Neuro-Oncology Advances
2(1), 1–7, 2020 | doi:10.1093/noajnl/vdaa082 | Advance Access date 30 October 2020

Characterizing benefit from temozolomide in MGMT promoter unmethylated and methylated glioblastoma: a systematic review and meta-analysis

Iyad Alnahhas, Mouaz Alsawas, Appaji Rayi, Joshua D. Palmer, Raju Raval, Shirley Ong, Pierre Giglio, Mohammad Hassan Murad, and Vinay Puduvalli

Division of Neuro-Oncology, Department of Neurology, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA (A.R., S.O., P.G., V.P.); Evidence-Based Practice Center, Mayo Clinic, Rochester, Minnesota, USA (M.A., M.H.M.); Department of Radiation Oncology, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA (J.D.P., R.R.); Division of Neuro-Oncology, Department of Neurology, Thomas Jefferson University, Philadelphia, Pennsylvania, USA (I.A)

Corresponding Author: Iyad Alnahhas, MD, MSc, Division of Neuro-Oncology, Department of Neurology, Thomas Jefferson Universit, 901 Walnut St. Room 310G. Philadelphia, PA 19107, USA (iyad.alnahhas@gmail.com).

Abstract

Background. The current standard of care for the management of patients with newly diagnosed glioblastoma (GBM) includes maximal safe resection followed by radiotherapy (RT) with concurrent and adjuvant temozolomide (TMZ). While it is well established that TMZ has better efficacy in patients with *MGMT* promoter methylation, it remains an area of debate whether TMZ should be omitted when treating GBM patients with unmethylated *MGMT*.

Methods. We conducted a systematic review and meta-analysis to provide separate estimates of median overall survival (OS) and progression-free survival (PFS) for patients with methylated and unmethylated GBM treated with RT with or without TMZ. We searched multiple databases from inception to January 13, 2020.

Results. The median OS for patients with unmethylated GBM treated with RT/TMZ pooled from 5 phase III studies ($N = 655$) was 14.11 months (95% confidence interval [CI], 13.18–15.04) with a median PFS of 4.99 months (95% CI, 4.25–5.72). In contrast, the median OS for patients with methylated GBM pooled from 6 studies ($N = 753$) was 24.59 months (95% CI, 22.19–26.99) with a median PFS pooled from 7 studies ($N = 805$) of 9.51 months (95% CI, 7.41–11.61). There is a paucity of prospective data pertaining to OS/PFS in unmethylated patients treated with RT only and therefore a direct comparison was not possible.

Conclusions. This meta-analysis provides estimates of survival for patients with *MGMT* methylated or unmethylated GBM treated with RT/TMZ. Further research is needed to delineate whether TMZ should be withheld for patients with unmethylated GBM outside of the setting of clinical trials.

Key Points

- This meta-analysis provides pooled survival estimates for GBM based on MGMT status.
- Pooled median OS: 14.11 and 24.59 months for unmethylated and methylated GBM, respectively.
- Whether TMZ can be omitted in unmethylated GBM cannot be answered definitively.

The EORTC-26981-22981 has established the current standard of care for the management of newly diagnosed glioblastoma (GBM) which includes maximal safe resection followed by concomitant radiotherapy (RT) and temozolomide (TMZ) followed by adjuvant TMZ.[1] *O*^{6}*-Methylguanine-DNA methyltransferase (MGMT)* gene promoter methylation has been demonstrated to be a prognostic and predictive factor of response to TMZ in patients with GBM.[2] This clinical benefit has been attributed to the fact that *MGMT* can remove the damaging alkyl groups from the *O*^{6} position of guanine and repairs the DNA

Importance of the Study

While it is well established that TMZ has better efficacy in patients with *MGMT* promoter methylation, it remains an area of debate whether temozolomide should be omitted when treating glioblastoma patients with unmethylated *MGMT*. Median survival differs vastly between *MGMT* methylated and unmethylated GBM and estimates from this analysis should be cited when discussing prognosis with patients.

damage caused by alkylating agents; *MGMT* promoter methylation therefore results in compromised DNA repair and promotes tumor cell death. However, it remains an area of debate whether TMZ should be used for *MGMT* unmethylated patients. While some strongly believe that TMZ is ineffective in this subgroup of GBM patients and advocate for omitting TMZ from the treatment of patients with *MGMT* unmethylated GBM, especially in the elderly population,[3] others have argued that there is insufficient evidence to withhold an approved treatment from those with the poorer prognosis.[4] Several published clinical trials (eg, RTOG 0525 and RTOG 0825) included preplanned analyses and stratifications based on *MGMT* methylation status and confirmed the prognostic value of *MGMT*.[5,6] We performed this systematic review and meta-analysis to provide cumulative estimates of survival for unmethylated and methylated GBM patients treated with TMZ.

Methods

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Eligibility Criteria and Search Strategy

Specific vocabulary supplemented with keywords was used to search for phase III trials that provided survival data separately for methylated and unmethylated GBM patients treated with RT alone or RT plus TMZ (as a control or intervention arm). The search strategy was designed and conducted by an experienced librarian with input from the study's investigators. The search was limited to the English language only and excluded animal studies. The comprehensive search included several databases from inception to January 13, 2020 (the earliest study was from 1999).

The databases included Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily, Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The actual strategy listing all search terms used and how they are combined is available in the Supplementary Appendix.

Only relevant papers that included median survival data along with confidence intervals (CIs) and stratified by *MGMT* status were included. Studies focusing on the elderly population were analyzed separately. Separate analyses were also done for overall survival (OS) and progression-free survival (PFS).

Study Selection and Data Extraction

Two investigators independently screened the papers for inclusion and were in agreement on more than 98% of the included studies. Any disagreements were resolved through discussion and consensus. Then, for each study, the OS and PFS data pertaining to RT or RT plus TMZ stratified by *MGMT* status were collected. When not available, these data were solicited from corresponding authors.

Risk of Bias Assessment of Included Studies

The methodological quality of the included studies was evaluated using the revised Cochrane risk of bias tool for randomized trials.[7]

Statistical Analysis

Due to the heterogeneity of study settings and populations, we used the random-effect model to perform a meta-analysis of median survival data and 95% CIs. Heterogeneity among studies was evaluated by the I^2 index. Statistical significance was reported using $P < .05$. Stata 15 software (StataCorp) was used to conduct the analyses.

Results

Study Selection

A total of 385 references were screened, 369 of which were excluded after review of the study details provided in the abstracts. Subsequently, 16 full-text references were assessed for inclusion. Six studies were then excluded for the following reasons: 3 studies lacked survival data stratified by *MGMT* methylation status and treatment arm,[8–10] 2 studies did not test *MGMT* methylation status,[11,12] and one study had a mixed control arm of patients who received or did not receive TMZ based on treating center.[13] Figure 1 shows the PRISMA flow diagram of study inclusion and exclusion for this systematic review and meta-analysis.[14]

Methodologic Quality

The methodological quality of the included studies was evaluated using the revised Cochrane risk of bias tool for randomized trials (ROB 2).[7] The methodological quality assessment is summarized in Supplementary Appendix. The majority of the studies had a moderate risk of bias; most

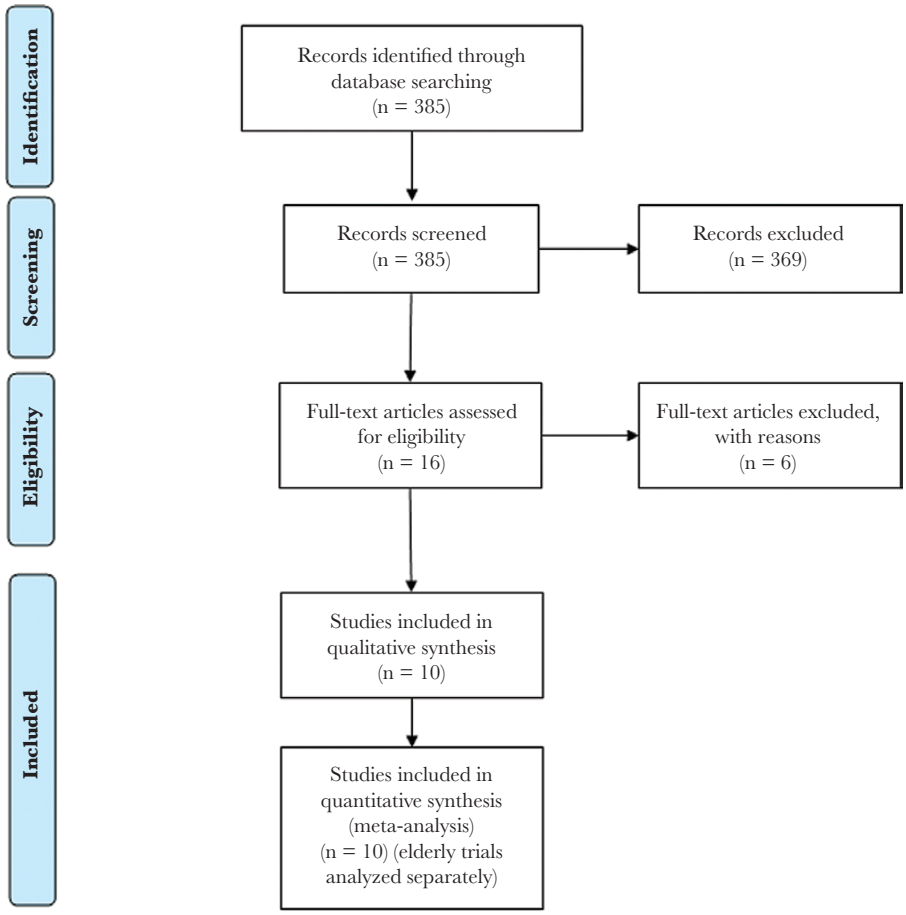

Figure 1. PRISMA flow diagram of study inclusion and exclusion. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

of the studies were not blinded, did not report the number of patients lost to follow-up, or did not adhere to treatment (Figure 2).

Study Characteristics

Table 1 summarizes the characteristics of the 10 trials included in the meta-analysis (including 3 elderly trials).

MGMT Unmethylated GBM

Five published phase III clinical trials were included in the meta-analysis for the unmethylated group. These included 5 phase III trials: Stupp'05,[1] Gilbert'13 (RTOG 0525),[5] Gilbert'14 (RTOG 0825),[6] Westphal'15,[15] and Stupp'17 (EF-14).[16]

OS in the unmethylated group.—The median OS for patients with unmethylated GBM pooled from phase III studies (N = 655) was 14.11 months (95% CI, 13.18–15.04; I^2 = 28.2%; Figure 3).

PFS in the unmethylated group.—The median PFS for patients with unmethylated GBM pooled from phase III studies (N = 655) was 4.99 months (95% CI, 4.25–5.72; I^2 = 64.6%; Figure 4).

MGMT Methylated GBM

Seven phase III studies were included in the meta-analysis for the methylated group: Stupp'05,[1] Gilbert'13 (RTOG 0525),[5] Gilbert'14 (RTOG 0825),[6] Stupp'14,[17] Westphal'15,[15] Stupp'17 (EF-14),[16] and Herrlinger'19.[18] Stupp'14[17] and Herrlinger'19[18] only included patients with *MGMT* methylated status and therefore were not included in the previous unmethylated analysis.

OS in the methylated group.—One study (Westphal'15)[15] was not included in this analysis given the upper limit of the CI was not reached. The median OS for patients with methylated GBM pooled from 6 studies (N = 753) was 24.59 months (95% CI, 22.19–26.99; I^2 = 22.3%; Figure 5).

PFS in the methylated group.—The median PFS for patients with methylated GBM pooled from 7 studies ($N = 805$) was 9.51 months (95% CI, 7.41–11.61; $I^2 = 54.3\%$; Figure 6).

Unmethylated GBM in the Elderly

Three phase III studies were included in the meta-analysis for the unmethylated elderly group: Wick'12 (NOA-08),[19] Malmström'12 (Nordic),[20] and Perry'17.[21] Results of the RT alone arms were combined.

The median OS for elderly patients with unmethylated GBM treated with RT alone pooled from 3 studies ($N = 223$) was 8.35 months (95% CI, 6.46–10.25; $I^2 = 78\%$; Supplementary Figure 1).

Discussion

We conducted a systematic review and meta-analysis to provide separate estimates of median OS and PFS for patients with *MGMT* methylated and unmethylated GBM treated with RT with or without TMZ. We decided to include only phase III trials to ensure better quality meta-analysis and limit heterogeneity. Multiple agents in neuro-oncology have succeeded in phase II trials but failed in phase III trials due to intrinsic limitations in phase II trial designs.

A meta-analysis by Zhao et al.[22], among many other studies, has confirmed the prognostic value of *MGMT* in newly diagnosed and recurrent GBM. While it is well established that TMZ has better efficacy in the *MGMT* methylated group, no study has prospectively compared RT versus RT plus TMZ in the *MGMT* unmethylated GBM subgroup. There is a paucity of historic data from previous trials examining this question as well. An additional challenge is that *MGMT* promoter methylation assays have not been standardized. Most trials included in this meta-analysis used methylation-specific PCR (MSP).[23] While MSP is a reliable test, cutoff values for differentiating between *MGMT* methylated and *MGMT* unmethylated gliomas have not been well defined.[24] It has been recommended to use a lower safety margin when interpreting the MSP results in clinical trials to avoid withholding TMZ from "low MGMT methylation" patients who may still benefit from this

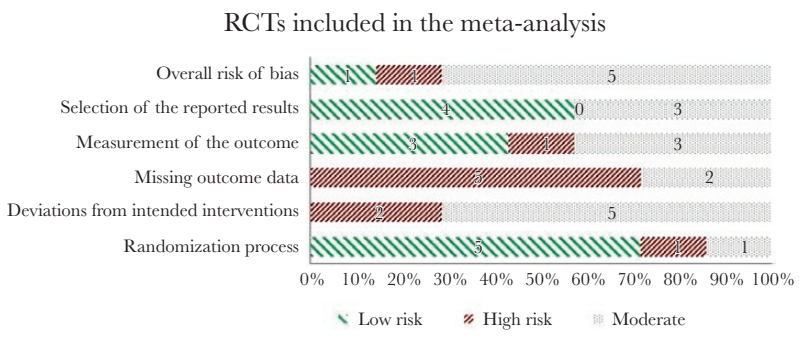

Figure 2. Risk of bias assessment for studies included in the meta-analysis.

Table 1. Characteristics of Phase III Studies Included in This Systematic Review and Meta-Analysis

Study	Reference	Age inclusion (years)	Control arm	Treatment arm
Stupp'05	1	≥18	RT	RT + TMZ
Gilbert'13 (RTOG 0525)	5	18–70	RT + TMZ	RT + dose-dense TMZ
Gilbert'14 (RTOG 0825)	6	≥18	RT + TMZ	RT + TMZ + bevacizumab
Stupp'14	17	≥18	RT + TMZ	RT + TMZ + cilengitide
Westphal'15	15	18–70	RT + TMZ	RT + TMZ + nimotuzumab
Stupp'17 (EF-14)	16	≥18	RT + TMZ	RT + TMZ + TTF
Herrlinger'19 (NOA-09)	18	18–70	RT + TMZ	RT + TMZ + CCNU
Wick'12	19	>65	RT (60 Gy)	Dose-dense TMZ
Malmström'12	20	>60	RT (34–60 Gy)	TMZ
Perry'17	21	≥65	RT (40 Gy)	RT + TMZ

TTF, tumor-treating fields (RT + TMZ refers to concomitant RT/TMZ followed by adjuvant TMZ); CCNU, lomustine.

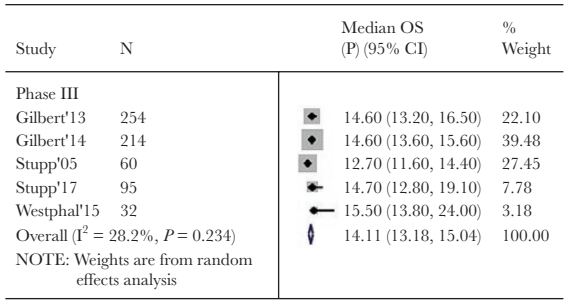

Figure 3. Forest plot showing pooled OS for patients with unmethylated GBM.

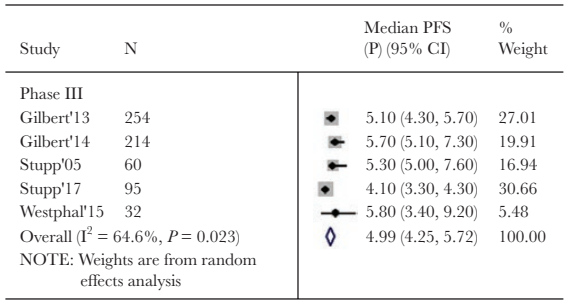

Figure 4. Forest plot showing pooled PFS for patients with unmethylated GBM.

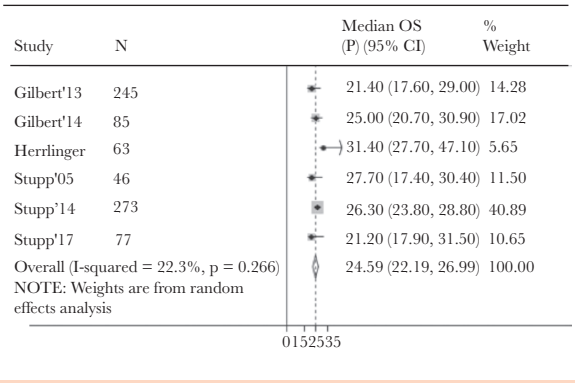

Figure 5. Forest plot showing pooled OS or patients with methylated GBM.

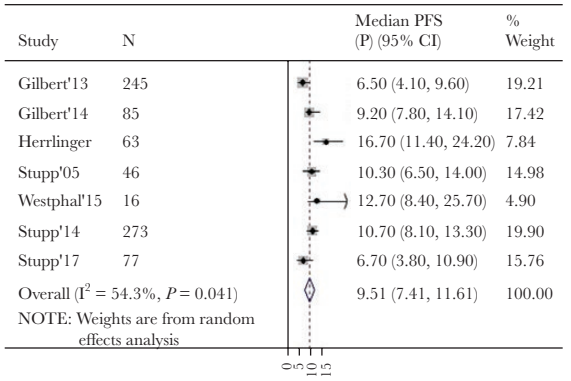

Figure 6. Forest plot showing pooled PFS for patients with methylated GBM.

treatment.[25] Similar limitations apply to pyrosequencing: A recent study suggested that 17% achieved the highest precision for correlation with clinical outcomes,[26] whereas 8–10% has been widely used in clinical practice.

A retrospective analysis of EORTC-26981-22981 first reported the lack of statistically significant difference between OS in *MGMT* unmethylated patients treated with RT only (*N* = 54; 11.8 months [95% CI, 9.7–14.1]) and with RT plus TMZ (*N* = 60; 12.7 months [95% CI, 11.6–14.4]).[2] PFS was 5.9 months (5.3–7.7) in the RT group (*N* = 46) and 10.3 months (6.5–14) in the RT plus TMZ group (*N* = 46). Another retrospective study of 225 GBM patients reported improved PFS and OS of patients with *MGMT* methylated GBM treated with RT alone compared to those with *MGMT* unmethylated tumors (31 vs 15 weeks and 63 vs 51 weeks, respectively), suggesting that *MGMT* promoter methylation could fundamentally be a prognostic factor for GBM.[27] No CIs were reported and therefore these results could not be combined with the EORTC-26981-22981 retrospective analysis. Finally, a prospective study of 301 patients of the German Glioma Network estimated median OS of 7.14 months for unmethylated patients treated with RT alone.[28] Beyond this, there is a paucity of data pertaining to OS in unmethylated patients treated with RT only in adult patients.

In our meta-analysis, the median OS of adult patients with unmethylated GBM pooled from 5 phase III studies (*N* = 655) was 14.11 months (95% CI, 12.85–17.97). The median PFS for patients with unmethylated GBM pooled from the same studies was 4.99 months (95% CI, 4.25–5.72). The CIs of our analyses still overlap with the large CIs from the RT only group in the retrospective analysis of EORTC-26981-22981. However, the published literature does not yield more robust survival data for unmethylated patients treated with RT alone. On the other hand, the median OS for patients with methylated GBM pooled from 6 studies (*N* = 753) was 24.59 months (95% CI, 22.19–26.99). The median PFS for patients with methylated GBM pooled from 5 studies (*N* = 805) was 9.51 months (95% CI, 7.41–11.61). One limitation of this analysis was that some major phase III trials had to be excluded from this meta-analysis, Weller'17[8] and Chinot'14,[9] because of lack of survival data stratified by *MGMT* methylation status and treatment arm. Additionally, the majority of the studies had a moderate risk of bias as most of the studies were not blinded and did not report the number of patients lost to follow-up. Moreover, the initial time point of randomization was different among trials as patients were randomized either before or after the concomitant RT/TMZ phase.

The argument against using TMZ for unmethylated patients in the elderly population is even more intense.

The lack of the definition of the elderly population further adds to the heterogeneity of the inclusion age of the various studies. The NOA-08 trial[19] compared RT alone versus TMZ alone in elderly patients with GBM. Event-free survival (EFS) was longer in patients with *MGMT* promoter methylation who received TMZ than in those who underwent RT, whereas the opposite was true for patients with no methylation of the *MGMT*. On the other hand, Perry et al.[21] compared short-course RT alone to short-course RT plus TMZ, in a randomized phase III study, and reported benefit of adding TMZ even in the unmethylated group, albeit not statistically significant (10 vs 7.9 months; hazard ratio 0.75; $P = .08$).[24] In our meta-analysis, the pooled median OS for unmethylated elderly GBM patients treated with RT alone was 8.35 months (6.46–10.25), compared to 10 months (8.3–10.7) in the RT + TMZ arm in the Perry trial. In a recent network meta-analysis for elderly patients with GBM, the pooled analysis suggested that the addition of TMZ to RT had the greatest probability of being ranked as the optimal treatment.[29]

In summary, we provide estimates for survival for patients with methylated and unmethylated GBM treated with RT and TMZ. These numbers should be cited when discussing prognosis with patients as the unmethylated and methylated groups vary vastly in terms of median OS (14.11 vs 24.59 months, respectively). There is paucity in historic data to drive any conclusions regarding withholding TMZ in unmethylated GBM, including the elderly with good functional status. The exclusion of TMZ in patients with an unmethylated *MGMT* gene promoter in favor of an experimental therapy that holds great promise based on phase II trial results and/or mechanism of action appears reasonable at this time. Such exclusion also appears reasonable in elderly patients with an unmethylated *MGMT* gene promoter with significant comorbidity and perceived higher risk from chemotherapy. However, we have otherwise continued to treat "low-risk", non-elderly patients with unmethylated *MGMT* gene promoter GBM with RT and TMZ based on a small improvement in median survival over RT alone noted in our analysis. We anticipate further refinements in our position as the true significance of *MGMT* gene promoter methylation assays (cutoffs, best assays) as well as more data become available.

Supplementary Data

Supplementary data are available at *Neuro-Oncology Advances* online.

Keywords

glioblastoma | MGMT | meta-analysis | systematic review | temozolomide

Funding

This study did not receive any financial support.

Conflicts of interest statement. The authors have no conflicts of interest to disclose.

Authorship Statement. Screened papers for inclusion: I.A. and A.R; statistical analysis: M.A; data interpretation and manuscript writing: all authors.

References

1. Stupp R, Mason WP, van den Bent MJ, et al.; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987–996.
2. Hegi ME, Diserens AC, Gorlia T, et al. *MGMT* gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med*. 2005;352(10):997–1003.
3. Hegi ME, Stupp R. Withholding temozolomide in glioblastoma patients with unmethylated *MGMT* promoter—still a dilemma? *Neuro Oncol*. 2015;17(11):1425–1427.
4. Taylor JW, Schiff D. Treatment considerations for *MGMT*-unmethylated glioblastoma. *Curr Neurol Neurosci Rep*. 2015;15(1):507.
5. Gilbert MR, Wang M, Aldape KD, et al. Dose-dense temozolomide for newly diagnosed glioblastoma: a randomized phase III clinical trial. *J Clin Oncol*. 2013;31(32):4085–4091.
6. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med*. 2014;370(8):699–708.
7. Sterne JA, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019 Aug 28;366:l4898.
8. Weller M, Butowski N, Tran DD, et al.; ACT IV Trial Investigators. Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial. *Lancet Oncol*. 2017;18(10):1373–1385.
9. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy–temozolomide for newly diagnosed glioblastoma. *N Engl J Med*. 2014 Feb 20;370(8):709–722.
10. Liau LM, Ashkan K, Tran DD, et al. First results on survival from a large phase 3 clinical trial of an autologous dendritic cell vaccine in newly diagnosed glioblastoma. *J Transl Med*. 2018;16(1):142.
11. Kim IH, Park CK, Heo DS, et al. Radiotherapy followed by adjuvant temozolomide with or without neoadjuvant ACNU-CDDP chemotherapy in newly diagnosed glioblastomas: a prospective randomized controlled multicenter phase III trial. *J Neurooncol*. 2011;103(3):595–602.
12. Kong DS, Nam DH, Kang SH, et al. Phase III randomized trial of autologous cytokine-induced killer cell immunotherapy for newly diagnosed glioblastoma in Korea. *Oncotarget*. 2017;8(4):7003–7013.
13. Westphal M, Ylä-Herttuala S, Martin J, et al.; ASPECT Study Group. Adenovirus-mediated gene therapy with sitimagene ceradenovec followed by intravenous ganciclovir for patients with operable high-grade glioma (ASPECT): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2013;14(9):823–833.
14. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate

health care interventions: explanation and elaboration. *Ann Intern Med.* 2009;151(4):W65–W94.

15. Westphal M, Heese O, Steinbach JP, et al. A randomised, open label phase III trial with nimotuzumab, an anti-epidermal growth factor receptor monoclonal antibody in the treatment of newly diagnosed adult glioblastoma. *Eur J Cancer.* 2015;51(4):522–532.
16. Stupp R, Taillibert S, Kanner A, et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. *JAMA.* 2017;318(23):2306–2316.
17. Stupp R, Hegi ME, Gorlia T, et al.; European Organisation for Research and Treatment of Cancer (EORTC); Canadian Brain Tumor Consortium; CENTRIC Study Team. Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated *MGMT* promoter (CENTRIC EORTC 26071-22072 study): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* 2014;15(10):1100–1108.
18. Herrlinger U, Tzaridis T, Mack F, et al.; Neurooncology Working Group of the German Cancer Society. Lomustine-temozolomide combination therapy versus standard temozolomide therapy in patients with newly diagnosed glioblastoma with methylated *MGMT* promoter (CeTeG/NOA-09): a randomised, open-label, phase 3 trial. *Lancet.* 2019;393(10172):678–688.
19. Wick W, Platten M, Meisner C, et al.; NOA-08 Study Group of Neuro-oncology Working Group (NOA) of German Cancer Society. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. *Lancet Oncol.* 2012;13(7):707–715.
20. Malmström A, Grønberg BH, Marosi C, et al.; Nordic Clinical Brain Tumour Study Group (NCBTSG). Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. *Lancet Oncol.* 2012;13(9):916–926.
21. Perry JR, Laperriere N, O'Callaghan CJ, et al.; Trial Investigators. Short-course radiation plus temozolomide in elderly patients with glioblastoma. *N Engl J Med.* 2017;376(11):1027–1037.
22. Zhao YH, Wang ZF, Cao CJ, et al. The clinical significance of O6-methylguanine-DNA methyltransferase promoter methylation status in adult patients with glioblastoma: a meta-analysis. *Front Neurol.* 2018;9:127.
23. Vlassenbroeck I, Califice S, Diserens AC, et al. Validation of real-time methylation-specific PCR to determine O6-methylguanine-DNA methyltransferase gene promoter methylation in glioma. *J Mol Diagn.* 2008;10(4):332–337.
24. Wick W, Weller M, Van Den Bent M, et al. *MGMT* testing—the challenges for biomarker-based glioma treatment. *Nat Rev Neurol.* 2014 Jul;10(7):372.
25. Hegi ME, Genbrugge E, Gorlia T, et al. *MGMT* promoter methylation cutoff with safety margin for selecting glioblastoma patients into trials omitting temozolomide: a pooled analysis of four clinical trials. *Clin Cancer Res.* 2019;25(6):1809–1816.
26. Radke J, Koch A, Pritsch F, et al. Predictive *MGMT* status in a homogeneous cohort of IDH wildtype glioblastoma patients. *Acta Neuropathol Commun.* 2019;7(1):89.
27. Rivera AL, Pelloski CE, Gilbert MR, et al. *MGMT* promoter methylation is predictive of response to radiotherapy and prognostic in the absence of adjuvant alkylating chemotherapy for glioblastoma. *Neuro Oncol.* 2010;12(2):116–121.
28. Weller M, Felsberg J, Hartmann C, et al. Molecular predictors of progression-free and overall survival in patients with newly diagnosed glioblastoma: a prospective translational study of the German Glioma Network. *J Clin Oncol.* 2009;27(34):5743–5750.
29. Nassiri F, Taslimi S, Wang JZ, et al. Determining the optimal adjuvant therapy for improving survival in elderly patients with glioblastoma: a systematic review and network meta-analysis. *Clin Cancer Res.* 2020;26(11):2664–2672.