

# The impact of extended adjuvant temozolomide in newly diagnosed glioblastoma multiforme: a meta-analysis and systematic review

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## Abstract

Surgical resection followed by concurrent radiation therapy and temozolomide (TMZ) chemotherapy is the current standard treatment for glioblastoma multiforme (GBM). The present meta-analysis investigated the impact of prolonged TMZ maintenance therapy (more than 6 cycles) in comparison with standard TMZ maintenance therapy (exactly six cycles) on overall survival (OS) and progression-free survival (PFS) of patients with GBM. A meta-analysis of the literature was conducted using Medline, PubMed, EMBASE and the Cochrane Library in accordance with PRISMA guidelines. Seven articles involving 1018 patients were included. The overall survival was higher in the case group (>6 cycles TMZ) compared to the control group (6 cycles TMZ) ( $Z=2.375$ ,  $P=0.018$ ). The lower and upper limits were between

1.002-10.467 months. The case group had higher progression-free survival compared with the control group ( $Z=3.84$ ;  $P<0.001$ ). The lower and upper limits were between 2.559-7.894 months. Evidence from this meta-analysis suggests that prolonged TMZ therapy compared to the standard 6-cycle TMZ therapy was associated with higher survival in patients with glioblastoma.

## Introduction

Glioblastoma multiforme (GBM) is the most common primary tumor of the central nervous system, with an average incidence rate of 3-4 cases per 100,000 individuals each year.<sup>1</sup> Glioblastoma is associated with poor prognosis and is resistant to treatment.<sup>2</sup> Despite the advancements in treatment modalities, overall survival is between 12 and 18 months. Its 2-year survival rate has been reported about 18 to 28%.<sup>3,4</sup> The current standard treatment of patients with glioblastoma is surgical resection followed by radiotherapy with concomitant and maintenance temozolomide chemotherapy.<sup>5</sup> In spite of the FDA approval of the treatment regimen of 6 adjuvant or maintenance cycles of TMZ, in daily practice, the prescribed number of cycles for patients without tumor progression after 6 months varies significantly.<sup>6</sup> Several studies and guidelines advocate prolonged use of adjuvant TMZ for more than 6 cycles.<sup>7-9</sup> But the impact of prolonging maintenance temozolomide therapy beyond six cycles remains a topic for discussion. In this meta-analysis, we investigated the effect of prolonged maintenance of TMZ therapy (more than 6 cycles) in comparison to exactly six cycles of treatment on OS and PFS of patients with GBM.

## Methods of research

### Search strategy

The present meta-analysis was conducted according to the criteria outlined in the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guideline.<sup>10</sup> The articles enrolled in this analysis were published between 2012 and 2017. The Mesh terms used for the literature search included 'Glioblastoma', 'Temozolomide', and 'Survival'.

### Inclusion and exclusion criteria

Studies that met the following criteria were included: i) articles comparing GBM patients that received standard 6-cycle TMZ with those whom received more than 6 cycles; and ii) interested outcomes (OS, PFS) were mentioned. We excluded studies if: i) they did not reveal an adequate statistical analysis; ii) reviews or case reports.

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## Study selection and data extraction

Search was done by two researchers. In initial appraisal, the title and abstracts of the studies were read and we recruited the papers regarding inclusion and exclusion criteria. In continues, in the secondary appraisal, the full text of the studies was read scrutiny and the following data were extracted: the first author's name, publication year, number of patients, overall survival, and progression-free survival.

## Quality assessment

The quality of the articles was checked by the Newcastle-Ottawa quality assessment scale.<sup>11-18</sup> We selected items that focused on the adequate assessment of outcome, representativeness of study patients, adequacy of follow-up, a demonstration that the outcome of interest was not present at the start of the study, and sufficient length of follow-up to allow outcomes to arise.

## Data analysis

Data were analyzed by CMA software. For heterogeneity, Cochran's Q test and I<sup>2</sup> were applied (the heterogeneities of the studies were divided into; less than 25% (low heterogeneity), 25% to 75% (moderate heterogeneity) and more than 75% (high heterogeneity). Considering the heterogeneity of the selected studies (I<sup>2</sup>=79.60, Q=29.42, P<0.001), DerSimonian and Laird's random-effects model was designed to combine studies and estimate the difference in means survival between two groups (case and control). For publication bias, Kendal's tau in Begg and Manzumdar test and Funnel plot were utilized.

## Results

A total of 114 studies were identified from the database search, of which 18 abstracts were retrieved for full-text evaluation. Seven studies met the inclusion criteria and were included in this meta-analysis<sup>4,18</sup> (Figure 1).

The characteristics of the included studies were shown in Table 1.

Overall, 1018 GBM patients were included. According to our analysis, the overall survival was higher in the case group (>6 cycles TMZ) compared to the control group (6 cycles TMZ) (Z=2.375, P=0.018). The lower and upper limits were between 1.002-10.467 months (Figure 2). The case group had higher progression-free survival compared with the control group (Z=3.84; P<0.001). The lower and upper limits were between 2.559-7.894 months (Figure 3).

Figure 4 shows the publication bias of the studies. The results indicate no publication bias with Kendall's tau test (Z=1.50; P=0.013).

## Discussions

Glioblastoma multiforme is the most common primary brain tumor in adults.<sup>12</sup> Median survival is generally less than one year from the time of diagnosis, and most patients die within 2 years.<sup>13</sup> Surgical resection followed by concurrent radiation therapy and TMZ chemotherapy is the current standard treatment of GBM.<sup>5</sup> Temozolomide (TMZ) is an oral chemotherapy agent that has demonstrated activity in malignant gliomas. TMZ has 100% bioavailability and easily crosses the blood-brain barrier.<sup>8-10</sup>

Several randomized and nonrandomized trials have demonstrated the efficacy and safety of TMZ for the treatment of GBM.<sup>5,14</sup> In 2005, Stupp and colleagues revealed the result of a phase III study conducted over 573 patients with high grade glioma from 85 centers. They compared patients that received radiotherapy alone with those received radiotherapy plus concurrent and six cycles of TMZ therapy. In their study, the median survival was 12.1 months with radiotherapy alone and 14.6 months with radiotherapy plus temozolomide. The two-year survival rate was 10.4% with radiotherapy alone and 26.5% with radiotherapy plus temozolomide.<sup>5</sup>

The updated 5-years survival result was 1.9% in radiotherapy alone group compared to 9.8% in the radiotherapy with TMZ.<sup>13</sup>

The current standard TMZ therapy for newly diagnosed GBM is based on Stupp protocol (*i.e.*, administration of 1 concurrent and up to 6 adjuvant cycles of TMZ, at the dose of 75 mg/m<sup>2</sup> and 150-200 mg/m<sup>2</sup> for 5 days, respectively).<sup>5,13</sup> Sun *et al.* in a meta-analysis found that the intensified regimens (like 50 mg/m<sup>2</sup>, day 1-28; 150 mg/m<sup>2</sup>, day 1-7 and then day 15-21; 100 mg/m<sup>2</sup>, day 1-21) did not show any survival advantage (HR 1.07, 95% CI 0.94-1.22; p=0.31) as compared to regimens with higher peak concentration during a short period of time (daily doses ≥150 mg/m<sup>2</sup>/day within ≤7 days/cycle).<sup>12</sup> They found that the intensified regimens also predispose patients to higher rates of leukopenia. Their study suggested that intensified approach of delivering TMZ might not be the way forward to achieve a better clinical outcome and alternative approaches like extended duration of standard TMZ schedule may be worth exploring.<sup>12</sup>

Several studies and guidelines advocate prolonged use of adjuvant TMZ for more than 6 cycle.<sup>4,9,15</sup> But the impact of extended TMZ therapy in newly diagnosed GBM remains a topic of discussion.

Hau *et al.* in 2007, published data collected from fifty German centers on the use of TMZ for at least 12 cycles in patients with GBM.<sup>14</sup>

Seventy-three patients with primary GBM and 65 cases with recurrent disease received a median of 13 TMZ cycles and 14 cycles, respectively. No evidence of tumor progression was observed during treatment in either group. In this study, the median

**Table 1. The studies characteristics included in the final stage of the appraisal.**

First author name	Year	Sample size in case group (>6 cyle TMZ)	Sample size in control group (6 cyle TMZ)	OS in case group (>6 cyle TMZ)	OS in control group (6 cyle TMZ)	PFS in case group (>6 cyle TMZ)	PFS in control group (6 cyle TMZ)
Bhandari	2017	20	20	23.8	15.4	16.8	12.8
Skardelly	2017	32	32	28.6	25.2	20.9	13.7
Gramatzki <i>et al.</i>	2017	61	81	25.6	26.2	13.5	10.2
Refae <i>et al.</i>	2015	30	29	24.1	18.1	18.8	12.1
Malkoun <i>et al.</i>	2012	29	23	24.6	16.5	24.6	16.5
Barbagallo <i>et al.</i>	2014	19	18	28	8	20	4
Blumenthal <i>et al.</i>	2017	291	333	27	24.9	12.2	10.4

OS was 30.6 months for patients with GBM and 22.4 months from initiation of TMZ and PFS was 14 months (range 10-40 months) for patients treated with first-line TMZ.

Hau *et al.* found an overall 2-year survival time of 68% (50 patients) in the primary GBM group of patients treated with prolonged TMZ and concluded that long term TMZ therapy is well tolerated.<sup>14</sup>

Seiz *et al.* reported a significant correlation between survival and the number of TMZ cycles in 59 of 114 patients treated with prolonged TMZ therapy (range 6-57 cycles).<sup>16</sup> The median survival of their patients was 15 months. TMZ therapy was stopped in the study of Seiz *et al.* due to toxicity (34%), tumor progression (23%), patient's wish (4%), or unspecified reasons.<sup>16</sup>

The Bhandari trial (2017) evaluated survival between patients received 6 cycles of TMZ and those received 12 cycles of TMZ. The median OS of patients with prolonged and standard treatment were 23.8 and 15.4 months, respectively (statistical significance was not found). The 2-year OS rates were 35.5% in the 12-cycle

TMZ arm *versus* 12.9% in the 6-cycle TMZ arm ( $P=0.044$ ).

In the Bhandari trial, the median PFS was 18.7 months in the 12-cycle TMZ group, compared to 16.4 months in the 6-cycle TMZ group (statistical significance was not found).<sup>17</sup>

In the Skardelly *et al.* cohort study, treating physicians determined the number of cycles of TMZ maintenance therapy. Patients were divided into three groups: patients stopped TMZ maintenance therapy before the sixth cycle (group A), patients completed six TMZ maintenance cycles (group B), and those continued with TMZ treatment after six cycles (group C).

The median OS was 25.2 months (95% CI: 17.7 to 55.5) in group B and 28.6 months (95% CI: 24.4, open) in the group C. However, results of the multivariate Cox regression indicated no statistically significant difference in OS between patients receiving more than 6 cycles TMZ and those who received exactly 6 cycles TMZ (relative risk [RR] 0.77; 95% CI: 0.39, 1.55;  $P=0.46$ ).

The median PFS was 13.7 months (95% CI: 10.6 to 17.5) in the group B and 20.9 months (95% CI: 15.2 to 43.5) in group C.

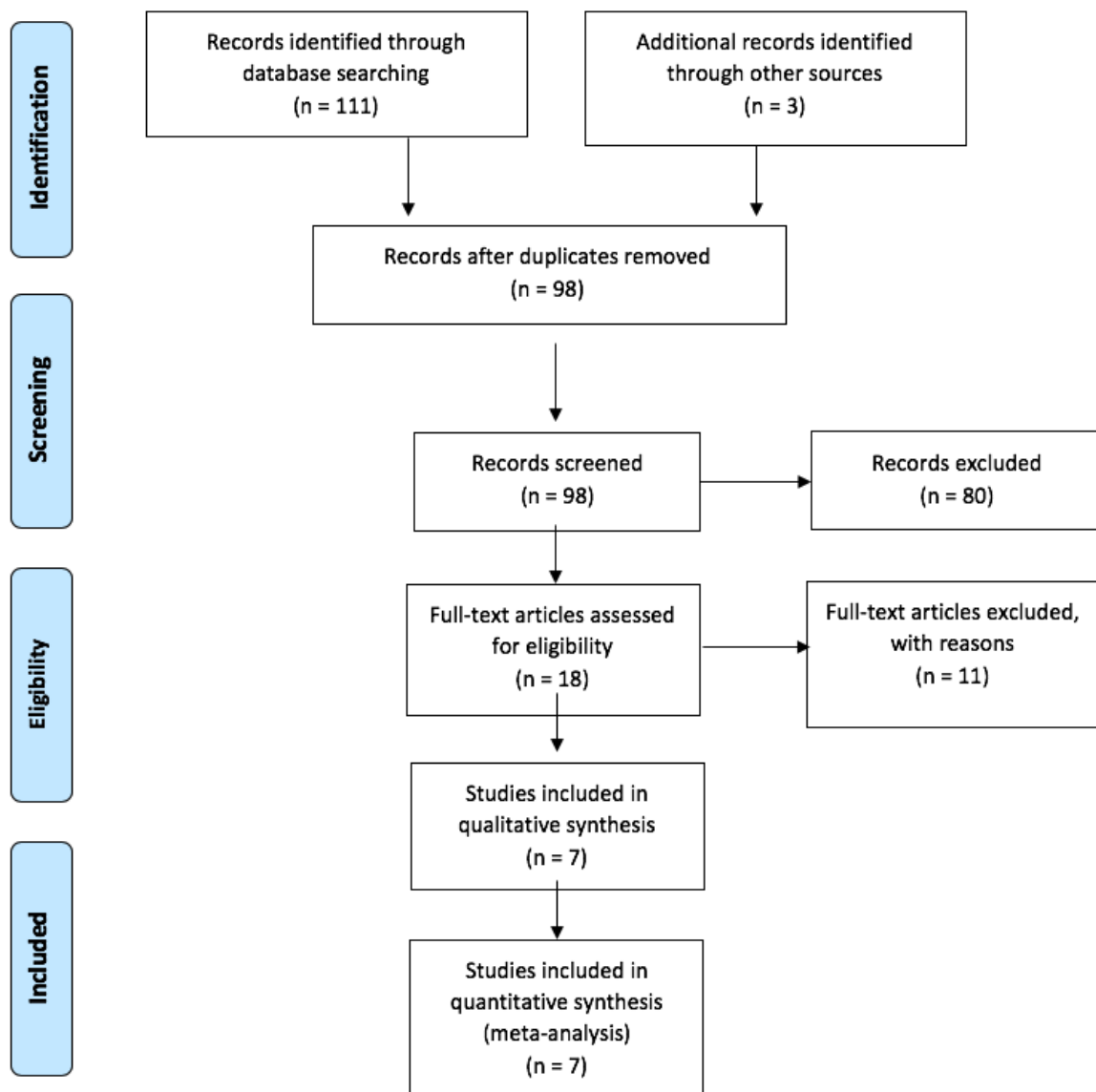


Figure 1. The PRISMA flowchart diagram.

Multivariate Cox regression showed a statistically significant difference in disease progression between patients receiving more than 6 cycles TMZ and those who received exactly 6 cycles TMZ (RR 0.52; 95% CI: 0.28 to 0.94; P=0.03).<sup>15</sup>

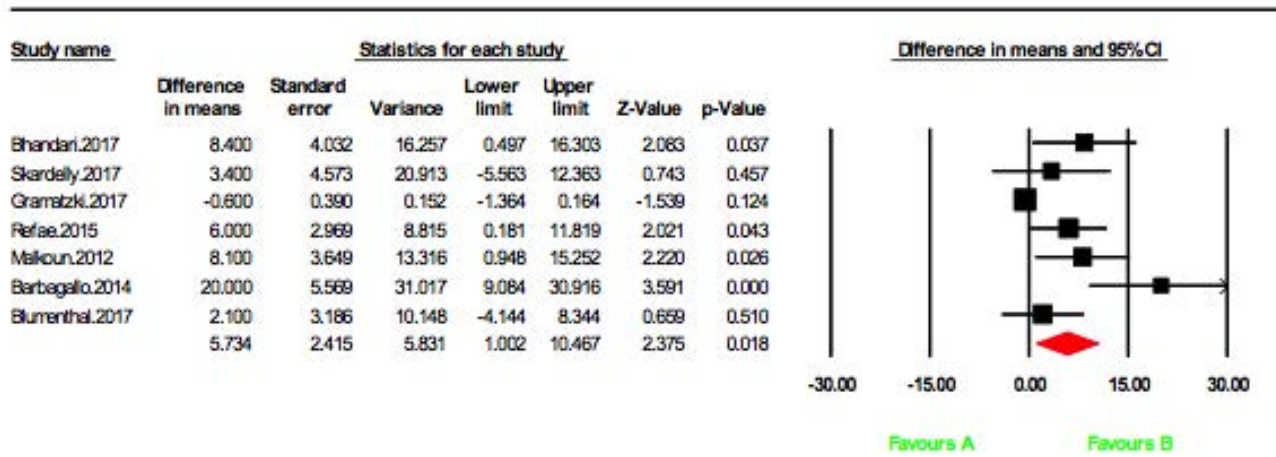
In 2017, Blumental *et al.* performed a pooled analysis of individual patient data from 4 randomized trials for newly diagnosed glioblastoma. They investigated a total of 2214 GBM patients in the four trials. 624 patients met their inclusion criteria. 333 cases discontinued TMZ after 6 cycles, while 291 patients continued maintenance TMZ up to 12 cycles or until progression. Extended TMZ therapy was associated with an improved PFS (P=0.03). However, there was not a relationship between OS and extended TMZ therapy (P=0.52).<sup>7</sup>

Refae *et al.* in the prospective phase II study, randomized 59 patients to 6 cycles of adjuvant TMZ (n=29) or >6 cycles of adju-

vant TMZ (n=30) groups. Both OS and PFS were statistically better in the patients receiving extended duration of TMZ (Median PFS of 12.1 months for patients with 6 cycles of adjuvant TMZ; P=0.015 and the median OS of 18.1 and 24.1 months for patients receiving 6 cycles and more than 6 cycles of adjuvant TMZ, respectively; P=0.048).<sup>18</sup>

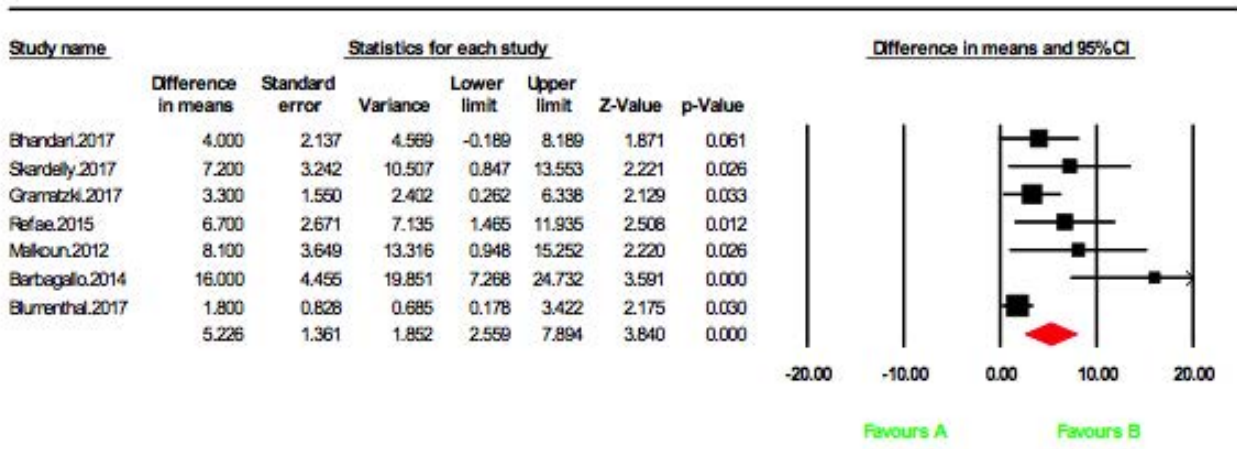
Darlix *et al.* in a retrospective French study reviewed files of 448 patients with GBM. They included 58 patients. All patients received radiotherapy with concomitant TMZ. Twenty patients received extended treatment, while 38 received standard treatment. They found that extended treatment improved both OS (P=0.01) and PFS (P=0.03) without a remarkable increase in toxicity.<sup>18</sup>

Toxicity is a factor that can limit the prolonged administration of chemotherapy agents. TMZ can cause myelosuppression and



**Meta Analysis**

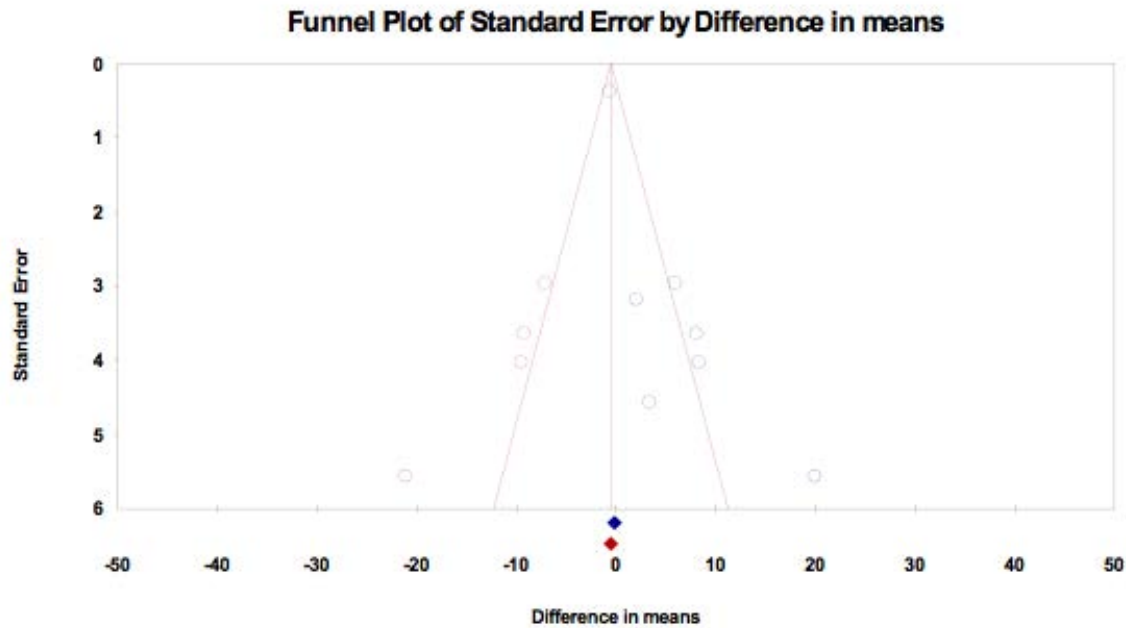
Figure 2. The summary of difference in overall survival of the studies.



**Meta Analysis**

Figure 3. The summary of progression free survival (PFS) of studies.





**Figure 4.** The funnel plot of the studies.

especially thrombocytopenia. Thrombocytopenia might be observed in approximately 12%-20% of cases.<sup>9,14</sup>

Also known that TMZ could have a profound impact on total lymphocyte count.

In Refae *et al.* study, almost all Grade 3-4 toxicity encountered during concurrent chemoradiotherapy. Out of 53 patients started concurrent chemoradiotherapy, 4 patients encountered grade 3-4 hematological toxicity which imposed stoppage of TMZ.<sup>18</sup>

Such a result is almost constant in most of the published studies. Hau *et al.* series had few G 3 - 4 toxicities.<sup>14</sup> Malkom *et al.* reported that in their retrospective study 8 out of 46 patients (17.3%) required dose adaptation because of side effects in the adjuvant phase of their study.

Malkom *et al.* also concluded the safety and feasibility of long-term adjuvant TMZ in a retrospective study.<sup>9</sup>

### Limitations

The studies regarding the clinical effectiveness of prolonged adjuvant TMZ for adult patients with high-grade gliomas were limited to two RCTs and few cohort and retrospective studies.

Due to the compromised quality and the small sample size in some of the included studies, the clinical effectiveness of prolonged TMZ therapy relative to the standard 6-cycle regimen for the target patients should be interpreted with caution,

There were no economic investigations performed to assess the cost-effectiveness of prolonged adjuvant TMZ compared with the standard 6-cycle TMZ in patients with high-grade gliomas.

### Conclusions

Evidence from this meta-analysis suggests that prolonged TMZ therapy compared to the standard 6-cycle TMZ therapy was associated with higher survival in patients with glioblastoma.

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