

# Phase I/II Study of Temozolomide Plus Nimustine Chemotherapy for Recurrent Malignant Gliomas: Kyoto Neuro-oncology Group

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## Abstract

The objective of this phase I/II study was to examine the efficacy and toxicity profile of temozolomide (TMZ) plus nimustine (ACNU). Patients who had received a standard radiotherapy with one or two previous chemotherapies were enrolled. In phase I, the maximum-tolerated dose (MTD) by TMZ (150 mg/m<sup>2</sup>/day) (Day 1-5) plus various doses of ACNU (30, 35, 40, 45 mg/m<sup>2</sup>/day) (Day 15) per 4 weeks was defined on a standard 3 + 3 design. In phase II, these therapeutic activity and safety of this regimen were evaluated. Forty-nine eligible patients were enrolled. The median age was 50 years-old. Eighty percent had a KPS of 70–100. Histologies were glioblastoma (73%), anaplastic astrocytoma (22%), anaplastic oligodendroglioma (4%). In phase I, 15 patients were treated at four cohorts by TMZ plus ACNU. MTD was TMZ (150 mg/m<sup>2</sup>) plus ACNU (40 mg/m<sup>2</sup>). In phase II, 40 patients were treated at the dose of cohort 3 (MTD). Thirty-five percent of patients experienced grade 3 or 4 toxicities, mainly hematologic. The overall response rate was 11% (4/37). Sixty-eight percent (25/37) had stable disease. Twenty-two percent (8/37) showed progression. Progression-free survival (PFS) rates at 6 and 12 months were 24% (95% CI, 12–35%) and 8% (95% CI, 4–15%). Median PFS was 13 months (95% CI, 9.2–17.2 months). Overall survival (OS) at 6 and 12 were 78% (95% CI, 67–89%) and 49% (95% CI, 33–57%). Median OS was 11.8 months (95% CI, 8.2–14.5 months). This phase I/II study showed a moderate toxicity in hematology and may have a promising efficacy in OS, without inferiority in PFS.

Key words: temozolomide, nimustine, recurrent malignant gliomas, phase I/II study

## Introduction

Malignant gliomas are devastating malignancies, destroying cognitive functions in the brain, altering the personality of a human, and leading to death. Generally, a standard treatment of a newly diagnosed malignant gliomas usually consists of cytoreductive surgery followed by radiotherapy (RT) concomitant with TMZ therapy,<sup>1</sup> though treatments for Grade 3 gliomas are controversial and have not been established.<sup>2,3</sup> The clinical benefit of adding bevacizumab

to the treatment is controversial.<sup>4–6,8</sup> Gliadel wafers also have been often used, if possible.<sup>8,9</sup> Despite the advent of multimodal treatments, this tumor always recurs within 1 or 2 years. Then, we don't have any established second-line treatments.

Nitrosoureas have been the mainstay of therapy, for example, ACNU, carmustine (BCUN) or lomustine (CCNU) until the advent of TMZ.<sup>10,11</sup> These have demonstrated an activity in malignant gliomas and are widely used for the treatment of malignant gliomas.<sup>12</sup> The rationale for the combination of these agents is that they may have synergistic activity due to TMZ's depletion of O6 alkylguanine-DNA

alkyltransferase (AGT), the DNA repair enzyme that is believed to contribute to nitrosoureas resistance.<sup>13)</sup>

Phase II studies of BCNU or CCNU plus TMZ have been reported.<sup>11,14–16)</sup> BCNU with TMZ have shown a strong toxicities and limited efficacy.<sup>11,14,16)</sup> CCNU plus TMZ have shown a promising efficacy with a moderate toxicity.<sup>15)</sup> But, ACNU plus TMZ have not been reported. Therefore, we tried the phase I/II study of TMZ plus ACNU chemotherapy.

## Patients and Methods

### Eligibility for study participation

Patients enrolled on this study had supratentorial anaplastic gliomas (AG) or glioblastoma (GBM) previously treated with surgery, a conventional radiotherapy (60 Gy), and one or two chemotherapy-regimens. Tumor progression was confirmed on contrast-enhanced (CE) MR imaging. If radiation necrosis or pseudoprogression was suspected, spectroscopic MR imaging was performed to confirm the presence of viable cells. If mainly necrosis was noted in those who underwent repeat surgery for a recurrence, adjuvant chemotherapy was continued. Patients were required to be at least 18 years old, have a KPS score over 60, and have a life expectancy over 12 weeks. An interval over 12 weeks from the completion of radiotherapy, over 4 weeks from prior chemotherapy (6 weeks from a ACNU-based regimen), and over 2 weeks from salvage surgery had to have elapsed for the patient to be eligible for this study enrollment. Adequate laboratory values were also required, including a neutrophil count over  $1500/\text{mm}^3$ , platelet count over  $100,000/\text{mm}^3$ , transaminase and alkaline phosphatase levels under three times the upper limit of laboratory normal, and serum creatinine and bilirubin levels under 1.5 times the upper limit of laboratory normal. In addition, patients were not pregnant, had an uncontrolled infection, or had any prior malignancy. All patients signed informed consent according to the principles of the Declaration of Helsinki and the rules of good clinical practice. These institutional review boards at local participant hospitals in Japan, have approved the protocol. All histological slides were reviewed by an independent central neuropathologist in Kyoto University.

### Study design and treatment

This was a dual-agent, open-label, phase I/II study. In phase I, eligible patients were enrolled and treated according to the schema in Fig. 1, using a standard 3 + 3 design.<sup>17,18)</sup> All patients were treated with a fixed dose of ACNU at  $30 \text{ mg}/\text{m}^2$  up to a maximum cumulative dose of  $45 \text{ mg}/\text{m}^2$ . ACNU was given intravenously for about 30 min. TMZ was orally administered on an

empty stomach 30 min after antiemetic prophylaxis; redosing was not allowed if vomiting occurred. The fixed dose of TMZ was  $150 \text{ mg}/\text{m}^2$ . TMZ was taken for 5 consecutive days (Day 1–5) followed by a 23-day rest period; one cycle was 28 days. ACNU was administered at day 14 on each cycle. A minimum of three patients and a maximum of 6 were enrolled per cohort. A dose-limiting toxicity (DLT) was defined as grade 3 or 4 nonhematologic or hematologic toxicity, based on the National Cancer Institute Common Toxicity Criteria (version 4), during cycle 1. If no DLTs were observed, treatment continued and three patients were treated in the subsequent cohort. However, if one of three patients experienced a DLT, another three patients were added at this cohort. If two of six patients experienced a DLT, this level was declared too toxic, and another six patients were added at the prior dose level. The maximal tolerated dose (MTD) was defined as the dose where 0/3 or 1/6 patients experienced a DLT (Fig. 1). No intrapatient dose escalation was permitted.

In phase II, the primary end point of this study was the percentage of PFS at 6 months (PFS-6). Secondary end points included the percentage of PFS at 3, 12, and 18 months; tumor response to treatment; overall survival; and time to disease progression. The regimen would be considered a success if at least 30% of enrolled patients responded to it, whereas the regimen would be considered ineffective if a success rate under 10% was observed. In the North Central Cancer Treatment Group (NCCTG) database of patients with recurrent GBM, the PFS-6 was 10%.<sup>19)</sup> Our design used 33 patients and had an alpha level of 0.04 and a power of 0.89 for detecting a true success probability of 30%. The original sample size of the study was 37 (33 patients with four additional patients in case of drop-outs), and 40 patients were accrued initially. Forty patients treated at phase II dose were six patients from phase I portion and 34 patients from phase II. All patients had a complete physical examination and a CE MRI scan at baseline and before beginning each new cycle. Each patient had a complete blood count every week and electrolyte and liver function tests every 4 weeks. All the hematological toxicity from the previous course of chemotherapy had resolved to Grade 2 or less, and all nonhematological toxicity had recovered to either Grade 0 or 1. If sufficient recovery had not occurred, the subsequent course was delayed until these criteria were met. No dose escalation was allowed. A dose reduction of ACNU, from  $40 \text{ mg}/\text{m}^2$  (cohort 3) to  $35 \text{ mg}/\text{m}^2$  (cohort 2), for toxicity was permitted. Only two dose reductions, from  $40 \text{ mg}/\text{m}^2$  (cohort 3) via  $35 \text{ mg}/\text{m}^2$  (cohort 2) to  $30 \text{ mg}/\text{m}^2$  (cohort 1), were allowed, and patients experiencing Grade 3 toxicity



**Table 1 Patient characteristics**

	Total (n = 49)	Phase I (n = 15)				Phase II	
		Cohort 1	Cohort 2	Cohort 3	Cohort 4	TMZ (150 mg/m <sup>2</sup> ) + ACNU (40 mg/m <sup>2</sup> )	
		(n = 3)	(n = 3)	(n = 6)	(n = 3)	MG (n = 40)*	GBM (n = 33)
Age							
Median	50	34	47	54	57	50	52
Range	22–75	27–45	47–63	42–75	45–67	22–75	27–75
< 50	27	3	2	2	1	20	15
≥ 50	24	0	1	4	2	20	18
Sex							
Male	33	2	2	4	1	28	25
Female	16	1	1	2	2	12	8
Histology							
Glioblastoma	36	1	1	5	1	33	33
Anaplastic astrocytoma	11	1	1	1	2	7	0
Anaplastic oligodendroglioma	2	1	1	0	0	0	0
Karnofsky performance status							
100	0	0	0	0	0	0	0
90	8	1	2	1	0	5	4
80	13	0	0	1	1	12	10
70	18	2	1	2	1	14	11
60	10	0	0	2	1	9	8
Time from first diagnosis to enrollment (weeks)							
Median	76	49	122	64	106	71	65
Range	48–322	48–59	81–144	48–5	88–272	48–322	48–258
Salvage surgery at last relapse							
Gross total resection	4	0	0	0	0	4	3
Partial resection	7	0	0	0	0	7	7
No surgery	38	3	3	6	3	29	23
Prior chemotherapy regimens							
TMZ alone	31	3	1	5	3	24	17
TMZ followed by ICE	5	0	0	0	0	5	5
TMZ followed by Bev	13	0	2	1	0	11	11

Bev: Bevacizumab, GBM: Glioblastoma, ICE: Ifosfamide carboplatin etoposide, MG: Malignant gliomas, TMZ: Temozolomide. The dose at Cohort 3: TMZ (150 mg/m<sup>2</sup>) + ACNU (40 mg/m<sup>2</sup>). \*Phase II (n = 40) includes 6 patients from cohort 3 of phase I.

prior systemic chemotherapy regimens, namely, those were second-relapsed.

### Safety and tolerability

*Phase I.* TMZ was administered at the dose of 150 mg/m<sup>2</sup> (Day 1-5). ACNU was at four various

cohorts (Day 14). Three patients at 30 mg/m<sup>2</sup> (cohort 1), 3 at 35 mg/m<sup>2</sup> (cohort 2), 6 at 40 mg/m<sup>2</sup> (cohort 3), and 3 at 45 mg/m<sup>2</sup> (cohort 4). One patient at 40 mg/m<sup>2</sup> of ACNU (cohort 3) developed a grade 3 neutropenia; according to a standard 3 + 3 design, another three patients were added to cohort 3.

No DLT was found in three other three patients at 40 mg/m<sup>2</sup> of ACNU. There were one patient in Grade 3 thrombocytopenia and other in grade 3 neutropenia at 45 mg/m<sup>2</sup> of ACNU (cohort 4). Two of three patients showed grade 3 neutropenia at 45 mg/m<sup>2</sup> (cohort 4). Hence, one of six patients at 40 mg/m<sup>2</sup> (cohort 3) showed a grade 3 toxicity, a 40 mg/m<sup>2</sup> of ACNU was declared as the MTD. Under 35 mg/m<sup>2</sup> of ACNU, all other toxicities were grade 1 or 2. In six patients on cohort 3, a dose reduction from 40 to 35 mg/m<sup>2</sup> of ACNU occurred in cycle 2 for one patient and in cycle 4 for other; one of these two patients required further dose reduction to 30 mg/m<sup>2</sup>. Prolonged hematologic toxicity led to the removal of one patient from study after cycle 5. No patient suffered a toxic mortality, although one patient died 20 weeks after study withdrawal at an outside institution from a pneumonia. None of patients developed thrombosis. After phase I, phase II was started at 40 mg/m<sup>2</sup> of ACNU from cohort 3 with TMZ (150 mg/mg/day, day 1-5), every 4 weeks.

**Phase II.** Toxicities, which were graded based on the NCI common toxicity criteria (version 4.0), were recorded for patients treated at the dose of phase II (n = 40) (Table 2). Grade 3 or 4 neutropenia occurred in six patients (15%), and grade 3 or 4 thrombocytopenia

occurred in 10 patients (25%). A lack of appetite, nausea or constipation sometimes persisted for 1 or 2 days, although antiemetic agents were available to patients. Grade 3 or 4 hepatic dysfunction, indicated by transaminase levels, occurred in three patients (8%). Grade 3 or 4 renal dysfunction, indicated by creatinine levels, was observed in two patients (5%). No one had encephalopathy or auditory toxicity. Although none of the patients had *Pneumocystis carinii*, two patients (5%) had a Grade 3 or 4 pulmonary infection. Nineteen patients (48%) were alive on follow-up over 12 months. The number of treatment cycles per patient ranged from 1 to 9. Five patients received only 1 cycle, seven received 2, 10 received 3, six received 4, seven received 5, and nine received over 6. The median number of cycles per patient was 3.8 (95% CI, 2–6 cycles).

Treatment was delayed for a median time of 1 week (recovery after 1–2 weeks) in three patients (7%) due to Grade 3 thrombocytopenia, neutropenia, or Grade 2 infection. The most common reason for drug discontinuation were disease progression, which occurred in 23 patients (58%), and hematologic toxicity in eight patients (20%). Treatment was discontinued in one patient (3%) because of a pulmonary embolism, in one because of surgery for an unrelated condition, in five (13%) because of Grade 2 fatigue (they withdrew consent), and in one (3%) because of pulmonary infection (Table 3). TMZ was not reduced in dose, but ACNU was often reduced in this study. Relative dose intensity in all cycles of ACNU was 87% (95% CI, 75–100%).

None of the deaths were considered treatment related. Twenty-one deaths were due to progression of disease and one was secondary to complications from pneumonia.

**Table 2 Toxicities (Phase II, n = 40)\***

	No. of patients (%) Grade 1–2	No. of patients (%) Grade 3–4
Patients with toxicities	34 (85)	14 (35)
Anemia	21 (53)	7 (18)
Thrombocytopenia	24 (60)	10 (25)
Neutropenia	21 (53)	6 (15)
Lymphocytopenia	20 (30)	7 (18)
Nausea / Vomiting	12 (29)	5 (13)
Transaminase	8 (20)	3 (8)
Creatinine	3 (8)	2 (5)
Alopecia	5 (13)	0 (0)
Constipation	11 (28)	2 (5)
Thrombosis	1 (3)	1 (3)
Fatigue	19 (48)	1 (3)
Convulsion	2 (5)	1 (3)
Diarrhea	4 (10)	0 (0)
Anorexia	4 (10)	0 (0)
Pulmonary infection	2 (5)	2 (5)
Rash	3 (8)	0 (0)

\*Phase II (n = 40) includes 6 patients from cohort 3 of phase I.

### Treatment responses

In phase II, 40 patients including the cohort 3 of phase I were evaluated (Table 4). Thirty-seven patients could be assessed for treatment response

**Table 3 Reasons for treatment discontinuation (Phase II, n = 40)\***

Reasons	No. of patients (%)
Disease progression	23 (58)
Hematologic toxicity	8 (20)
Grade 2 fatigue and withdrew consent	5 (13)
Thromboembolic complications	1 (3)
Required surgery for unrelated conditions	1 (3)
Pulmonary infections	1 (3)

\*Phase II (n = 40) includes 6 patients from cohort 3 of phase I.

because three patients underwent almost total resection at salvage surgery before this treatment. These three patients have 3, 5, and 6 months of PFS. There was 0 CR (0%) and 4 PRs (11%) in phase II. The overall response rate (CR + PR) was 11% (4 of 37 patients, 95% CI 4–16%). The median duration of disease stabilization (PR + SD) in 29 patients (78%) was 12 weeks (range 6–75 weeks). All responding patients were taking either a stable dose or no corticosteroids at the time of the best response. The rate of stable disease was 63% (95% CI, 54–77%), 25 of 40 patients.

### Disease progression

In 40 patients of phase II (Fig. 2), the median PFS was 13 weeks (95% CI 7–24 weeks). PFS at 6 and 12 months after this treatment were 24% (95% CI 12–35%) and 8% (95% CI 3–15%), respectively, (Table 4). In 33 patients with GBM of phase II, the median PFS was 10 weeks (95% CI 6–22 weeks). PFS at 6 and 12 months after this treatment were 21% (95% CI 11–33%) and 6% (95% CI 2–13%), respectively. On univariate analysis, there was no

difference in the possibility of progression based on surgical treatment at relapse ( $p = 0.55$ ), the extent of surgery ( $p = 0.31$ ), prior to chemotherapy ( $p = 0.47$ ), patient age ( $p = 0.34$ ), or KPS score ( $p = 0.45$ ). On multivariate analysis, the factors predictive of disease progression were treatment response or disease stabilization attained with this therapy ( $p = 0.005$ ) and the number of treatment cycles (1 or 2;  $p = 0.007$ ). At the relapse after this treatment, eight received bevacizumab, four patients received interferon- $\beta$ , five patients underwent radiosurgery, and three patients underwent salvage surgery.

### Overall survival

The median survival time in 40 patients of phase II (Fig. 2), calculating from the start of this chemotherapy, was 11.8 months (95% CI 8.2–14.5 months), and 78% (95% CI 67–96%) and 49% (95% CI 27–63%) of the patients were alive at 6 and 12 months after the treatment, respectively (Table 4). In 33 patients with GBM of phase II, the median OS was 10.3 months (95% CI 6.7–13.1 months). OS at 6 and 12 months after this treatment were 74% (95% CI 63–95%) and

**Table 4** Survival, progression-free survival and response rate of temozolomide plus nimustine therapy

	Phase I (n = 15)				Phase II	
	Cohort 1	Cohort 2	Cohort 3	Cohort 4	TMZ (150 mg/m <sup>2</sup> ) + ACNU (40 mg/m <sup>2</sup> )	
	(n = 3)	(n = 3)	(n = 6)	(n = 3)	MG (n = 40)*	GBM (n = 33)
Median survival, months	16	18	13	11	11.8	10.3
Range, months	10–18	7–24	8–24	6–17	3–24	3–22
1-year survival, %	100	100	83	66	49	44
Median PFS, weeks	12	57	10	57	13	10
PFS-6 months, %	0	0	17	0	24	21
Best response						
CR	0	0	0	0	0	0
PR	0	0	1	0	4	3
SD	3	3	2	2	25	20
PD	0	0	4	1	8	7
Non-evaluable lesions	0	0	0	0	3	3
Duration of disease stabilization (PR + SD), weeks						
Mean	11.6	8.0	7.9	8.7	13	11
Median	12	57	10	8.1	12	10
Range	11–12	8–22	8–75	4–16	6–75	6–59
Patients on this therapy for > 6 months	0	0	1	0	9	7

CR: Complete response, GBM: glioblastoma, MG: Malignant gliomas, PD: Progressive disease, PFS: Progression-free survival, PR: Partial response, SD: Stable disease. Responses assessed by Macdonard's criteria on MRI. \*Phase II (n = 40) includes 6 patients from cohort 3 of phase I.

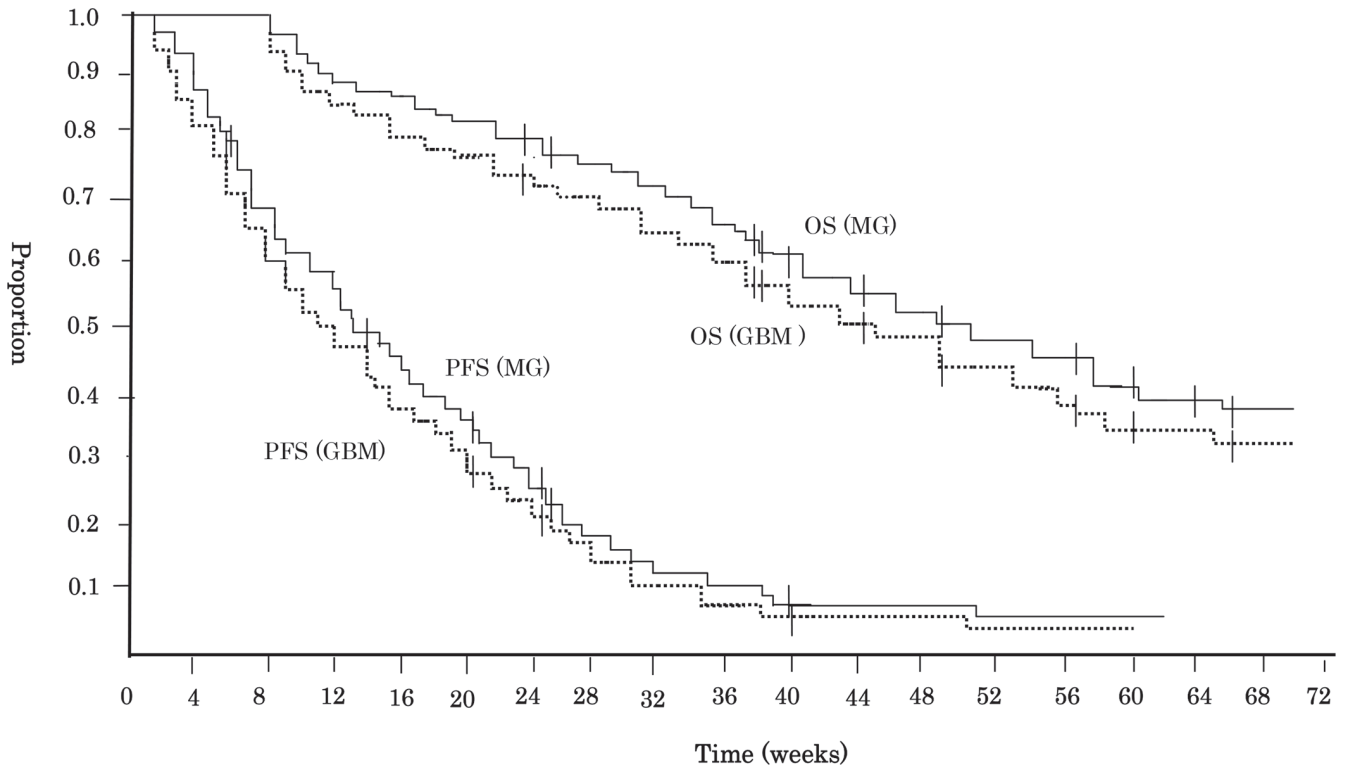


Fig. 2 Kaplan-Meier estimates of progression-free survival (PFS) and overall survival (OS) in patients with recurrent malignant gliomas and glioblastoma (GBM). Tick marks represent censored patients. GBM: glioblastoma, MG: malignant gliomas.

44% (95% CI 32–69%), respectively. On univariate analysis, there was no difference in the possibility of overall survival based on surgical treatment at relapse ( $p = 0.55$ ), the extent of surgery ( $p = 0.28$ ), prior to chemotherapy ( $p = 0.30$ ), patient age ( $p = 0.33$ ), or KPS score ( $p = 0.44$ ). On multivariate analysis, factors predictive of OS were treatment response or disease stabilization attained with this therapy ( $p = 0.003$ ).

## Discussion

TMZ is an orally bioavailable imidazotetrazine derivative of decarbazine.<sup>21)</sup> The active metabolite is monomethyl triazenoimidazole carboxamide, and cytotoxicity is primarily due to methylation at the O6 position of guanine. TMZ also acts as an inhibitor of DNA mismatch repair and can induce apoptosis.<sup>22)</sup> ACNU forms a chloroethyl adduct at the O6 position of guanine,<sup>10,23,24)</sup> whereas TMZ appears to act by methylation at this site. Both the methyl and chloroethyl adducts are repaired by the DNA repair protein O6-alkylguanine-DNA alkyltransferase (AGT). Both TMZ and ACNU belong to alkylating agents. But these mechanisms of DNA damage between them are different. TMZ damages

DNA by base pair substitution. On the other hand, ACNU bring about chromosomal deletion by interstrand crosslink in double strands. The synergistic mechanism of TMZ plus ACNU may be expected. A potential therapeutic effect in tumor cells may also occur. Most commonly used agents in daily practice for malignant gliomas are nitrosoureas, particularly ACNU in Japan, and TMZ.

In schedules for administration of TMZ plus BCNU or CCNU, various types of regimens have been reported.<sup>11,14–16)</sup> Considering compliance and conveniences of administration to patients in daily practice, we have chosen a schedule for TMZ (Day 1–5) plus ACNU (Day 14) in this study.

Toxicities in this study show that TMZ plus ACNU chemotherapy were certainly more toxic than either one (Table 2). The toxicity profile for this study was predominantly hematologic, and 22% of patients were under four cycles of therapy due to toxicities. The dose schedule for this study was selected based on this phase I study. However, it is important to note that the determination of dose-limiting toxicities and MTD in phase I study was based on the tolerance of the first cycle only. It is difficult to speculate in advance how patients may tolerate during long extended cycles in phase II.

We should keep in mind that the necessity of toxicity assessment during several cycles in phase II study.<sup>25,26)</sup> This is often limited because of the refractory nature of the disease and the likelihood of early progression. When ACNU is used in combination with procarbazine, 80 mg/m<sup>2</sup> of ACNU was found to be too toxic.<sup>27)</sup> When ACNU with carboplatin, etc., 60 mg/m<sup>2</sup> of ACNU was moderate toxicity.<sup>28)</sup> A dose of 80 mg/m<sup>2</sup> of ACNU was also too toxic even when used as a single agent.<sup>27)</sup> The toxicity of TMZ plus ACNU on dose escalation was myelosuppression, similar to results in reported studies of various combinations of TMZ plus BCNU.<sup>11,14,16)</sup> Recently, RTOG 9813 reported that RT plus TMZ did not appear to significantly improve OS or PFS for anaplastic astrocytoma, compared with RT plus BCNU. RT plus TMZ was better tolerated.<sup>29)</sup> The major toxicity in this study was also myelosuppression, and although it was tolerable, dose reductions were sometimes occurred. The toxicity of ACNU may not be so strong comparing with BCNU. ACNU is water-soluble and BCNU is lipid-soluble. The difference in properties between such agents might influence the efficacy and side effects.<sup>30,31)</sup>

Several studies have generally reported response rates under 20% and a PFS-6 under 30% in recurrent GBM (Table 5). In 33 patients with GBM of this phase II, PFS-6 was 21%, which was almost equal or not inferior, and OS at 12 months was 44% which could be better than other studies. This

regimen could delay the speed of tumor growth even during the progressive phase by Macdnard criteria. Some treatments including salvage administrations of bevacizumab,<sup>32)</sup> interferon- $\beta$ ,<sup>41)</sup> ICE (ifosfamide, carboplatine and etoposide),<sup>34)</sup> and so on, after progression, may influence this promising OS. The methylation of the MGMT promoter and the mutation of IDH1/2 are associated with a favorable outcome after TMZ chemotherapy for patients with newly diagnosed GBM.<sup>35,36)</sup> In this study, because of the limited tumor material obtained from surgeries, these correlative studies on the methylation of MGMT promoter and the mutation of IDH1/2 could not be performed.

This study has equal or not inferior efficacy in PFS and moderate or durable myelotoxicity but may be a promising in OS, comparing with other studies. This regimen could be an option for patients with recurrent malignant gliomas, though further study is needed.

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**Table 5 Clinical trials in recurrent glioblastoma after temozolomide treatment**

Authors and year	Regimens	No. of pts	PFS-6: % (95% CI)	OS-12: % (95% CI)	Median OS (95% CI)
Han et al. 2014 <sup>37)</sup>	TMZ (7/7)	40	10 (3–24)	~28 (NR)	5.4 (4.2–7.7)
Weller et al. 2015 <sup>38)</sup> (DIRECTOR)	TMZ (7/7)	52	17.1 (8.2–28.8)	41.0 (26.7–54.8)	9.8 (6.7–13.0)
	TMZ (21/7)	53	25.5 (14.3–37.3)	32.7 (20.2–45.9)	10.6 (8.1–11.6)
Nagane et al. 2012 <sup>32)</sup>	Bev	31	33.9 (19.2–48.5)	34.5 (20.0–49.0)	10.5 (8.2–12.4)
Friedmann et al. 2009 <sup>39)</sup>	Bev	85	42.6 (29.6–55.5)	25 (NR)	9.2 (8.2–10.7)
	Bev + CPT-11	82	50.3 (36.8–63.9)	30 (NR)	8.7 (7.8–10.9)
Taal et al. 2014 <sup>6)</sup> (BELOB trial)	Bev	50	16 (7–27)	26 (15–39)	8 (6–9)
	CCNU	46	13 (5–24)	30 (18–44)	8 (6–11)
	Bev + CCNU	52	42 (29–55)	48 (34–61)	12 (8–13)
Brandes et al. 2004 <sup>40)</sup>	BCNU + CPT-11	42	30.3 (18–51)	44.1 (26.4–73.6)	11.4 (NR)
Reithmeier et al. 2010 <sup>41)</sup>	BCNU	35	13 (NR)	5 (NR)	5.5 (4.5–6.5)
Happold et al. 2009 <sup>42)</sup>	ACNU	32	20 (NR)	26 (NR)	6.7 (3.35–10.1)
Aoki et al. 2010 <sup>34)</sup>	ICE	42	35 (22–50)	37 (27–63)	10.7 (7.9–13.6)
This study*	TMZ + ACNU	33	21 (11–33)	44 (32–69)	10.3 (6.7–13.1)

ACNU: Nimustine, BCNU: Carmustine, Bev: Bevacizumab, CCNU: Lomustine, CPT-11: Irinotecan, GBM: Glioblastoma, ICE: Ifosfamide carboplatin etoposide, NR: Not reported, OS: Overall survival, OS-12: Overall survival at 12 months, PFS-6: Progression-free survival at 6 months, pts: patients, 7/7, 7 days on / 7 days off, 21/7, 21 days on / 7 days off, TMZ: Temozolomide.  
\*This data depends on 33 patients with glioblastoma from Phase II portion.



## Conflicts of Interest Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices in the article. All authors who are members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members. This manuscript has no COI that should be disclosed.

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