# Role of Temozolomide Regimen on Survival Outcomes in Molecularly Stratified WHO Grade II Gliomas: A Systematic Review

### Abstract

Objective/Introduction: Although a critical chemotherapeutic, temozolomide's optimal regimen for 2016 World Health Organization (WHO) Grade II gliomas remains elusive, hence there is utility in not only cataloging survival outcomes of Grade II glioma subtypes against the background of temozolomide regimens, but also quantifying differences in progression-free survival (PFS) and overall survival (OS). Materials and Methods: A systematic review of MEDLINE, Embase, and Cochrane Central Register of Controlled Trails was conducted by using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis and the Cochrane Handbook of Systemic Reviews of Interventions. Results: Each molecular subtype of WHO Grade II glioma had a different temozolomide regimen identified as optimal in prolonging PFS and OS. For PFS, with temozolomide, the 25<sup>th</sup>, 50<sup>th</sup>, and 75<sup>th</sup> percentiles, were as follows (in months), respectively–A-wt II: 6.90, 12.95, and 19.95; A-mt II: 34.45, 36.01, and 39.60; OD II: 37.90, 46.00, and 55.03 (P = 0.016). For OS, the first quartile (25%), median (50%), third quartile (75%), were respectively identified (in months-A-wt II: 21.6 (median; n = 1); A-mt II: 60.6, 85.2, and 109.8; OD II: 86.1, 96.2, and 106.3 (P = 0.37). Conclusion: For each tumor molecular subtype, a different temozolomide regimen was identified as optimal for prolonging PFS and OS. Furthermore, regardless of temozolomide regimen, A-wt II had a significantly shorter PFS than A-mt II and OD-II. Overall, the data can provide useful prognostic insight to patients when making critical treatment decisions. Moreover, by cataloging and assessing survival outcomes per temozolomide regimen, such may facilitate future clinical trial design.

**Keywords:** Astrocytoma, glioma, low-grade glioma, oligodendroglioma, overall survival, progression-free survival, temozolomide

# Introduction

Limited knowledge of life expectancy and disease outcome can be barriers for patients to accurately understand their prognoses. Without appropriate insight, a patient may make treatment decisions that do not reflect his/her true values.<sup>[1]</sup> Such a burden may be amplified especially for low-grade gliomas (LGG), which not only are usually diagnosed during the second to fourth decades of life in typically functional patients, but also transform unpredictably to higher grades.<sup>[2,3]</sup> Unfortunately, precise data on overall survival (OS) and progression-free survival (PFS) for World Health Organization (WHO) Grade II gliomas remains elusive, as there persists to be lack of randomized controlled trials comparing treatment modalities.<sup>[4]</sup> Hence, optimal management remains contested, ranging from watch-and-wait to maximal

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resection, along with combinations of chemoradiotherapy.<sup>[4]</sup> Moreover, unlike WHO Grade IV gliomas, where a specific temozolomide regimen (i.e., Stupp protocol) has demonstrated survival benefit, the appropriate utilization of temozolomide in Grade II gliomas remains unknown–such is particularly important for under-resourced communities where maximal safe resection may not be available.<sup>[5,6]</sup>

Since the updated 2016 WHO classification for central nervous system tumors – which now relies upon an integrated diagnosis combining molecular markers with histology, along with evidence that Grade II gliomas stratified by molecular subtype have distinct survival outcomes and tumor microenvironments, there is possibility that optimal temozolomide regimen varies depending on Grade II glioma molecular subtype.<sup>[6-8]</sup>

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Hence, utilizing the 2016 WHO classification, this systematic review sought to provide a comprehensive catalog of all temozolomide regimens and outcomes (i.e., PFS and OS) for molecularly stratified WHO Grade II gliomas. By assessing differences in survival per specific temozolomide regimen, a better understanding can develop regarding how temozolomide regimens modulate outcome per molecular subtype. Therefore, there is potential to not only identify an optimal regimen per molecular subtype and subsequently facilitate future clinical trial design, but also provide patients with greater prognostic insight when contemplating difficult treatment decisions.

# **Materials and Methods**

The systematic review was designed in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis and the Cochrane Handbook of Systematic Reviews of Interventions.<sup>[9-11]</sup>

# **Eligibility criteria**

### Study types

Only nonexperimental nonanimal clinical investigations were included.

### Participants

Subjects were adult humans (18 years or older) stratified by molecular subtyped WHO Grade II gliomas.<sup>[6]</sup> Genotype definitions were as follows: Wild type astrocytomas, IDH-wild type; mutant astrocytoma, IDH-mutant with non-1p/19q codeletion; oligodendroglioma, IDH-mutant with 1p/19q codeletion. If studies characterized Grade II gliomas as positive 1p/19q codeletion (without IDH status), such tumors were imputed as oligodendrogliomas, as the vast majority of 1p/19q codeletion patients have IDH-mt.<sup>[12]</sup>

### Interventions

Interventions targeting WHO Grade II gliomas were limited to those utilizing temozolomide, while excluding those exclusively involving surgery, radiotherapy, or other chemotherapies.

### **Outcomes**

OS and progression-free survival in unit of time (days, months, years) or rate, were the values collected. OS was defined as the time of intervention to death. PFS was defined as the time of intervention to tumor recurrence/ progression, characterized by radiological or clinical deterioration. Clinical deterioration involved worsening/ new focal deficits or symptoms of elevated intracranial pressure. Radiologic deterioration involved increased/ new tumor contrast enhancement or FLAIR hyperintensity signal changes, increased mass effect or midline shift, or volume enlargement. Definition of outcome measures from each study was also collected to confirm external consistency.

### Follow up time

Follow-up time was restricted at 48 months.

### Language

Only articles written in English were included.

#### Information sources

Medical subheadings and text words related to LGG, molecular subtypes, and treatment, were utilized for the search strategy. Medline (PubMed interface, 2008 onwards), Embase (Ovid interface, 2008 onwards), and Cochrane Central Register for Controlled Trials (Wiley interface, current issue), were all searched. 1 January 2008 was selected as the start date for the search, based the first paper subcategorizing gliomas on the IDH molecular marker.<sup>[13]</sup> In relevant literature, references were manually searched for additional trials.

# Search strategy

Other than dates, no database search limitations were utilized. An electronic search examined Embase (January 1, 2008 to December 11, 2018), MEDLINE (January 1, 2008 to December 11, 2018), and Cochrane Central Register of Controlled Trails (January 1, 2008 to December 11, 2018); Appendix 1 provides the search protocols, including keywords. Specific search strategies were developed under guidance of Queen Square Institute of Neurology library and statistical services staff with expertise in systemic review searches.<sup>[14]</sup> To assess the search sensitivity and quality, robust target references were utilized–all of which were identified.<sup>[7,15-18]</sup>

# **Study records**

### Data management

Results of the literature search were imported to EndNote X9 (Clarivate Analytics, Philadelphia, Pennsylvania). Software utilization sought to reduce data entry errors and bias (i.e., deduplicating references). All investigation reports were reviewed to assess for inconsistencies (e.g., design description, outcome presentation, total patients analyzed).

### Selection process

Authors screened all titles and abstracts independently on the basis of the inclusion criteria. Literature meeting inclusion criteria was reviewed in full, to assess appropriateness for ultimate entry into in the systematic review.

### Data items

In accordance with recommendations from the Cochrane Handbook for Systematic Reviews of Interventions (chapter 7), the following data was collected into a Microsoft Excel spreadsheet: Author, publication year, journal citation; setting; inclusion and exclusion

criteria; study design; study population; tumor details at diagnosis (tumor size, location, and histology); risk of bias (including assessment of bias); length of follow-up; outcomes (OS, PFS).<sup>[19]</sup>

# Data synthesis

Data was placed into tables permitting for comparison of OS and PFS, stratified by tumor type and temozolomide regimen. A quantile-quantile plots were produced for the PFS and OS data, which demonstrated both datasets as nonnormally distributed (even with transformations). Secondary to the nonnormal distribution, when the data was pooled (cases with n = 1 were excluded), the summary measures included the 25-percentile, median, and 75-percentile; 95-percentile confidence interval of the median could not be determined due to the small number of identified studies. Meanwhile, a nonparametric Kruskal-Wallis test was performed to determine if the survival outcomes stratified by genotype were significantly different; next an analysis was conducted utilizing the independent Wilcoxon rank sum test.<sup>[20,21]</sup> All analysis was run through R Statistical Software (R Foundation for Statistical Computing, Vienna, Austria).<sup>[22]</sup>

# Results

The search of Medline, Embase, and Central yielded a total of 8311 abstracts [Figure 1]. Four more manuscripts

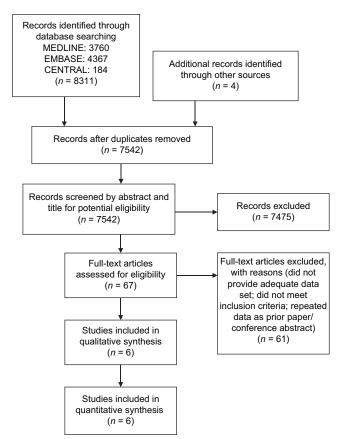


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analysis

were added upon sifting through systematic reviews identified in our search. After duplicates were removed, we screened 7542 texts by reading the title and full abstracts. From these, 7475 were excluded for not conforming to inclusion criteria, while 67 were flagged for further review in the full-text assessment phase. Of the 67, 61 articles were removed for not examining temozolomide, for not providing raw PFS/OS data in the form of day/month/year (many abstracts met inclusion criteria, however provided data in the form of hazards ratios, *P* values, or Kaplan–Meier graphs without the ability to extract raw PFS or OS), or being systematic reviews. Ultimately, six manuscripts were included for quantitative synthesis in the form of Tables 1 and 2.

# Progression-free survival data

From the six studies, five provided PFS data [Table 1]. Four studies were prospective (with one randomized) and one retrospective.<sup>[7,17,23-25]</sup> Two examined a dose-dense regimen, one a low-dose, and two others varied by the number of cycles (i.e., greater than or less than 12-cycles).<sup>[7,17,23-25]</sup>

Examining high risk tumors, Baumert *et al.* conducted a randomized open label phase 3 intergroup study of a dose-dense temozolomide regimen, consisting of 75 mg/m<sup>2</sup> daily for 21 days, repeated every 28 days for 12 cycles maximum [Table 1]; median PFS for OD-II, A-mt II, and A-wt II were as follows: 55.03, 36.01, and 23.69 months.<sup>[7]</sup> The other dose-dense regimen was from another prospective single arm phase II study by Pellerino *et al.*, which investigated temozolomide 1 week on/1 week off, for a median of 11 cycles (range, 2–18 cycles); OD-II had a PFS of 46 months.<sup>[24]</sup>

Meanwhile, Houillier *et al.* retrospectively investigated the role of temozolomide administered daily for 5-days at 200 mg/m<sup>2</sup>, repeated every 28 days for at least 12 cycles (or up to 30 cycles).<sup>[23]</sup> PFS for OD-II, A-mt II, and A-wt II were respectively: 37.9, 32.9, and 18.7 months.<sup>[23]</sup> Similarly, examining temozolomide administered daily for 5-days at 200 mg/day repeated every 28 days, but rather for 12 cycles maximum, the prospective trial by Wahl *et al.* found PFS for OD-II, A-mt II, and A-wt II to be respectively: 58.8, 43.2, and 7.2 months.<sup>[17]</sup>

Lastly, one study (prospective phase II open label) examined low-dose temozolomide 50 mg/mq/day, 1 week on/1 week off, until progression or for a maximum of 24 months, found PFS for OD-II and A-wt II to be 35 and 6 months, respectively.<sup>[25]</sup>

After pooling data based on genotype, a Kruskal-Wallis test found significant differences in median PFS (P = 0.016) after temozolomide treatment, subsequently Wilcoxon ranked sum tests identifying A-wt II PFS as significantly different to A-mt II and OD-II [Table 2]. The 25<sup>th</sup> percentile, median (50<sup>th</sup> percentile), and 75<sup>th</sup> percentile for PFS was then found, respectively–A-wt II: 6.90, 12.95,

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29       Astrocytoma-wild       Ratiotherapy       100,90,95% CI: No Significant         20       Astrocytoma-wild       Emocolonide (dose dense, 75 mg/m² dally, for 21 days, 555425)       Ne semtent:         20       Astrocytoma-wild       Emocolonide (dose dense, 75 mg/m² dally, for 21 days, 5554225)       Ne semtent:         100 <sup>201</sup> 63.4 months       74       Oligodendrogioma       12.7.25.60)       we atment:         100 <sup>201</sup> 63.4 months       74       Oligodendrogioma       These       37.9       Mifferences         100 <sup>2021</sup> Astrocytoma-nutuant       Temocolonide (daily for 5 days, at 200 mg/m², repeated       32.9       did not reach         217 <sup>203</sup> 64 months       21       Oligodendrogioma       32.9       did not reach         217 <sup>204</sup> 64 months       21       Digodendrogioma       18.7       46       71.40         217 <sup>204</sup> 64 months       21       Digodendrogioma       Temocolonide (daily for 5 days, at 200 mg/m², repeated       32.9       did not reach         217 <sup>204</sup> 64 months       21       Digodendrogioma       11       71.40         217 <sup>204</sup> 64 months       21       Digodendrogioma       11.40       71.40         217 <sup>204</sup> 64 months       11       11 <td></td> <td></td> <td></td> <td>II, high risk</td> <td>repeated every 28 days, for 12 cycles maximum)</td> <td>37.95-NR)</td> <td>differences</td> <td></td> <td>CI: 30.71-62.35)</td>				II, high risk	repeated every 28 days, for 12 cycles maximum)	37.95-NR)	differences		CI: 30.71-62.35)
type II, high risk         11:1:2:3.6.69         treatment- type II, high risk           1         Opped II, high risk         11:1:2:3.6.69         14:0:0:0:0:0:0:0:0:0:0:0:0:0:0:0:0:0:0:0			29	Astrocytoma-wild	Radiotherapy	19.09 (95% CI:	No Significant		0% (95% CI:
20       Astrocytoma-wild       Temozolomide (dose dense, 75 mg/m <sup>2</sup> daily, for 21 days, 236) (95%, C1:       dependent         100 <sup>231</sup> TH       10       Uppe II, high risk       reparted every 28 days, for 12 cycles an aximum)       5.55-42.25)       differences         100 <sup>231</sup> TH       10       Collopedendroglioma       revery 28 days, at least 12 cycles or up to 30)       37.9       differences         10 <sup>231</sup> Astrocytoma-mutant       revery 28 days, at least 12 cycles or up to 30)       3.2.9       did not reach         11       Tancoytoma-mide       revery 28 days, at least 12 cycles or up to 30)       3.2.9       did not reach         11       Tancoytoma-mide       revery 28 days, at least 12 cycles or up to 30)       3.2.9       did not reach         11       Astrocytoma-mide       revery 28 days, at least 12 cycles or up to 30)       3.2.9       did not reach         117 <sup>241</sup> H months       21       Oligodendroglioma       revery 28 days, at least 12 cycles or up to 30)       3.2.9       did not reach         117 <sup>241</sup> H months       21       Oligodendroglioma       revery 28 days, at least 12 cycles or up to 30)       3.2.9       did not reach         117 <sup>241</sup> H       11       revery 28 days, at least 12 cycles or up to 30)       3.2.9       did not reach				type II, high risk		11.27-25.69)	treatment-		(00.0-0.00)
r       9ype II, high risk, repeated every 28 days, for 12 cycles maximum)       555-42.25)       differences         100 <sup>021</sup> 1       1       555-42.25)       differences         1010 <sup>121</sup> 1       1       Errozolomide (daily for 5 days, at 200 mg/m², repeated       37.9       These         11       Errozolomide (daily for 5 days, at 200 mg/m², repeated       37.9       differences         37.0       Astrocytoma-mutant       Terrozolomide (daily for 5 days, at 200 mg/m², repeated       37.9       differences         11       Errozolomide (daily for 5 days, at 200 mg/m², repeated       32.9       differences       11.40         11       Errozolomide (daily for 5 days, at 200 mg/m², repeated       3.9       differences       11.40         21       Oligodendrogliom       Errozolomide (daily for 5 days, at 200 mg/m², repeated       3.4       45.80         31       Astrocytoma-wild       Terrozolomide (daily for 5 days, at 200 mg/day, repeated       3.2       43.8       45.80         31       Astrocytoma-wild       Terrozolomide (daily for 5 days, at 200 mg/day, repeated       3.2       45.80         31       Astrocytoma-wild       Terrozolomide (daily for 5 days, at 200 mg/day, repeated       3.4       45.80         31       Astrocytoma-wild       Terrozolomide (daily for 5 days, at 200			20	Astrocytoma-wild	Temozolomide (dose dense, 75 mg/m <sup>2</sup> daily, for 21 days,	23.69 (95% CI:	dependent		17.78% (95%
r       63.4 months       74       Oligodendtoglioma       Temozolomide (daity for 5 days, at 1200 mg/m², repeated       37.9       These         100 <sup>213</sup> 11       cvery 28 days, at least 12 cycles or up to 30)       differences       differences         11       Temozolomide (daity for 5 days, at 200 mg/m², repeated       32.9       diff not reach         2       Astrocytoma-mutant       Temozolomide (daity for 5 days, at 200 mg/m², repeated       18.7       39         3       Astrocytoma-wild       every 28 days, at least 12 cycles or up 0.30)       46       71.40         17 <sup>1241</sup> 11       cvery 28 days, at 200 mg/m², repeated       18.7       39       45.80         17 <sup>1243</sup> 11       11       every 28 days, at 200 mg/m², repeated       18.7       34       45.80         17 <sup>1243</sup> 11       11       every 28 days, up to 12 cycles)       34       45.80       34         17 <sup>1244</sup> 11       11       for days, repeated       18.7       34       45.80         17 <sup>1244</sup> 11       11       every 28 days, up to 12 cycles)       34       45.6AA)       34       45.80         11       11       for days, repeated       13.3       45.6AA)       34       45.6AA)       36       45.6AA)				type II, high risk	repeated every 28 days, for 12 cycles maximum)	5.55-42.25)	differences		CI: 3.69-40.48)
100 <sup>231</sup> IIcvery 28 days, at least 12 cycles or up to 30)differencesArrocytoma-mutantevery 28 days, at 200 mg/m², repeated3.9did not reachType IIevery 28 days, at least 12 cycles or up to 30)significance3.9did not reachType IIevery 28 days, at least 12 cycles or up to 30)3.04.671.40Type IIevery 28 days, at least 12 cycles or up to 30)4.671.40Type IIevery 28 days, at least 12 cycles or up to 30)4.671.4017 <sup>234</sup> 2101igodendrogliomaFemozolomide (dose dense, 1 week on/1 week off, 4.671.4024DH-wild typeTemozolomide (dose dense, 1 week on/1 week off, 4.671.4024DH-wild typeTemozolomide (dose dense, 1 week on/1 week off, 4.54.545.8024DH-wild typeTemozolomide (dost) for 5 days, at 200 mg/day, repeated5.8 (5.6/KM)45.5/KM)24DH-wild typeTemozolomide (duity for 5 days, at 200 mg/day, repeated5.8 (5.6/KM)45.6/KM)31Astrocytoma-mutantTemozolomide (duity for 5 days, at 200 mg/day, repeated5.6 (5.6/KM)45.6/KM)31Astrocytoma-wildTemozolomide (duity for 5 days, at 200 mg/day, repeated2.6 (5.6/KM)45.6/KM)31Astrocytoma-wildTemozolomide (duity for 5 days, at 200 mg/day, repeated2.6 (5.6/KM)45.6/KM)31Astrocytoma-wildTemozolomide (duity for 5 days, at 200 mg/day, repeated2.6 (5.6/KM)45.6/KM)32Astrocytoma-wildTemozolomide (duity for 5 days, at 200 mg/day,	Houillier	63.4 months	74	Oligodendroglioma	Temozolomide (daily for 5 days, at 200 mg/m <sup>2</sup> , repeated	37.9	These		
Astrocytoma-mutant       Temozolomide (daity for 5 days, at 200 mg/m <sup>2</sup> , repeated       32.9       did not reach         II       every 28 days, at least 12 cycles or up to 30)       significance         Astrocytoma-wild       Temozolomide (daity for 5 days, at 200 mg/m <sup>2</sup> , repeated       18.7       71.40         Astrocytoma-wild       Temozolomide (daity for 5 days, at 200 mg/m <sup>2</sup> , repeated       18.7       71.40         Astrocytoma-wild       Temozolomide (daity for 5 days, at 200 mg/m <sup>2</sup> , repeated       18.7       45.80         17Pal       II       median 11 cycles, range 2-18 cycles)       46       71.40         at/,       90 months       44       01godendroglioma       Temozolomide (daity for 5 days, at 200 mg/day, repeated       58.8 (95% CI:       45.6NA)         11       median 11 cycles, range 2-18 cycles)       38.8 (95% CI:       P=0.01         12       Astrocytoma-mutant       Temozolomide (daity for 5 days, at 200 mg/day, repeated       35.6 6.4.8)       56.6.4.8)         13       Astrocytoma-wild       Temozolomide (daity for 5 days, at 200 mg/day, repeated       13.2 (95% CI:       P=0.01         13       Astrocytoma-wild       Temozolomide (daity for 5 days, at 200 mg/day, repeated       13.2 (95% CI:       P=0.01         13       Astrocytoma-wild       Temozolomide (daity for 5 days, at 200 mg/day, repeated <td< td=""><td><i>et al.</i>, 2010<sup>[23]</sup></td><td></td><td></td><td>Π</td><td>every 28 days, at least 12 cycles or up to 30)</td><td></td><td>differences</td><td></td><td></td></td<>	<i>et al.</i> , 2010 <sup>[23]</sup>			Π	every 28 days, at least 12 cycles or up to 30)		differences		
IIsignificance $2^{1}$ Astrocytoma-wildrevery 28 days, at least 12 cycles or up to 30)significance $7$ Type IIevery 28 days, at least 12 cycles or up to 30) $7$ $7$ $17^{pell}$ 24DH-wild typeremozolomide (dose dense, 1 week on/1 week off, at $46$ $71.40$ $117^{pell}$ 24DH-wild typeremozolomide (dose dense, 1 week on/1 week off, at $46$ $71.40$ $al_n$ 90 months24DH-wild typeremozolomide (dose dense, 1 week on/1 week off, at $45$ $45.60$ $al_n$ 90 months44Oligodendrogliomremozolomide (dose dense, 1 week on/1 week off, at $45$ $45.6NA$ $al_n$ 90 months44Oligodendrogliomremozolomide (daity for 5 days, at 200 mg/day, repeated $58.8 (95\% CI:$ $P=0.01$ $11$ 11 (imputed)every 28 days, up to 12 cycles) $25.64.8$ $25.64.8$ $25.64.8$ $11$ 54 months10Oligodendrogliomrevery 28 days, up to 12 cycles) $25.64.8$ $72.(95\% CI:$ $11$ 54 months10Oligodendrogliomremozolomide (low dose, 50 mg/day, repeated $25.64.8$ $72.(95\% CI:$ $11$ 54 months1010mediation to 2 cycles) $25.64.8$ $72.(95\% CI:$ $11$ 54 months1010mediation to 2 cycles) $25.64.8$ $72.(95\% CI:$ $12$ 54 months1010mediation to 2 cycles) $72.(95\% CI:$ $9.0.04$ $12$ 1010mediation12 cycles) $7$				Astrocytoma-mutant	Temozolomide (daily for 5 days, at 200 mg/m <sup>2</sup> , repeated	32.9	did not reach		
Astrocytoma-wild       Temozolomide (daiy for 5 days, at 200 mg/m², repeated       18.7         Type II       Type II       every 28 days, at least 12 cycles or up to 30)       46       71.40         017 <sup>241</sup> 21       Oligodendrogliom       Temozolomide (dose dense, 1 week on/1 week off, at 60 mouths)       46       71.40         177 <sup>241</sup> 24       DH-wild type       Temozolomide (dose dense, 1 week on/1 week off, at 60 mouths)       46       71.40         ad, 90       90       months       41       Oligodendrogliom       Temozolomide (dose dense, 1 week on/1 week off, at 72       45.6-NA)       45.6-NA)         11       0       months       44       Oligodendrogliom       45.6-NA)       45.6-NA)         12       Astrocytoma-mutant       Temozolomide (daity for 5 days, at 200 mg/day, repeated 43.2 (95% CI: every 28 days, up to 12 cycles)       25.64.8)       7.2 (95% CI: every 28 days, up to 12 cycles)         13       Astrocytoma-wild       Temozolomide (daity for 5 days, at 200 mg/day, repeated 7.2 (95% CI: every 28 days, up to 12 cycles)       25.64.8)       7.0.04         11       Infimuted)       every 28 days, up to 12 cycles)       25.64.8)       7.2 (95% CI: every 28 days, up to 12 cycles)         12       Astrocytoma-wild       Temozolomide (low dose, 50 mg/mg/day, repeated       7.2 (95% CI: every 28 days, up to 12 cycles)       2.5.				Π	every 28 days, at least 12 cycles or up to 30)		significance		
Type II       Every 28 days, at least 12 cycles or up to 30)       71.40         17 <sup>[74]</sup> I       Oligodendroglioma       Temozolomide (dose dense, 1 week on/1 week off, at the median II cycles, range 2-18 cycles)       46       71.40         al,       90 months       24       DH-wild type       Temozolomide (dose dense, 1 week on/1 week off, at the median II cycles, range 2-18 cycles)       34       45.80         al,       90 months       44       Oligodendroglioma       Temozolomide (daity for 5 days, at 200 mg/day, repeated at 58.8 (95% CI: P=0.01       45.6-NA)         31       Astrocytoma-mutant       Temozolomide (daity for 5 days, at 200 mg/day, repeated at 32.95% CI: P=0.01       45.6-NA)         31       Astrocytoma-wild       Temozolomide (daity for 5 days, at 200 mg/day, repeated at 2.5-64.8)       25-64.8)         31       Astrocytoma-wild       Temozolomide (daity for 5 days, at 200 mg/day, repeated at 2.6-65%)       25-64.8)         32       Astrocytoma-wild       Temozolomide (daity for 5 days, at 200 mg/day, repeated at 32.095% CI: P=0.01         31       Astrocytoma-wild       Temozolomide (daity for 5 days, at 200 mg/day, repeated at 32.095% CI: P=0.01         33       Astrocytoma-wild       Temozolomide (daity for 5 days, at 200 mg/day, repeated at 32.095% CI: P=0.01         34       Astrocytoma-wild       Temozolomide (daity for 5 days, at 200 mg/day, repeated at 32.095% CI: P=0.01				Astrocytoma-wild	Temozolomide (daily for 5 days, at 200 mg/m <sup>2</sup> , repeated	18.7			
5       64 months       21       Oligodendroglioma       Temozolomide (dose dense, 1 week on/1 week off, 46       71.40         117 <sup>241</sup> II       median II cycles, range 2-18 cycles)       34       45.80         al.,       90 months       44       Oligodendroglioma       Temozolomide (daily for 5 days, at 200 mg/day, repeated 43.6, NA)       45.6-NA)         al.,       90 months       44       Oligodendroglioma       Temozolomide (daily for 5 days, at 200 mg/day, repeated 43.2, 05% CI:       45.6-NA)         al.,       90 months       44       Oligodendroglioma       Temozolomide (daily for 5 days, at 200 mg/day, repeated 43.2, 05% CI:       45.6-NA)         al.       31       Astrocytoma-wuld       Temozolomide (daily for 5 days, at 200 mg/day, repeated 43.6, 05% CI:       45.6-NA)         al.       54 months       10       Oligodendroglioma       Temozolomide (daily for 5 days, at 200 mg/day, repeated 43.6, 05% CI:       25.64.8)         al.       54 months       10       Oligodendroglioma       Temozolomide (daily for 5 days, at 200 mg/day, repeated 72.05% CI:       45.6-NA)         astrocytoma-wuld       Temozolomide (daily for 5 days, at 200 mg/day, repeated 72.05% CI:       25.64.8)       25.64.8)         astrocytoma-wuld       Temozolomide (daily for 5 days, at 200 mg/day, repeated 72.05% CI:       45.6-NA)         astrocytoma-wuld </td <td></td> <td></td> <td></td> <td>Type II</td> <td>every 28 days, at least 12 cycles or up to 30)</td> <td></td> <td></td> <td></td> <td></td>				Type II	every 28 days, at least 12 cycles or up to 30)				
117 <sup>p-41</sup> II     median 11 cycles, range 2-18 cycles)     34     45.80       al.,     24     IDH-wild type     Temozolomide (dose dense, 1 week onl' week off;     34     45.80       al.,     90 months     44     Oligodendroglioma     Temozolomide (daily for 5 days, at 200 mg/day, repeated     58.8 (95% CI:     P=0.01       1     I (imputed)     Temozolomide (daily for 5 days, at 200 mg/day, repeated     58.8 (95% CI:     P=0.01       1     Astrocytoma-mutant     Temozolomide (daily for 5 days, at 200 mg/day, repeated     43.5.6-NA)     45.6-NA)       13     Astrocytoma-wuld     remozolomide (daily for 5 days, at 200 mg/day, repeated     43.2 (95% CI:     P=0.01       13     Astrocytoma-wuld     remozolomide (daily for 5 days, at 200 mg/day, repeated     43.6.6-NA)     43.2 (95% CI:       13     Astrocytoma-wuld     remozolomide (daily for 5 days, at 200 mg/day, repeated     43.2 (95% CI:     P=0.01       13     Astrocytoma-wuld     remozolomide (laily for 5 days, at 200 mg/day, repeated     43.6.6-NA)     55.64.8)       13     Astrocytoma-wuld     remozolomide (laily for 5 days, at 10 mg/day, repeated     12.95% CI:     48.NA)       2     No Ip19q     remozolomide (low dose, 50 mg/mq/day, 1 week on/1     35     P=0.04       2     No Ip19q     remozolomide (low dose, 50 mg/mq/day, 1 week on/1     36	Pellerino	64 months	21	Oligodendroglioma	Temozolomide (dose dense, 1 week on/1 week off,	46		71.40	28.60%
24IDH-wild typeTemozolomide (dose dense, 1 week orf, nedian 11 cycles, range 2-18 cycles)3445.80al.,90 months44OligodendrogliomaTemozolomide (daily for 5 days, at 200 mg/day, repeated every 28 days, up to 12 cycles)58.8 (95% CI: 45.6-NA) $P=0.01$ 31Astrocytoma-mutant Temozolomide (daily for 5 days, at 200 mg/day, repeated in45.6-NA) $45.6-NA$ ) $56.6NA$ )31Astrocytoma-mutant Temozolomide (daily for 5 days, at 200 mg/day, repeated the $43.2 (95% CI:$ $2.5-64.8)$ $P=0.01$ 13Astrocytoma-wild Temozolomide (daily for 5 days, at 200 mg/day, repeated type II $25.64.8$ ) $25.64.8$ )13Astrocytoma-wild Temozolomide (low dose, 50 mg/mq/day, 1 week on/1 I (imputed) $35.64.8$ ) $P<0.04$ 2No 1p19qTemozolomide (low dose, 50 mg/mq/day, 1 week on/1 Temozolomide (low dose, 50 mg/mq/day, 1 week on/1 $35$ $P<0.04$ 2No 1p19qTemozolomide (low dose, 50 mg/mq/day, 1 week on/1 $36$ $P<0.009$ 7DH-mutant Temozolomide (low dose, 50 mg/mq/day, 1 week on/1 $36$ $P<0.009$ 7DH-mutant Temozolomide (low dose, 50 mg/mq/day, 1 week on/1 $36$ $P<0.009$ 8Astrocytoma-wildTemozolomide (low dose, 50 mg/mq/day, 1 week on/1 $36$ $P<0.009$ 7DH-mutant Temozolomide (low dose, 50 mg/mq/day, 1 week on/1 $5$ $P<0.009$ 8Astrocytoma-wildTemozolomide (low dose, 50 mg/mq/day, 1 week on/1 $5$ $P<0.009$ 7DH-mutantTemozolomide (low dose, 50 mg/mq/day, 1	<i>et al.</i> , $2017^{[24]}$			II	median 11 cycles, range 2-18 cycles)				
al.,       90 months       44       Oligodendroglioma       Temozolomide (daily for 5 days, at 200 mg/day, repeated       58.8 (95% CI:         11 (imputed)       every 28 days, up to 12 cycles)       45.6-NA)         31 Astrocytoma-mutant       Temozolomide (daily for 5 days, at 200 mg/day, repeated       58.8 (95% CI:         11 (imputed)       every 28 days, up to 12 cycles)       43.2 (95% CI:         13 Astrocytoma-mutant       Temozolomide (daily for 5 days, at 200 mg/day, repeated       43.2 (95% CI:         13 Astrocytoma-wild       Temozolomide (daily for 5 days, at 200 mg/day, repeated       43.2 (95% CI:         13 Astrocytoma-wild       Temozolomide (daily for 5 days, at 200 mg/day, repeated       43.2 (95% CI:         13 Astrocytoma-wild       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       35         14 (imputed)       week off, until progression or for maximum of 24 months)       7         15 (DH-mutant       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       5         16 (low dose, 50 mg/mq/day, 1 week on/1       56       56         17 (DH-mutant       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       56         18 Astrocytoma-wild       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       56         19 Astrocytoma-wild       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       56         10 Dh-mutant			24	IDH-wild type	Temozolomide (dose dense, 1 week on/1 week off,	34		45.80	25.00%
al.,       90 months       44       Oligodendroglioma       Temozolomide (daily for 5 days, at 200 mg/day, repeated       58.8 (95% CI:         11 (imputed)       every 28 days, up to 12 cycles)       45.6-NA)         31       Astrocytoma-mutant       Temozolomide (daily for 5 days, at 200 mg/day, repeated       58.8 (95% CI:         11       months       11       every 28 days, up to 12 cycles)       45.6-NA)         12       Astrocytoma-mutant       Temozolomide (daily for 5 days, at 200 mg/day, repeated       43.2 (95% CI:         13       Astrocytoma-wild       Temozolomide (daily for 5 days, at 200 mg/day, repeated       43.2 (95% CI:         13       Astrocytoma-wild       Temozolomide (low dose, 50 mg/mg/day, 1 week on/1       35         14       No lp19q       Temozolomide (low dose, 50 mg/mg/day, 1 week on/1       35         16       Oligodendroglioma       Temozolomide (low dose, 50 mg/mg/day, 1 week on/1       36         2       No lp19q       Temozolomide (low dose, 50 mg/mg/day, 1 week on/1       5         2       No lp19q       Temozolomide (low dose, 50 mg/mg/day, 1 week on/1       5         3       IDH-mutant       Temozolomide (low dose, 50 mg/mg/day, 1 week on/1       5         4       Astrocytoma-wild       Temozolomide (low dose, 50 mg/mg/day, 1 week on/1       5					median 11 cycles, range 2-18 cycles)				
II (imputed)       every 28 days, up to 12 cycles)       45.6-NA)         31       Astrocytoma-mutant       Temozolomide (daily for 5 days, at 200 mg/day, repeated       43.2 (95% CI:         13       Astrocytoma-mutant       Temozolomide (daily for 5 days, at 200 mg/day, repeated       43.2 (95% CI:         13       Astrocytoma-wild       Temozolomide (daily for 5 days, at 200 mg/day, repeated       43.2 (95% CI:         13       Astrocytoma-wild       Temozolomide (low dose, 50 mg/md/day, 1 week on/1       35         14       No lp19q       Temozolomide (low dose, 50 mg/md/day, 1 week on/1       35         2       No lp19q       Temozolomide (low dose, 50 mg/md/day, 1 week on/1       36         7       IDH-mutant       Temozolomide (low dose, 50 mg/md/day, 1 week on/1       36         7       IDH-mutant       Temozolomide (low dose, 50 mg/md/day, 1 week on/1       36         7       IDH-mutant       Temozolomide (low dose, 50 mg/md/day, 1 week on/1       36         4       Astrocytoma-wild       Temozolomide (low dose, 50 mg/md/day, 1 week on/1       36         7       IDH-mutant       Temozolomide (low dose, 50 mg/md/day, 1 week on/1       36         8       Astrocytoma-wild       Temozolomide (low dose, 50 mg/md/day, 1 week on/1       36         9       typelt       Temozolomide (low dose, 50	Wahl <i>et al.</i> ,	90 months	44	Oligodendroglioma	Temozolomide (daily for 5 days, at 200 mg/day, repeated	58.8 (95% CI:	P=0.01		
31       Astrocytoma-mutant       Tenozolomide (daily for 5 days, at 200 mg/day, repeated       43.2 (95% CI:         11       every 28 days, up to 12 cycles)       25-64.8)         13       Astrocytoma-wild       Temozolomide (daily for 5 days, at 200 mg/day, repeated       43.2 (95% CI:         13       Astrocytoma-wild       Temozolomide (daily for 5 days, at 200 mg/day, repeated       7.2 (95% CI:         13       Astrocytoma-wild       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       35         11       (imputed)       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       35         2       No 1p19q       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       35         2       No 1p19q       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       36         7       IDH-mutant       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       36         7       IDH-mutant       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       36         4       Astrocytoma-wild       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       36         4       Astrocytoma-wild       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       6         7       IDH-mutant       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       36         8       Astrocytoma-wild       Temozolomide (low dose, 50 mg/m	$2017^{[17]}$			II (imputed)	every 28 days, up to 12 cycles)	45.6-NA)			
II       every 28 days, up to 12 cycles)       25-64.8)         13       Astrocytoma-wild       Temozolomide (daily for 5 days, at 200 mg/day, repeated       7.2 (95% CI: 4.8)         type II       every 28 days, up to 12 cycles)       4.8-NA)         et al., 54 months       10       Oligodendroglioma       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       35         timputed)       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       35       4.8-NA)         2       No 1p19q       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       5         2       No 1p19q       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       5         7       IDH-mutant       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       5         7       IDH-mutant       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       36         7       IDH-mutant       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       36         4       Astrocytoma-wild       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       6         4       Astrocytoma-wild       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       6         7       two H       two H       two H       6			31	Astrocytoma-mutant	Temozolomide (daily for 5 days, at 200 mg/day, repeated	43.2 (95% CI:			
13       Astrocytoma-wild       Temozolomide (daily for 5 days, at 200 mg/day, repeated       7.2 (95% CI:         type II       every 28 days, up to 12 cycles)       4.8-NA)         et al., 54 months       10       Oligodendroglioma       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       35         11 (imputed)       week off, until progression or for maximum of 24 months)       4.8-NA)         2       No 1p19q       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       5         7       IDH-mutant       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       5         7       IDH-mutant       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       5         7       IDH-mutant       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       36         7       IDH-mutant       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       36         7       IDH-mutant       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       36         8       Astrocytoma-wild       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       36         8       Astrocytoma-wild       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       6         9       type II       week off. until progression or for maximum of 24 months)       6				Π	every 28 days, up to 12 cycles)	25-64.8)			
et al., 54 months       10       Oligodendroglioma       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       35         et al., 54 months       10       Oligodendroglioma       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       35         2       No 1p19q       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       5         7       IDH-mutant       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       5         7       IDH-mutant       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       36         7       IDH-mutant       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       36         8       Astrocytoma-wild       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       36         9       Astrocytoma-wild       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       36         9       Astrocytoma-wild       Temozolomide (low dose, 50 mg/mq/day, 1 week on/1       6         10       type II       week off. until progression or for maximum of 24 months)       6			13	Astrocytoma-wild	Temozolomide (daily for 5 days, at 200 mg/day, repeated	7.2 (95% CI:			
<i>et al.</i> , 54 months 10 Oligodendroglioma Temozolomide (low dose, 50 mg/mq/day, 1 week on/1 35 II (imputed) week off, until progression or for maximum of 24 months) 2 No 1p19q Temozolomide (low dose, 50 mg/mq/day, 1 week on/1 5 Codeletion week off, until progression or for maximum of 24 months) 7 IDH-mutant Temozolomide (low dose, 50 mg/mq/day, 1 week on/1 36 week off, until progression or for maximum of 24 months) 4 Astrocytoma-wild Temozolomide (low dose, 50 mg/mq/day, 1 week on/1 36 type II week off. until progression or for maximum of 24 months)				type II	every 28 days, up to 12 cycles)	4.8-NA)			
II (imputed)week off, until progression or for maximum of 24 months)2No 1p19qTemozolomide (low dose, 50 mg/mq/day, 1 week on/157IDH-mutantTemozolomide (low dose, 50 mg/mq/day, 1 week on/1368Astrocytoma-wildTemozolomide (low dose, 50 mg/mq/day, 1 week on/1364Astrocytoma-wildTemozolomide (low dose, 50 mg/mq/day, 1 week on/164Astrocytoma-wildTemozolomide (low dose, 50 mg/mq/day, 1 week on/16	Villani <i>et al.</i> ,	54 months	10	Oligodendroglioma	Temozolomide (low dose, 50 mg/mq/day, 1 week on/1	35	P < 0.04		
No 1p19qTemozolomide (low dose, 50 mg/mq/day, 1 week on/15Codeletionweek off, until progression or for maximum of 24 months)5IDH-mutantTemozolomide (low dose, 50 mg/mq/day, 1 week on/136Astrocytoma-wildTemozolomide (low dose, 50 mg/mq/day, 1 week on/16Astrocytoma-wildTemozolomide (low dose, 50 mg/mq/day, 1 week on/16type IIweek off. until progression or for maximum of 24 months)6	$2017^{[25]}$			II (imputed)	week off, until progression or for maximum of 24 months)				
Codeletionweek off, until progression or for maximum of 24 months)IDH-mutantTemozolomide (low dose, 50 mg/mq/day, 1 week on/136Matrocytoma-wildTemozolomide (low dose, 50 mg/mq/day, 1 week on/16Astrocytoma-wildTemozolomide (low dose, 50 mg/mq/day, 1 week on/16type IIweek off. until progression or for maximum of 24 months)6			0	No 1p19q	Temozolomide (low dose, 50 mg/mq/day, 1 week on/1	5			
IDH-mutantTemozolomide (low dose, 50 mg/mq/day, 1 week on/136week off, until progression or for maximum of 24 months)Astrocytoma-wildTemozolomide (low dose, 50 mg/mq/day, 1 week on/16type IIweek off. until progression or for maximum of 24 months)				Codeletion	week off, until progression or for maximum of 24 months)				
week off, until progression or for maximum of 24 months) Astrocytoma-wild Temozolomide (low dose, 50 mg/mq/day, 1 week on/1 type II week off. until progression or for maximum of 24 months)			2	IDH-mutant	Temozolomide (low dose, 50 mg/mq/day, 1 week on/1	36	P < 0.009		
Astrocytoma-wild Temozolomide (low dose, 50 mg/mq/day, 1 week on/1 type II week off. until progression or for maximum of 24 months)					week off, until progression or for maximum of 24 months)				
			4	Astrocytoma-wild tyne II	Temozolomide (low dose, 50 mg/mq/day, 1 week on/1 week off. until neoression or for maximum of 24 months)	9			

Asian Journal of Neurosurgery | Volume 16 | Issue 1 | January-March 2021

Study	Median	и	n Molecular subtype Treatment	Treatment	Median OS	Р	Median OS	Median OS
	follow-up (months)				(months)		(3-Years %)	(5-Years %)
Gao <i>et al.</i> , 2018 <sup>[26]</sup>	48 months	41	Astrocytoma-mutant II, High Risk	41 Astrocytoma-mutant Temozolomide (dose dense, 75 mg/m <sup>2</sup> daily, for 21 days, II, High Risk repeated every 28 days, for 12 cycles maximum)	36	<0.01		
		51	51 Astrocytoma-mutant Radiotherapy II, High Risk	Radiotherapy	55.4			
Pellerino et al., 2017 <sup>[24]</sup>	64 months		Oligodendroglioma II	<ol> <li>Oligodendroglioma Temozolomide (dose dense, 1 week on/1 week off, II median 11 cycles, range 2-18 cycles)</li> </ol>	76		90.50%	66.70%
Wahl <i>et al.</i> , 2017 <sup>[17]</sup>	90 months	44 4	Oligodendroglioma II	<ul> <li>44 Oligodendroglioma Temozolomide (daily for 5 days, at 200 mg/day, repeated II every 28 days, up to 12 cycles)</li> </ul>	116.4 (95% CI: 87.6-NA)	<0.001		
		31	Astrocytoma-mutant II	<ul> <li>Astrocytoma-mutant Temozolomide (daily for 5 days, at 200 mg/day, repeated II every 28 days, up to 12 cycles)</li> </ul>	134.4 (95% CI: 82.8-NA)			
		13	13 Astrocytoma-wild type II	Temozolomide (daily for 5 days, at 200 mg/day, repeated every 28 days, up to 12 cycles)	21.6 (95% CI: 13.2-NA)			

and 19.95 months; A-mt II: 34.45, 36.01, and 39.60 months; OD-II: 37.90, 46.00, and 55.03 months [Table 2]. Figure 2 exhibits a graphical representation stratified by temozolomide regimen and tumor genotype.

### **Overall survival data**

Only three studies provided OS data [Table 1], yet all were prospective.<sup>[17,24,26]</sup>

Two of the studies examined dose-dense regimens.<sup>[24,26]</sup> For OD-II treated by dose-dense temozolomide 1 week on/1 week off for a median of 11 cycles (range 2–18 cycles), Pellerino *et al.* identified an OS of 76 months.<sup>[24]</sup> Meanwhile, in the other dose-dense regimen, Gao *et al.* found a median OS of 36 months, for high risk A-wt II treated postoperatively with oral temozolomide 75 mg/m<sup>2</sup> daily for 21 days, repeated every 28 days for 12 cycles maximum.<sup>[26]</sup>

Finally, for patients with gross residual disease postsurgical resection, Wahl *et al.* found those who received temozolomide daily for 5-days at 200 mg/day repeated every 28 days (up to 12 cycles), the OS for OD-II, A-mt II, and A-wt II, was respectively 116.4, 134.4, and 21.6 months.<sup>[17]</sup>

The data for temozolomide treated tumors stratified by genotype was pooled and analyzed by a Kruskal-Wallis test, which did not find the three tumor types to have significantly different median OS (P = 0.37). Wilcoxon ranked sum tests further confirmed variation in OS by genotype to not be significantly different [Table 2]. Nevertheless, the 25<sup>th</sup> percentile, median (50<sup>th</sup> percentile), and 75<sup>th</sup> percentile for OS stratified by genotype were found, respectively–A-wt II (n = 1): 21.6, 21.6, and 21.6 months; A-mt II: 60.6, 85.2, and 109.8 months; OD-II: 86.1, 96.2, and 106.3 months [Table 2]. Figure 2 provides a graphical representation of OS stratified by temozolomide regimen and tumor genotype.

### **Discussion**

#### **General considerations**

Despite limitations in available number of studies, this systematic review provides a comprehensive catalog of all temozolomide investigations examining WHO grade II gliomas stratified by genotype. Furthermore, there are several core findings which can be extracted to provide direction for future clinical trial design. First, regardless of temozolomide regimen, A-wt II tumors had the shortest PFS at 12.95 months (25<sup>th</sup> and 75<sup>th</sup> percentiles: 6.90, 19.95 months), significantly shorter than both A-mt II (median: 36.01 months) and OD-II (46.00 months) [Table 2], confirming trends in prior studies that regardless of treatment type genotype dictates prognosis.<sup>[14,27-30]</sup>

Second, for OS, our data demonstrated no statistically significant differences between OD-II, A-mt II, or

-			stratified	by tumor molecula	r subtype	
PFS	PFS 25 <sup>th</sup> quartile	PFS Median	PFS 75 <sup>th</sup> quartile	Kruskal-Wallis Test		nked Sum Test d Difference
	(months)	(months)	(months)	(Kruskal-Wallis χ²)	Astrocytoma-mutant II	Oligodendroglioma II
Astrocytoma-wild	6.90	12.95	19.95	8.2154	25.1 (95% CI: 9.21-37.20)	31.62 (95% CI: 14.21-51.60)
Type II				P=0.016	W=0, P=0.057	W=0, P=0.016
Astrocytoma-mutant II	34.45	36.01	39.60			9.99 (95% CI: -8.2-25.9)
Oligodendroglioma II	37.90	46.00	55.03			W=3, P=0.25
OS	OS 25 <sup>th</sup>	OS	OS 75 <sup>th</sup>	Kruskal-Wallis	Wilcoxon ra	anked sum test
	quartile	Median	quartile	Test	Estimate	d difference
	(months)	(months)	(months)	(Kruskal-Wallis χ²)	Astrocytoma-mutant II	Oligodendroglioma II
Astrocytoma-wild	21.6	21.6	21.6	2	63.6 (95% CI: 14.4-112.8)	74.6 (95% CI: 54.4-94.8)
type II				P=0.3679	W=0, P=0.67	W=0, P=0.67
Astrocytoma-mutant II	60.6	85.2	109.8			11 (95% CI: -54.4-80.4)
Oligodendroglioma II	86.1	96.2	106.3			W=2, <i>P</i> =1

# Table 2: Interquartile range, median, and confidence interval for progression-free survival and overall survival stratified by tumor molecular subtype

CI – Confidence interval; OS – Overall survival; PFS – Progression free survival

Progres	ssion Free Survival	
	Daily for 5 days, at 200mg/day, repeated every 28 days, up to 12 cycles; n = 44 (Wahl et al., 2017)	•
	Dose dense, 75mg/m <sup>2</sup> daily, for 21 days, repeated every 28 days, for 12 cycles maximum; $n = 59$ (Baumert <i>et al.</i> , 2016)	•
Oligodendroglio	ma II Dose dense, 1 week on/1 week off, median 11 cycles, range 2-18 cycles; n = 21 (Pellerino et al., 2017)	•
	Daily for 5 days, at 200mg/m <sup>2</sup> , repeated every 28 days, at least 12 cycles or up to 30; n < 74 (NA*) (Houillier <i>et al.</i> , 2017)	•
Lo	w dose, 50mg/mq/day, 1 week on/1 week off, until progression or for maximum of 24 months; n = 10 (Villani et al., 2017)	•
	Daily for 5 days, at 200mg/day, repeated every 28 days, up to 12 cycles; n = 31 (Wahl et al., 2017)	•
Astrocytoma Mutant	II Dose dense,75mg/m <sup>2</sup> daily, for 21 days, repeated every 28 days, for 12 cycles maximum; <i>n</i> = 76 (Baumert <i>et al.</i> , 2016)	•
	Daily for 5 days, at 200mg/m <sup>2</sup> , repeated every 28 days, at least 12 cycles or up to 30; n < 74 (NA*) (Houillier <i>et al.</i> , 2010)	•
_	Dose dense, $75 \text{mg/m}^2$ daily, for 21 days, repeated every 28 days, for 12 cycles maximum; $n = 20$ (Baumert <i>et al.</i> , 2016)	•
Astrocytoma	Daily for 5 days, at 200mg/m², repeated every 28 days, at least 12 cycles or up to 30; n < 74 (NA*) (Houillier <i>et al.</i> , 2010) - II	•
Wild Type	Daily for 5 days, at 200mg/day, repeated every 28 days, up to 12 cycles; n = 13 (Wahl et al., 2017)	•
L	.ow dose, 50mg/mq/day, 1 week on/1 week off, until progression or for maximum of 24 months; n = 4 (Villani et al., 2017)	•
Overall	Survival	
Oligodendroglio	Daily for 5 days, at 200mg/day, repeated every 28 days, up to 12 cycles, n = 44 (Wahl et al., 2017) - ma II	•
	Dose dense, 1 week on/1 week off, median 11 cycles, range 2-18 cycles; n = 15 (Pellerino et al., 2017) -	•
Astrocytoma	Daily for 5 days, at 200mg/day, repeated every 28 days, up to 12 cycles; n = 31 (Wahl et al., 2017) - II	•
Mutant	Dose dense, 75mg/m <sup>2</sup> daily, for 21 days, repeated every 28 days, for 12 cycles maximum; n = 41 (Gao et al., 2018)	•
Astrocytoma Wild Type	II Daily for 5 days, at 200mg/day, repeated every 28 days, up to 12 cycles; n = 13 (Wahl et al., 2017)	•
NA* = exact i	- number of patients not available, attempts to contact study authors were also made	0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 PFS or OS (months)

Figure 2: Progression-free survival and overall survival stratified by 2016 World Health Organization Grade II glioma subtype and temozolomide treatment

A-wt II tumors [Table 2]. However, likewise to PFS, A-wt II tumors (median: 21.6 months) had a shortest OS, followed by A-mt II (85.2 months) and OD II (96.2). The observation may be explained by mass spectroscopy data that tumor subtypes have distinct immunosuppressive microenvironments.<sup>[8]</sup> The variation in microenvironment may potentially enhance responsiveness of OD II to temozolomide much more, than to A-wt II and A-mt II tumors.<sup>[8]</sup> Moreover, this observation could have arisen secondary to OD-II tumors having earlier treatment with temozolomide than A-mt II, and with A-mt II tumors more likely to undergo postoperative watch-and-wait.<sup>[31,32]</sup>

Regardless, the finding highlights the utility in stratifying treatments and exclusively examining temozolomide regimens.

# *Progression-free survival*-World Health Organization, grade II astrocytoma, *wild type*

When examining the raw data for PFS, several trends are recognized [Figure 2]. For A-wt II patients, the temozolomide treatment that yielded the longest PFS (23.69 months) was with a postoperative dose dense regimen, 75 mg/m<sup>2</sup> daily for 21 days, repeated every 28 days for 12 cycles maximum.<sup>[7]</sup> This same dose dense regimen also yielded the longest PFS for A-wt II when accounting for all other nontemozolomide forms of treatment.<sup>[7,14]</sup> The second longest PFS (18.7 months) was another dose-dense temozolomide regimen administered daily for 5-days at 200 mg/m<sup>2</sup>, repeated every 28 days for at least 12 cycles (or up to 30 cycles).<sup>[23]</sup> When this same regimen was administered for up to 12 cycles, PFS dropped to 7.2 months, thus implying more cycles of temozolomide may improve survival.<sup>[17,23]</sup> Finally, the low dose temozolomide regimen of 50 mg/mg/day, 1 week on/1 week off, until progression or for a maximum of 24 months, resulted in the shortest PFS of 6 months.<sup>[25]</sup> Hence, to lengthen PFS for A-wt II tumors, dose dense temozolomide at 75 mg/m<sup>2</sup> daily for 21 days, repeated every 28 days for 12 cycles maximum appears the optimal choice, especially when considering the toxicity profile of dose dense and standard schedule are comparable, yet the small number of studies precludes safe conclusions from being made.<sup>[33]</sup>

# Overall survival-World Health Organization, grade II astrocytoma, wild type

Regarding OS, only one temozolomide study was cataloged for A-wt II. The regimen of temozolomide daily for 5-days at 200 mg/m<sup>2</sup>, repeated every 28 days up to 12 cycles, yielded an OS of 21.6 months.<sup>[17]</sup> Hence, for elucidating the best chemotherapy regimen for A-wt II tumor OS stratified by temozolomide, more studies are needed [Figure 2].

# Progression-free survival-World Health Organization, grade II astrocytoma, mutant

For A-mt II tumors, the treatment regimen with temozolomide daily for 5-days at 200 mg/m<sup>2</sup>, repeated every 28 days up to 12 cycles provided the longest PFS, at 43.2 months [Figure 2].<sup>[17]</sup> Meanwhile, when the number of cycles was extended past 12, PFS dropped to 32.9 months.<sup>[23]</sup> Hence, for A-mt II tumors, less cycles of the same temozolomide regimen prolonged PFS, contrary to A-wt II tumors where PFS decreased with less cycles of the same regimen. Such a distinction between tumor genotype and number of cycles potentially results from different immunosuppressive microenvironments between A-wt and A-mt tumors, which in turn modulates the tumor susceptibility to temozolomide dosage.<sup>[8]</sup> Meanwhile, when given a dose-dense regimen of temozolomide 75 mg/m<sup>2</sup>

daily for 21 days, repeated every 28 days for 12 cycles maximum, PFS was an intermediate value of 36.01 months.<sup>[7]</sup>

# Overall survival-World Health Organization, grade II astrocytoma, mutant

Two studies were available for examining OS of A-mt II tumors.<sup>[17,26]</sup> Paralleling PFS, the regimen of temozolomide daily for 5-days at 200 mg/m<sup>2</sup>, repeated every 28 days up to 12 cycles, yielded the longer OS, at 134.4 months; hence, this regimen may be most optimal for A-mt II with regards to OS and PFS.<sup>[17]</sup> Meanwhile, the dose dense regimen of 75 mg/m<sup>2</sup> daily for 21 days, repeated every 28 days for 12 cycles maximum, yielded a lower OS of 36 months.<sup>[26]</sup> Despite the large difference between regimens, a robust investigation with a homogenous study population is needed prior to making conclusions supporting one regimen over another.

# Progression-free survival-World Health Organization, grade II oligodendroglioma

For OD-II, five studies investigated temozolomide dosages.<sup>[7,17,23-25]</sup> Of these, the regimen of temozolomide daily for 5-days at 200 mg/m<sup>2</sup>, repeated every 28 days up to 12 cycles produced the longest PFS (58.8 months); notably longer than the same regimen extended for at least 12 cycles (37.9 months).<sup>[17,23]</sup> The two dose-dense regimens yielded the second and third respective longest PFS, at 55.03 and 46 months.<sup>[7,24]</sup> Finally, the low-dose regimen of 50 mg/mq/day, 1 week on/1 week off, until progression or for a maximum of 24 months, resulted in the shortest PFS at 35 months [Figure 2].<sup>[25]</sup> However, relative to temozolomide treatments, those that utilize a combination of RT with CT are recognized to produce the longest PFS (120.2 and 162 months) for OD-II, yet notwithstanding our results indicate OD-II is potentially sensitive to different temozolomide dosages.<sup>[7,14,17,23-25]</sup>

# Overall survival-World Health Organization, grade II oligodendroglioma

Amongst OD-II tumors, OS values stratified by temozolomide dosage was only comparable between two regimens [Figure 2]. Those receiving temozolomide daily for 5-days at 200 mg/m<sup>2</sup>, repeated every 28 days up to 12 cycles, experienced the longer OS of 116.4 months, relative to the dose-dense regimen of 1 week on/1 week off for a median of 11 cycles yielded 76 months.<sup>[17,24]</sup> Likewise, with PFS, for OD-II the nontemozolomide treatment regimens yield the longest OS values (i.e., 235.4 months with RT; 212.4 months with RT and CT).<sup>[34]</sup>

### Study limitations

To place the data collected from this systematic review into context, a number of limitations should be recognized. First, several studies implied definitions for PFS and OS, rather than explicitly defining the parameters. Moreover, in the studies where tumors were resected, there was no data providing raw PFS and OS values stratified by extent of tumor resection and temozolomide regimen; the potential for heterogeneity in extent of resection across studies is important to note, as extent of resection has been shown to independently influence survival.<sup>[16,18]</sup> Furthermore, in the method sections of some studies, inclusion and exclusion criteria were minimally described. Likewise, demographic data was not uniformly presented or available stratified by molecular marker and temozolomide regimen, thus limiting application of results to the broader population.

In addition, although only one study was retrospective, the inconsistent follow-up times amongst the investigations reduces the strength in comparing results side by side. Finally, most of the studies involved small samples sizes, further limiting the conclusions of any one investigation. Notwithstanding these limitations, by conducting this review and presenting survival outcomes, highlights not only the large variability in temozolomide regimens utilized globally and how an optimal regimen has yet to be agreed upon, but also the restrictions current studies impose when externally comparing results. Hence, recognizing these problems will allow future clinical trial design to potentially improve. Yet, by extension currently no treatment recommendations can be made from this review. In the future, investigations stratifying by molecular subtypes should also aim at collecting data on temozolomide resistance and adverse effects, as well as proportion of tumors which progress to higher grades - for such information could provide valuable insight in selecting treatments.

### Conclusion

This systematic review provided a comprehensive catalog of all temozolomide regimens stratified by WHO Grade II glioma molecular subtype. Several observations were made regarding survival outcomes. Median OS for A-wt II (21.6 months), A-mt II (85.2 months), and OD-II (96.2 months) were found, as were median PFS for A-wt II (12.95 months), A-mt (36.01 months), and OD-II (46.00 months). Overall, A-wt II was confirmed to have a significantly shorter PFS than A-mt II and OD II; however, there was no significant difference found between PFS of OD II with A-mt II. Additionally, for temozolomide treatment, all three molecular subtypes were not found to have statistically significant differences in OS, despite differences in PFS. Moreover, there was a general observation that a different optimal temozolomide regimen exists depending on the WHO grade II glioma's genotype. Hence, despite the limitations precluding robust conclusions, by cataloguing the survival outcomes of temozolomide regimens amongst the background of tumor genotype, this review provides an avenue for improving future clinical trial design, as well as better informing patients about their prognosis.

### **Ethical approval**

This article does not contain any studies with human participants or animals performed by any of the authors.

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Nil.

#### **Conflicts of interest**

There are no conflicts of interest.

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# **Appendix Legend**

### **Appendix 1: Search terms**

### **Pubmed (MEDLINE)**

### (A)

- (1) molecula\*
- (2) genetic\* or genetics or genetic
- (3) mutation\* or mutation
- (4) molecular genetic\* or molecular genetic or molecular genetics

### (B)

- (1) overall survival\* or overall survival or overall survivals
- (2) survival\* or survival or survivals
- (3) "os"

# **(C)**

- (1) progression free survival\* or progression free survival or progression free survivals
- (2) progression\* or progression or progressions or PFS or PFSs
- (1) low grade glioma or LGG or LGGs
- (2) grade 2 gliomas or grade ii gliomas
- (3) astrocytoma\* or astrocytomas
- (4) oligodendroglioma\* or oligodendrogliomas

### **(D)**

- (1) Treatment\* or treatments or treatment
- (2) Treat\* or treat or treats

# Publication date from 2008/01/01 to 2018/12/31

Search ((((((((((((overall survival\*) OR overall survival) OR overall survivals) OR survival\*) OR survival) OR survivals) OR "os"))) OR ((((((((progression free survival\*) OR progression free survival) OR progression free survivals) OR progression\*) OR progression) OR progressions) OR PFS) OR PFSs)))) AND ((((molecula\*) OR (((genetic\*) OR genetics) OR genetic)) OR ((mutation\*) OR mutation)) OR (((molecular genetics) OR molecular genetic) OR molecular genetic\*))) AND ((((((low grade glioma) OR LGG) OR LGGs)) OR ((grade 2 gliomas) OR grade ii gliomas)) OR ((astrocytoma\*) OR astrocytomas)) OR ((oligodendroglioma\*) OR oligodendrogliomas))) AND ((((((treatment\*) OR treatments) OR treatment) OR treat\*) OR treat) OR treats)

#### **Embase Ovid**

- 1. exp glioma/
- 2. glioma\*.mp.
- 3. LGG\*.mp.
- 4. astrocytoma\*.mp.
- 5. oligodendroglioma\*.mp.
- 6. (grade adj ii).mp.
- 7. 1 or 2 or 3 or 4 or 5 or 6

8. exp progression free survival/ 9. (progression adj free).mp. 10. progression\*.mp. 11. PFS\*.mp. 12.8 or 9 or 10 or 11 13. exp overall survival 14. (overall adj survival\*).mp. 15. OS\*.mp. 16.13 or 14 or 15 17. exp molecular genetics 18. (molecular adj genetic\*).mp. 19. molecul\*.mp. 20. genetic\*.mp. 21.17 or 18 or 19 or 20 22. treatment\*.mp. 23.12 or 16 24.7 and 21 and 22 and 23

25.24 and 2008:2018.(sa\_year).

#### Key:

mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term wor

### CENTRAL

- 1. MeSH descriptor: [Glioma] explode all trees
- 2. glioma\*
- 3. astrocytoma\*
- 4. oligodendroglioma\*
- 5. LGG\*
- 6. #2 or #3 or #4 or #5
- 7. # 1 or #6
- 8. MeSH descriptor: [Disease-Free Survival] explode all trees
- 9. progression\*
- 10. survival\*
- 11. PFS\*
- 12. #9 or #10 or #11
- 13.#8 or #12
- 14. OS\*
- 15. overall\*
- 16.#14 or #15
- 17.#13 or #16
- 18. MeSH descriptor: [Molecular Biology] explode all trees
- 19. genetic\*
- 20. molecul\*
- 21. #18 or #19 or #20
- 22. MeSH descriptor: [Therapeutics] explode all trees
- 23. treatment\*
- 24.#22 or #23
- 25. #7 and #17 and #21 and #24