators calculated with Greenwood's formula. To explore the prognostic factors for PFS and OS, univariable Cox proportional hazards models were performed. A multivariable Cox proportional hazard model with a backward elimination criterion of  $p > 0.2$  was applied. The 2-year PFS, which was the primary outcome of the study, was considered statistically significant when the one-sided p-value was less than 0.2. Otherwise, the results were regarded as statistically significant when the two-sided p-value was less than 0.05. Statistical analyses were performed using SAS ver. 9.4 (SAS Institute Inc., Cary, NC).

### 6. Ethical statement

A total of 14 Korean institutions participated in this study with ethics approval from their institutional review boards before enrollment started. All patients gave written informed consent according to national guidelines. Patients were not compensated for their participation.

**Table 1.** Baseline characteristics of patients

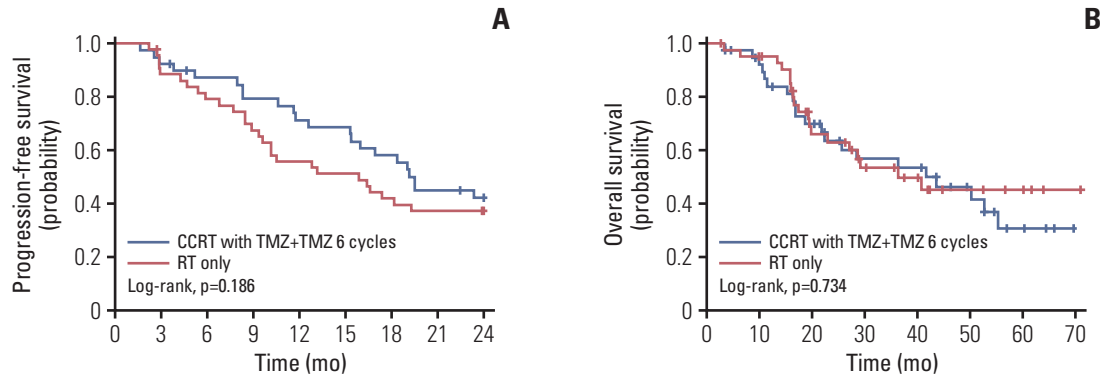
	Total (n=84)	CCRT with temozolomide plus adjuvant temozolomide (n=40)	Radiotherapy alone (n=44)	p-value
<b>Age (yr)</b>	44.7±13.2	44.7±13.3	44.8±13.2	0.980 <sup>a)</sup>
<b>Sex</b>				
Male	46 (54.8)	23 (57.5)	23 (52.3)	0.631 <sup>b)</sup>
Female	38 (45.2)	17 (42.5)	21 (47.7)	
<b>ECOG performance status</b>				
0	34 (40.5)	12 (30.0)	22 (50.0)	0.143 <sup>c)</sup>
1	44 (52.4)	24 (60.0)	20 (45.5)	
2	6 (7.14)	4 (10.0)	2 (4.5)	
<b>Extent of tumor resection</b>				
Gross total resection	37 (44.1)	17 (42.5)	20 (45.5)	0.681 <sup>b)</sup>
Subtotal resection	17 (20.2)	9 (22.5)	8 (18.2)	
Partial resection	14 (16.7)	5 (12.5)	9 (20.5)	
Biopsy only	16 (19.1)	9 (22.5)	7 (15.9)	
<b>MGMT promotor methylation</b>				
Unmethylation	42 (64.6)	21 (65.6)	21 (63.6)	0.867 <sup>b)</sup>
Methylation	23 (35.4)	11 (34.4)	12 (36.4)	
Missing	19	8	11	
<b>IDH1 mutation</b>				
Negative	44 (62.9)	22 (64.7)	22 (61.1)	0.756 <sup>b)</sup>
Positive	26 (37.1)	12 (35.3)	14 (38.9)	
Missing	14	6	8	
<b>Follow-up duration, median (range, mo)</b>	44.9 (2.8-71.1)	52.9 (3.6-69.7)	42.1 (2.8-71.1)	0.209 <sup>d)</sup>

Values are presented as mean±standard deviation or number (%) unless otherwise indicated. CCRT, concurrent chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; MGMT, O<sup>6</sup>-methylguanine-DNA methyltransferase; IDH1, isocitrate dehydrogenase 1. <sup>a)</sup>Student's t test, <sup>b)</sup>Chi-square test, <sup>c)</sup>Fisher exact test, <sup>d)</sup>Log-rank test.

**Table 2.** Details and intensities of the treatment

	CCRT with temozolomide plus adjuvant temozolomide	Radiotherapy alone	p-value
<b>Total dose of radiotherapy (Gy)</b>	60.1±1.3	60.2±3.6	0.771 <sup>a)</sup>
<b>Duration of radiotherapy (wk)</b>	6.3±0.9	6.1±0.7	0.188 <sup>a)</sup>
<b>Duration of temozolomide with CCRT (wk)</b>	5.7±0.9	-	-
<b>Duration of temozolomide after CCRT (cycle, missing=2)</b>	5.3±1.6	-	-
<b>Response of treatment at TMZ or after radiotherapy cycle 1 (missing=1)</b>			
Complete response	2 (5.1)	1 (2.3)	0.869 <sup>b)</sup>
Partial response	9 (23.1)	12 (27.3)	
Stable disease	22 (56.4)	24 (54.6)	
Progressive disease	3 (7.7)	5 (11.4)	
Not assessed	3 (7.7)	2 (4.5)	
<b>Response of treatment at end of treatment (missing=19)</b>			
Complete response	0	1 (3.0)	0.851 <sup>c)</sup>
Partial response	7 (21.2)	5 (15.2)	
Stable disease	19 (57.6)	20 (60.6)	
Progressive disease	6 (18.2)	6 (18.2)	
Not assessed	1 (3.0)	1 (3.0)	

CCRT, concurrent chemoradiotherapy; TMZ, temozolomide. <sup>a)</sup>Student's t test, <sup>b)</sup>Chi-square test, <sup>c)</sup>Fisher exact test.



**Fig. 1.** Kaplan-Meier curve of progression-free survival (A) and overall survival (B). CCRT, concurrent chemoradiotherapy; TMZ, temozolomide; RT, radiotherapy.

**Table 3.** Progression-free survival and overall survival according to treatment

	CCRT with temozolomide plus adjuvant temozolomide	Radiotherapy alone	p-value <sup>a)</sup>
<b>Progression-free survival</b>			
Median (mo)	19.5	15.9	
At 3 mo (%)	92.5	90.7	0.773
At 6 mo (%)	87.3	79.1	0.317
At 12 mo (%)	71.4	55.8	0.139
At 18 mo (%)	58.2	41.9	0.137
At 24 mo (%)	42.2	37.2	0.652
<b>Overall survival</b>			
Median (mo)	43.7	36.7	
At 12 mo (%)	84.0	95.2	0.100
At 24 mo (%)	63.7	63.0	0.945

CCRT, concurrent chemoradiotherapy. <sup>a)</sup>Landmark analysis (Z test).

## Results

### 1. Patients and treatment

From March 2012 to February 2015, 146 patients were screened, and 90 patients were randomly assigned to treatment groups. Six patients did not start treatment because of either consent withdrawal (n=4) or disease progression (n=2), and a total of 84 were included in the final analysis. There were 46 males (54.8%) and 38 females (45.2%). The mean age of patients was 44.7±13.2 years. Fifty-four patients (64.3%) underwent removal of over 75% of the tumor mass, including gross total removal or subtotal removal, and 30 patients (35.8%) underwent partial removal or biopsy only. The results were available for the MGMT promoter methy-

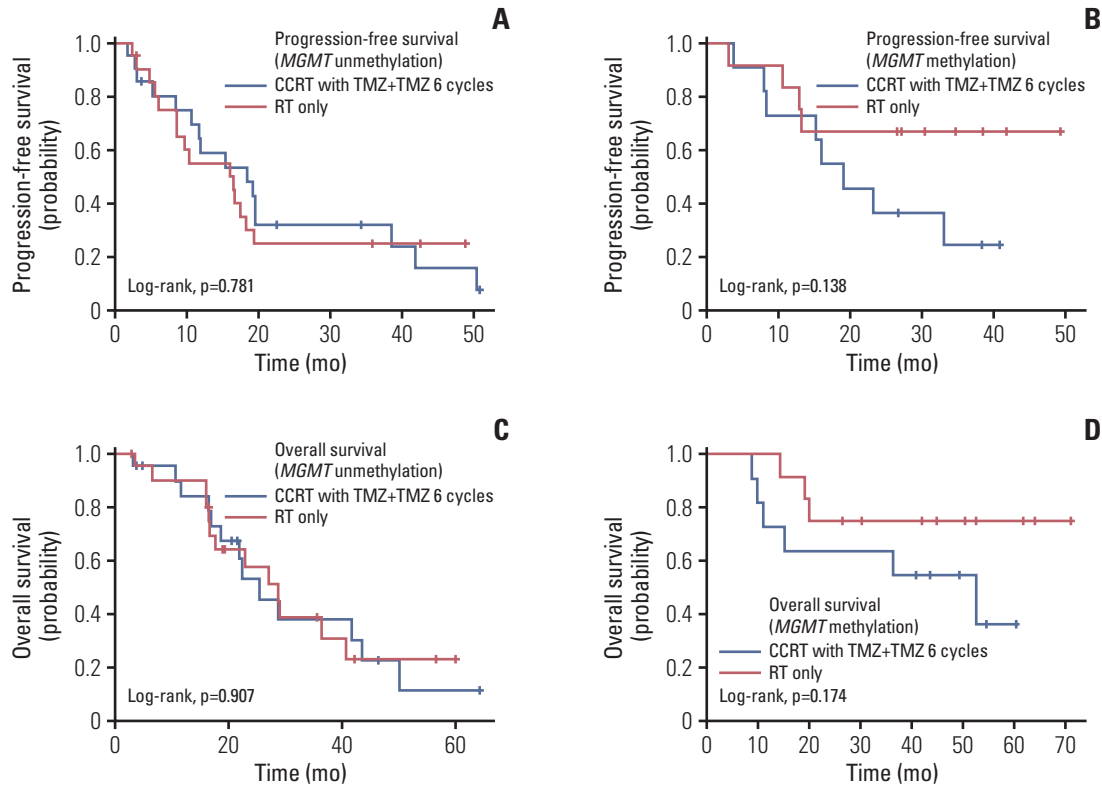
lation status for 65 of 84 patients (77.4%) and the isocitrate dehydrogenase 1 gene (*IDH1*) mutation status for 70 of 84 patients (83.3%) at the time of the preliminary analysis. Patients were randomly assigned to each treatment group according to the study protocol as follows: 44 patients received radiotherapy alone, and 40 patients received CCRT with temozolomide plus adjuvant temozolomide. The characteristics of patients in these two groups were well balanced at the baseline (Table 1).

In this trial, radiotherapy was completed in all but one of 84 patients (1.2%) in whom it was started. Among 40 patients assigned to the CCRT with temozolomide plus adjuvant temozolomide group, 39 patients (97.5%) completed radiotherapy with concurrent temozolomide. The mean therapeutic radiation dose was 60.1±1.3 Gy, and the mean duration of temozolomide with CCRT was 5.7±0.9 weeks. After exclud-

Table 4. Cox proportional hazard model of prognostic factors of PFS and OS

Treatment	PFS			OS		
	Univariable		Multivariable	Univariable		Multivariable
	HR (95% CI)	p-value	HR (95% CI)	HR (95% CI)	p-value	p-value
<b>Radiotherapy alone</b>	1		1	1		
<b>CCRT with temozolomide plus adjuvant temozolomide</b>	0.85 (0.50-1.45)	0.555	-	1.12 (0.60-2.08)	0.732	-
<b>Extent of resection</b>						
Partial resection and biopsy only	1		1	1		
Gross total resection and subtotal resection	0.47 (0.28-0.80)	0.005	-	0.51 (0.27-0.96)	0.038	-
<b>Age (yr)</b>						
≤ 40	1		1	1		
> 40	2.01 (1.07-3.74)	0.029	2.08 (1.04-4.16)	1.32 (0.68-2.56)	0.416	-
<b>Sex</b>						
Male	1		1	1		
Female	1.25 (0.73-2.13)	0.676	-	1.11 (0.60-2.06)	0.746	-
<b>MGMT methylation</b>						
Unmethylation	1		1	1		
Methylation	0.56 (0.29-1.10)	0.090	-	0.40 (0.18-0.86)	0.018	-
<b>IDH1 mutation</b>						
Negative	1		1	1		
Positive	0.28 (0.13-0.59)	0.001	0.28 (0.13-0.59)	0.19 (0.07-0.50)	0.001	0.001

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; CCRT, concurrent chemoradiotherapy; MGMT, O<sup>6</sup>-methylguanine-DNA methyltransferase; IDH1, isocitrate dehydrogenase 1.



**Fig. 2.** Kaplan-Meier curve of progression-free survival (A, B) and overall survival (C, D) according to  $O^6$ -methylguanine-DNA methyltransferase (*MGMT*) promoter methylation status. CCRT, concurrent chemoradiotherapy; TMZ, temozolomide; RT, radiotherapy.

ing one patient who progressed before starting adjuvant temozolomide, 32 of 38 patients (84.2%) completed adjuvant temozolomide with a mean of  $5.3 \pm 1.6$  cycles. Table 2 summarizes the details of the treatment delivered to the two treatment groups. There were no statistically significant differences in total radiation dose, duration of radiotherapy, or response to treatment between the treatment groups.

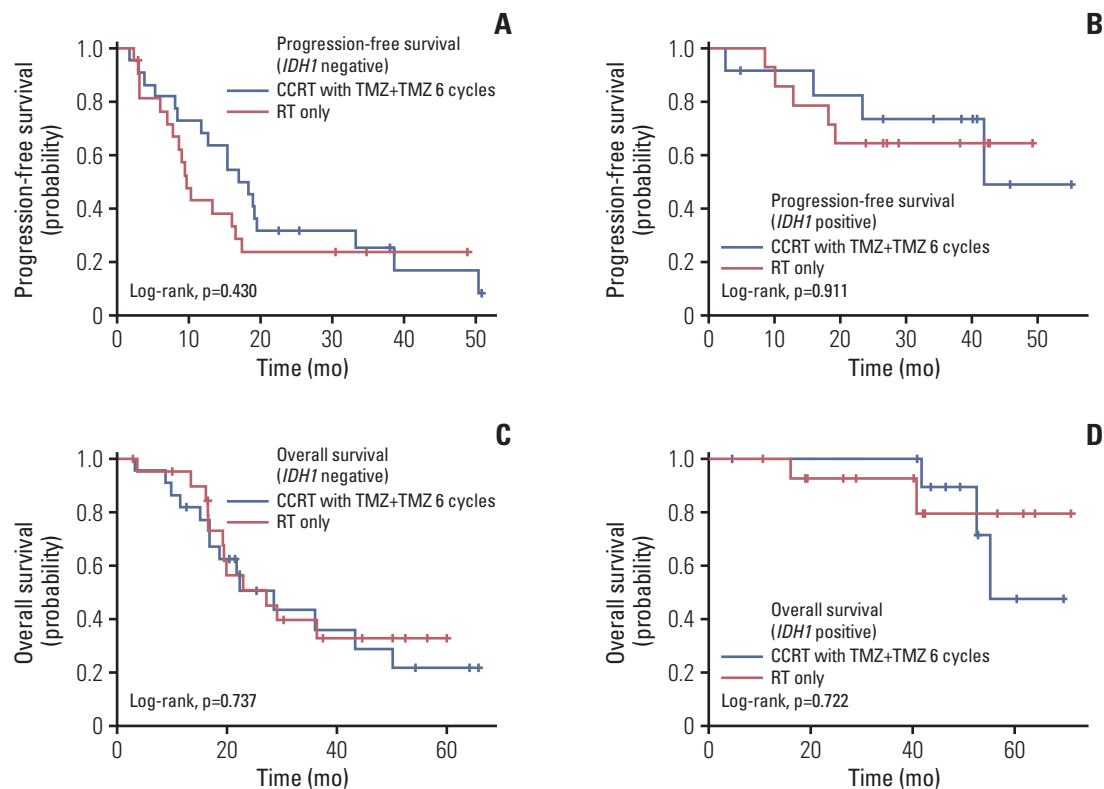
## 2. Tumor control and survival

After treatment, the objective response rate (complete response and partial response) and the tumor control rate (complete response, partial response, and stable disease) among patients who received radiotherapy alone were 18.8% and 81.3%, respectively. For patients who received CCRT with temozolomide plus adjuvant temozolomide, the response rate and the tumor control rate were 21.9% and 81.3%, respectively. The response to each treatment at the end of treatment showed no statistical significance (Table 2).

Kaplan-Meier survival curves of the patients according to the treatment are illustrated in Fig. 1. CCRT with temozolomide plus adjuvant temozolomide was associated with an

improved 2-year PFS (log-rank  $p=0.186$ ), as we set one-sided type I error as 0.2, but not with OS. For patients who received radiotherapy alone, the median PFS was 15.9 months, and the 2-year PFS was 37.2%. The median OS was 36.7 months, and the 12- and 24-month OS rates were 95.2% and 63.0%, respectively. Among patients who received CCRT with temozolomide plus adjuvant temozolomide, the median PFS was 19.5 months, and the 2-year PFS was 42.2%. The median OS was 43.7 months, and the 12- and 24-month OS rates were 84.0% and 63.7%, respectively. The PFS and OS landmark values are presented in Table 3.

Prognostic factors, including the treatment, extent of resection, age, sex, methylation of the *MGMT* promoter, and *IDH1* mutation were analyzed. In the univariable analysis, the extent of resection, age, and *IDH1* mutation were significant prognostic factors for PFS. By the multivariable analysis, the hazard ratio (HR) for PFS adjusted for baseline stratification factors among patients with *IDH1* mutation was 0.28 (95% confidence interval [CI], 0.13 to 0.59;  $p=0.001$ ). Age was a significant risk factor for PFS (HR, 2.08; 95% CI, 1.04 to 4.16;  $p=0.039$ ). For OS, the significant prognostic factor in the univariable analysis was the extent of resection, the methylation



**Fig. 3.** Kaplan-Meier curve of progression-free survival (A, B) and overall survival (C, D) according to isocitrate dehydrogenase 1 (*IDH1*) mutation status. CCRT, concurrent chemoradiotherapy; TMZ, temozolomide; RT, radiotherapy.

of the *MGMT* promoter, and *IDH1* mutation. However, *IDH1* mutation was the only significant prognostic factor for OS (HR, 0.19; 95% CI, 0.07 to 0.50;  $p=0.001$ ) by multivariable analysis (Table 4).

### 3. Subgroup analysis according to genotypical characteristics

Since we started this trial, mutations in *IDH1* have been widely known to be associated with improved outcomes and incorporated into the 2016 WHO classification of glioma [14,15]. To clarify whether the presence of *MGMT* promoter methylation or *IDH1* mutation could show differences in survival according to treatment, PFS and OS according to treatment and genotypical characteristics were analyzed. In a subgroup analysis, however, Kaplan-Meier survival curves showed no significant differences between both treatment groups according to the *MGMT* promoter methylation status (Fig. 2) or *IDH1* mutation status (Fig. 3).

### 4. Toxic effects

There were 24 patients, 16 of 40 patients (40.0%) in the treatment group and eight of 44 patients (18.2%) in the control group, who had adverse events over grade 3 after treatment. The difference between each group was statistically significant ( $p=0.027$ ). During CCRT with temozolomide plus adjuvant temozolomide, 11 patients (27.5%) showed nervous system disorder (including 3 hydrocephalus and 2 seizures), five patients (12.5%) exhibited procedural complications (including 3 radiation recall reactions), three patients (7.5%) experienced investigations (including 2 hematological toxicities), and so on. In the two patients (5.0%) with reported hematological toxicity category, one patient had leukocytopenia and another patient had thrombocytopenia. For patients who underwent radiotherapy alone, there were four patients (9.1%) with nervous system disorders, three patients (6.8%) with musculoskeletal disorders, two patients (4.5%) with psychiatric disorders, and so on. The distribution of the adverse events associated with the treatment is presented in Table 5.



**Table 5.** Adverse event over grade 3

	Total	CCRT with temozolomide plus adjuvant temozolomide	Radiotherapy alone
Gastrointestinal disorders	3 (3.8)	3 (7.5)	0
General disorders and administration site conditions	1 (1.3)	0	1 (2.3)
Immune system disorders	1 (1.3)	1 (2.5)	0
Infections and infestations	1 (1.3)	1 (2.5)	0
Injury, poisoning, and procedural complications	6 (7.5)	5 (12.5)	1 (2.3)
Investigations	3 (3.8)	3 (7.5)	0
Metabolism and nutrition disorders	4 (5.0)	3 (7.5)	1 (2.3)
Musculoskeletal and connective tissue disorders	4 (5.0)	3 (7.5)	3 (6.8)
Nervous system disorders	15 (18.8)	11 (27.5)	4 (9.1)
Psychiatric disorders	2 (2.5)	0	2 (4.5)
Renal and urinary disorders	1 (1.3)	0	1 (2.3)
Vascular disorders	1 (1.3)	0	1 (2.3)

Values are presented as number (%). CCRT, concurrent chemoradiotherapy.

## Discussion

This phase 2 trial of 84 patients demonstrated significant benefits for PFS with temozolomide during and after radiotherapy in patients with newly diagnosed WHO grade III glioma without the chromosome 1p/19q co-deletion. Although there was no significant difference in OS between the two arms, our further analysis showed that age over 40 years was an independent risk factor for PFS (HR, 2.08) and that the presence of *IDH1* mutation had a risk reduction for PFS (HR, 0.28) and OS (HR, 0.19).

The standard treatment protocol for WHO grade III gliomas has developed for many decades. Based on observations from previous studies, WHO grade III gliomas have been regarded as at least as chemosensitive as glioblastomas, and patients postoperatively treated with radiotherapy alone or chemotherapy alone fared worse than those treated with concurrent or adjuvant chemotherapy with radiotherapy [16,17]. Traditionally, anaplastic oligodendrogliomas are generally known to be chemosensitive and have had high rates of radiographic response in several trials after treatment with PCV [18]. However, chemotherapy with PCV has shown unacceptable toxicity, and the concurrent or adjuvant setting remains controversial. In the meantime, the efficacy found with adjuvant chemotherapy to radiotherapy for anaplastic astrocytoma, i.e., the 1p/19q non-co-deleted anaplastic gliomas in the revised 2016 WHO classification, seemed more doubtful. Several studies found no significant survival benefits for adjuvant PCV [19-21]. However, CATNON trial identified adjuvant temozolomide prolongs survival for non-co-deleted anaplastic gliomas after radiotherapy [8]. In addition, our study showed the possibility that CCRT with temo-

zolomide followed by adjuvant temozolomide has survival benefits for patients with WHO grade III gliomas.

This study adds to the literature for several reasons. This trial is the first investigator-initiated, multi-institutional, randomized trial for Korean adult patients with grade III glioma. For non-glioblastoma, compared to Whites, the incidence rate among Asians was substantially lower [22]. However, there have been fewer clinical trials only for Asian population. Especially, Koreans are one ethnic family, so long-term follow-up for unique ethnic group would be worth studying in terms of racial variation. And There should not be administrative, financial, and/or systemic difficulties in terms of performing clinical trials. We established a well-made system for this study and produced meaningful results. In addition, this trial included only patients with anaplastic gliomas without the chromosome 1p/19q co-deletion. Since patients without 1p/19q co-deletion gliomas had worse outcomes in the trials of PCV chemotherapy for anaplastic oligodendroglioma, we decided to take this approach [7,18,23]. Until now, there have been limited trials examining the efficacy and safety of temozolomide for patients with WHO grade III gliomas based on prospective molecular stratification. Furthermore, for patients with WHO grade III gliomas, the addition of temozolomide to radiotherapy, rather than PCV, is unusual [24]. Available data demonstrate with fair clarity that temozolomide is less toxic, easier to prescribe and less complicated for patients [25]. Although patients in this trial had 1p/19q non-co-deletion anaplastic gliomas, temozolomide showed a clear benefit. Finally, we assessed not only the treatment outcome itself but also the consequence of the quality-of-life for patients who underwent the treatment protocol. The results of the quality-of-life will be reported separately.

At the time of the beginning of this trial, genotypical characteristics were not considered in the WHO 2007 classification of glioma [26]. In 2009, mutations in IDH1 and IDH2 were reported to occur in 70%-80% of all grade II and III diffuse gliomas [14]. These mutations are associated with improved survival and are now the cornerstone of the revised WHO classification of gliomas [15,27,28]. Later, we incorporated analysis of the *IDH1* mutation status and again demonstrated a significant survival benefit for patients with *IDH1* mutation. However, in a subgroup analysis of *MGMT* promoter methylation and *IDH1* mutation, there were no significant differences according to treatment modalities. This result could be due to the small sample size, or those markers might not have predictive value for benefit from CCRT with temozolomide. Further analysis with a large sample size is needed.

Our study has some limitations. (1) The number of patients remains relatively small compared with other trials for patients with adult gliomas. A future study with a larger sample size and more statistical power is necessary to validate findings from this study. (2) Only 2 years have passed since the last participant was enrolled in this study, and a more long-term follow-up is needed. In other trials for patients with WHO grade III gliomas, the survival curves begin to diverge 5-6 years after randomization. The lack of significance may have been due to limitations of follow-up periods, and the survival benefit of our regimen needs further analysis with long-term follow-ups. (3) As we sorted patients according to the WHO 2007 classification of glioma, there was a slight heterogeneity of the patient population. WHO grade III gliomas are now known to consist of heterogeneous groups of different histologic features, biological behaviors, and prognoses. As relevant molecular markers show their implications in response to therapy and survival, future studies should be based on discriminated molecular factors.

In conclusion, temozolomide during and after radiotherapy in Korean adult patients with newly diagnosed non-co-deleted WHO grade III gliomas showed an improved 2-year PFS. Temozolomide, given its superior tolerability compared with PCV, showed acceptable adverse events. The survival benefit of this regimen requires further analysis with long-term follow-up at least more than 10 years. More prospective studies into the biology and prognostic significance of *MGMT* promoter methylation and other molecular mark-

ers are also required.

#### Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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