

# Radiotherapy combined with nivolumab or temozolomide for newly diagnosed glioblastoma with unmethylated *MGMT* promoter: An international randomized phase III trial

Antonio Omuro<sup>†</sup>, Alba A. Brandes<sup>†</sup>, Antoine F. Carpentier, Ahmed Idbaih<sup>○</sup>, David A. Reardon, Timothy Cloughesy, Ashley Sumrall, Joachim Baehring, Martin van den Bent<sup>○</sup>, Oliver Bähr, Giuseppe Lombardi<sup>○</sup>, Paul Mulholland, Ghazaleh Tabatabai<sup>○</sup>, Ulrik Lassen, Juan Manuel Sepulveda, Mustafa Khasraw<sup>○</sup>, Elodie Vauleon, Yoshihiro Muragaki, Anna Maria Di Giacomo, Nicholas Butowski, Patrick Roth, Xiaozhong Qian<sup>‡</sup>, Alex Z. Fu<sup>‡</sup>, Yanfang Liu<sup>‡</sup>, Von Potter<sup>‡</sup>, Alexandros-Georgios Chalamandaris, Kay Tatsuoka<sup>‡</sup>, Michael Lim<sup>||</sup>, and Michael Weller<sup>||</sup><sup>○</sup>

Department of Neurology, Yale School of Medicine, New Haven, Connecticut, USA (A.O., J.B.); Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, New York, USA (A.O.); AUSL-IRCCS Institute of Neurological Sciences, Bologna, Italy (A.A.B.); Université de Paris, Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpital Saint-Louis, Service de Neurologie, Paris, France (A.F.C.); Sorbonne Université, Institut du Cerveau – Paris Brain Institute – ICM, Inserm, CNRS, AP-HP, Hôpital Universitaire La Pitié Salpêtrière, DMU Neurosciences, Paris, France (A.I.); Dana-Farber Cancer Center, Harvard Medical School, Boston, Massachusetts, USA (D.A.R.); Department of Neurology, University of California, Los Angeles, California, USA (T.C.); Levine Cancer Institute, Charlotte, North Carolina, USA (A.S.); Brain Tumor Center at Erasmus MC Cancer Institute, Rotterdam, the Netherlands (M.V.D.B.); Dr. Senckenberg Institute of Neurooncology, Goethe University Hospital, Frankfurt, Germany (O.B.); Department of Oncology, Oncology 1, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy (G.L.); University College London Hospitals, London, UK (P.M.); Department of Neurology and Interdisciplinary Neuro-Oncology, Hertie Institute for Clinical Brain Research, Center for Neuro-Oncology, Comprehensive Cancer Center Tübingen-Stuttgart, University Hospital Tuebingen, Eberhard Karls University, Tuebingen, Germany (G.T.); Department of Oncology, Rigshospitalet, Copenhagen, Denmark (U.L.); Hospital Universitario 12 de Octubre, Madrid, Spain (J.M.S.); The University of Sydney, Sydney, New South Wales, Australia (M.K.); Centre Eugene Marquis, Rennes, France (E.V.); Tokyo Women's Medical University Hospital, Tokyo, Japan (Y.M.); Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy (A.M.D.G.); Department of Neurological Surgery, University of California, San Francisco, California, USA (N.B.); Department of Neurology and Brain Tumor Center, University Hospital and University of Zurich, Zurich, Switzerland (P.R., M.W.); Bristol Myers Squibb, Princeton, New Jersey, USA (X.Q., A.Z.F., Y.L., V.P., K.T.); Bristol Myers Squibb, Braine-L'Alleud, Belgium (A.-G.C.); The Johns Hopkins Hospital, Baltimore, Maryland, USA (M.L.)

Present affiliation: IRCCS Istituto Scienze Neurologiche, Bologna, Italy; Nervous System Medical Oncology Department, Bologna, Italy (A.A.B.)

**Corresponding Author:** Antonio Omuro, MD, Yale Cancer Center, 15 York Street, New Haven, CT 06520, USA ([antonio.omuro@yale.edu](mailto:antonio.omuro@yale.edu)).

<sup>†</sup>Co-lead authors.

<sup>‡</sup>Not currently employed at Bristol Myers Squibb.

<sup>||</sup>Co-senior authors.

## Abstract

**Background.** Addition of temozolomide (TMZ) to radiotherapy (RT) improves overall survival (OS) in patients with glioblastoma (GBM), but previous studies suggest that patients with tumors harboring an unmethylated *MGMT* promoter derive minimal benefit. The aim of this open-label, phase III CheckMate 498 study was to evaluate the efficacy of nivolumab (NIVO) + RT compared with TMZ + RT in newly diagnosed GBM with unmethylated *MGMT* promoter.

**Methods.** Patients were randomized 1:1 to standard RT (60 Gy) + NIVO (240 mg every 2 weeks for eight cycles, then 480 mg every 4 weeks) or RT + TMZ (75 mg/m<sup>2</sup> daily during RT and 150–200 mg/m<sup>2</sup>/day 5/28 days during maintenance). The primary endpoint was OS.

**Results.** A total of 560 patients were randomized, 280 to each arm. Median OS (mOS) was 13.4 months (95% CI, 12.6 to 14.3) with NIVO + RT and 14.9 months (95% CI, 13.3 to 16.1) with TMZ + RT (hazard ratio [HR], 1.31; 95% CI, 1.09 to 1.58;  $P = .0037$ ). Median progression-free survival was 6.0 months (95% CI, 5.7 to 6.2) with NIVO + RT and 6.2 months (95% CI, 5.9 to 6.7) with TMZ + RT (HR, 1.38; 95% CI, 1.15 to 1.65). Response rates were 7.8% (9/116) with NIVO + RT and 7.2% (8/111) with TMZ + RT; grade 3/4 treatment-related adverse event (TRAE) rates were 21.9% and 25.1%, and any-grade serious TRAE rates were 17.3% and 7.6%, respectively.

**Conclusions.** The study did not meet the primary endpoint of improved OS; TMZ + RT demonstrated a longer mOS than NIVO + RT. No new safety signals were detected with NIVO in this study. The difference between the study treatment arms is consistent with the use of TMZ + RT as the standard of care for GBM. ClinicalTrials.gov NCT02617589

### Key Points

- NIVO did not improve survival in newly diagnosed GBM with unmethylated *MGMT* promoter.
- No new safety signals were detected with NIVO + standard of care in this study.
- Immunotherapy with NIVO is not a suitable replacement for chemotherapy with TMZ.

### Importance of the Study

Given the survival benefits of immunotherapy in cancer, it was hypothesized that it may also offer promise in difficult-to-treat cancers, such as glioblastoma (GBM). Worse outcomes are observed in patients with GBM with unmethylated versus methylated *MGMT* promoter. Temozolomide (TMZ), the standard chemotherapy, is associated with limited efficacy in unmethylated *MGMT* tumors. Here we report data

from the largest phase III study in patients with GBMs and unmethylated *MGMT* promoter and the first prospective phase III study examining TMZ omission in this chemoresistant phenotype. Nivolumab + radiotherapy (NIVO + RT) showed a shorter survival benefit vs TMZ + RT, suggesting that NIVO is not a suitable replacement for TMZ. Results also suggest that in the absence of other treatment options, TMZ should continue to be the standard of care for all patients with GBM regardless of *MGMT* promoter status.

Glioblastoma (GBM), the most common primary malignant brain tumor, is associated with a dismal prognosis and poor quality of life.<sup>1–4</sup> The mainstay of treatment for newly diagnosed disease is surgical resection followed by radiotherapy (RT) with concomitant and adjuvant temozolomide (TMZ).<sup>4–6</sup> The benefit of this treatment was demonstrated in a phase III study, which showed improved overall survival (OS) from 12.1 months with RT alone to 14.6 months with TMZ chemoradiotherapy (hazard ratio [HR], 0.63;  $P < .001$ ).<sup>5</sup>

Chemosensitivity to alkylating agents has been strongly linked to epigenetic silencing of the *MGMT* gene in various cancers.<sup>7,8</sup> Methylation of the *MGMT* promoter results in decreased *MGMT* expression, which reduces DNA repair capacity and confers chemosensitivity.<sup>8–10</sup> Analyses from the pivotal phase III study validating TMZ in GBM suggested that patients with tumors harboring a methylated *MGMT* promoter derived a survival benefit from TMZ + RT (median, 21.7 vs. 15.3 months), whereas patients with unmethylated *MGMT* promoter derived

minimal and statistically insignificant benefit (median, 12.7 vs 11.8 months).<sup>8</sup> *MGMT* promoter methylation is also an independent prognostic factor in GBM; patients with a methylated *MGMT* promoter achieve significantly better outcomes.<sup>8,10,11</sup> Given the lack of treatment alternatives, TMZ is offered to all patients with GBM, regardless of tumor *MGMT* promoter methylation status—with or without tumor-treating fields.<sup>4,6,12</sup> Because of TMZ's minimal benefit and known toxicities, reassessment of its role in GBM with unmethylated *MGMT* promoter remains of interest, and novel treatment alternatives are clearly needed for this patient population.<sup>13</sup>

Nivolumab (NIVO) is a fully human immunoglobulin G4 monoclonal antibody targeting the programmed cell death 1 protein (PD-1) immune checkpoint. NIVO has been shown to improve survival in multiple cancers, including melanoma, lung cancer, and renal cell carcinoma, and has demonstrated activity in brain metastasis from melanoma.<sup>14–16</sup> Gliomas have been shown to express PD-1 ligand (PD-L1),

and expression levels have been associated with tumor grade.<sup>17,18</sup> Preclinical studies in GBM models suggest that efficacy of PD-1 inhibitors could be enhanced through combination with RT.<sup>19</sup> RT may expose antigenic mutations, induce the expression of peptides that can activate T cells, and recruit antigen-presenting and immune effector cells to the tumor microenvironment (TME).<sup>20–22</sup> Given the chemoresistance observed in tumors with unmethylated *MGMT* promoter, we conducted a phase III study to evaluate whether immunotherapy with NIVO could improve survival when combined with RT (NIVO + RT) compared with conventional chemoradiotherapy with TMZ + RT in this patient population.

## Materials and Methods

### Study Design and Participants

In this open-label, phase III study, patients were stratified by degree of tumor resection (complete vs. partial) at baseline and randomized 1:1 to receive NIVO + RT or TMZ + RT. In both arms, focal RT consisted of 60 Gy in 2-Gy fractions. In the NIVO + RT arm, RT was combined with NIVO 240 mg every 2 weeks for eight doses followed by NIVO 480 mg every 4 weeks until unacceptable toxicity or disease progression. In the TMZ + RT arm, RT was combined with the standard TMZ regimen, 75 mg/m<sup>2</sup> once daily during RT (concomitant),<sup>23</sup> followed by a 4-week treatment break and then adjuvant treatment with TMZ 150 to 200 mg/m<sup>2</sup> once daily on days 1 to 5 of a 28-day cycle for ≤ 6 cycles (maintenance). The median dose and duration of RT was 60.0 Gy and 6.1 weeks in both arms, respectively. Per investigator's discretion, patients receiving NIVO were permitted to continue treatment beyond suspected progression until confirmation of progression on follow-up MRI.

Eligible patients were aged ≥ 18 years and had newly diagnosed, histologically confirmed, supratentorial GBM with unmethylated *MGMT* promoter determined centrally by a methylation-specific polymerase chain reaction assay.<sup>24</sup> Other key eligibility criteria included no prior treatment for GBM beyond surgery and Karnofsky Performance Scale (KPS) ≥ 70. At randomization, patients must have been receiving ≤ 20 mg prednisone or ≤ 3 mg dexamethasone (or equivalent). Patients were excluded if they had recurrent or secondary GBM; undergone biopsy only for GBM at surgery; tumors harboring *IDH-1* or *-2* mutation; unresolved CNS hemorrhage; metastatic extracranial or leptomeningeal disease; active, known, or suspected autoimmune disease; tumor-treating fields therapy (not a recommended treatment at time of study start); or used a biodegradable carmustine wafer.

### Procedures

Tumor samples were assessed for *MGMT* promoter methylation status; testing was performed by Covance laboratory services. A sample was determined to be *MGMT* unmethylated when the ratio of the gene copy numbers of methylated *MGMT* to control ( $\beta$ -actin)  $\times$  1000 was < 2 and the gene copy numbers of *MGMT* and control were within the reportable range ( $\beta$ -actin ≥ 10 copies and

*MGMT* ≥ 10 copies). Disease status was assessed using contrast-enhanced MRI at baseline and beginning 4 weeks ( $\pm$  7 days) after RT completion. Then, disease status was evaluated every 8 weeks ( $\pm$  7 days) until progression per Response Assessment in Neuro-Oncology (RANO) criteria.<sup>25</sup> As detailed in the RANO criteria, classification of tumor progression during the first 12 weeks after completion of RT requires either that the new enhancement be located outside of the radiation field (beyond the high-dose region or the 80% isodense line) or unequivocal pathological confirmation of progressive disease. Confirmation was determined at a subsequent MRI performed within 8 weeks after the initial radiological assessment of progression. Theoretically, patients treated with immunotherapy may derive clinical benefit despite initial evidence of disease progression; therefore, patients in the NIVO + RT arm were allowed to continue NIVO in the setting of suspected progression at investigator discretion until progression was confirmed. Progression-free survival (PFS) was defined as time from randomization to documented progression or death from any cause. OS was defined as time from randomization to death from any cause. Tumor-sample sections for PD-L1 expression were retrospectively assessed centrally (LabCorp Clinical Trials, Research Triangle Park, NC, USA); PD-L1 positivity was defined as percentage of membranous staining of tumor cells with 1% and 5% cutoff values. Adverse events (AEs) were assessed continuously during the study per National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Patient-reported outcomes (PROs) related to patients' health-related quality of life (HRQoL) were assessed using the European Organisation for Research and Treatment of Cancer QLQ-C30 and EQ-5D-3L questionnaires, collected at baseline, week 11, and then every 8 weeks during treatment until disease progression. The time to deterioration in PRO score was assessed by time from randomization to first worsening of PRO score from baseline during treatment—meeting or exceeding the minimal change in responder definition threshold—without subsequent improvement based on the responder definition.<sup>26</sup>

### Outcomes

The primary endpoint was OS. Secondary endpoints included investigator-assessed PFS based on RANO criteria and OS at 24 months using Kaplan-Meier methodology. Key exploratory endpoints included safety and tolerability, HRQoL, and efficacy based on tumor PD-L1 expression.

### Treatment Beyond Suspected Progression

Patients in the NIVO + RT arm with evidence of progression in imaging findings were allowed to continue study therapy until disease progression was confirmed.

### Statistical Analyses

OS, defined as the time between the date of randomization and the date of death due to any cause, was compared between treatment arms using a two-sided log-rank test

stratified by extent of surgical resection (complete or partial). The final OS analysis was planned after follow-up of  $\geq 23$  months or when  $\geq 390$  deaths were reported, providing  $\approx 90\%$  power with an overall type I error of 0.05. At the time of the database lock, some patients had  $< 24$  months of follow-up. However, given the number of events at the time of the database lock, it was considered that the number of patients with follow-up of  $< 24$  months at the time of the current analysis would not have affected the data maturity or interpretability of the results. Kaplan-Meier methodology was used to estimate OS and PFS curves, medians with 95% CIs, and OS and PFS rates at fixed time points with 95% CIs. HRs and corresponding two-sided 95% CIs were estimated using a stratified Cox proportional hazards model. A stratified Cox proportional hazards regression model was used to estimate the HR between treatment groups. Baseline characteristics in all randomized patients and safety in all treated patients were assessed using descriptive statistics.

### Study Oversight

The study was conducted in accordance with Good Clinical Practice guidelines per the International Conference on Harmonisation and with ethical principles of the European Union Directive and US Code of Federal Regulations. The study is registered at ClinicalTrials.gov (NCT02617589). The protocol was approved by an institutional review board or independent ethics committee at each site before study activation. All patients provided written informed consent in accordance with the Declaration of Helsinki.

### Role of the Funding Source

The study was designed by the authors in collaboration with the funder (Bristol Myers Squibb). The authors and funder were responsible for data collection, and the funder was responsible for data analysis. The authors and funder were involved in data interpretation, development of the report, and the decision to submit. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

## Results

### Patients and Treatment

From March 1, 2016, through October 25, 2018, 560 patients with newly diagnosed GBM with unmethylated *MGMT* promoter were randomized to receive NIVO + RT ( $n = 280$ ) or TMZ + RT ( $n = 280$ ) (Figure 1). Patients were enrolled at 124 sites across 19 countries. Of 560 randomized patients, 278 of 280 (99.3%) in the NIVO + RT arm and 275 of 280 (98.2%) in the TMZ + RT arm eventually received treatment. No marked imbalances were observed in baseline characteristics or demographics between arms (Table 1 and Supplementary Table S1).

Complete surgical resection had been performed in 151 patients (53.9%) in the NIVO + RT arm and 144 patients (51.4%) in the TMZ + RT arm. Baseline PD-L1 expression was  $\geq 1\%$  in 104 patients (37.8%) in the NIVO + RT arm and 125 patients (44.6%)

in the TMZ + RT arm; PD-L1 expression was  $< 1\%$  in 171 patients (62.2%) and 155 patients (55.4%), respectively (PD-L1 was not evaluable in one patient and tumor tissue samples were not collected for four patients in the NIVO + RT arm). Seventy-eight patients (27.9%;  $n = 280$ ) in the NIVO + RT arm and 95 patients (33.9%;  $n = 280$ ) in the TMZ + RT arm were receiving corticosteroids at baseline, with 5.7% and 7.9% of patients receiving  $> 3$  mg/day of dexamethasone equivalents, respectively.

The median duration of study treatment was 22.1 weeks (range, 0.1–140.9) in the NIVO + RT arm and 6.1 weeks (range, 0.6–8.3; concomitant) and 15.4 weeks (range, 0.1–121.1; maintenance) in the TMZ + RT arm. A median of 10.0 doses of NIVO was received (range, 1–40); the median number of TMZ cycles for all patients who entered the maintenance phase was 4.0 (range, 1–31).

At data cutoff, four patients (1.4%) in the NIVO + RT arm and one patient (0.4%) in the TMZ + RT arm were still receiving treatment. Among treated patients, discontinuations occurred in 274 patients (98.6%) in the NIVO + RT arm and 274 patients (99.6%) in the TMZ + RT arm. The most common reasons for treatment discontinuation were disease progression (NIVO + RT,  $n = 214$  [77.0%]; TMZ + RT,  $n = 137$  [49.8%]) and study drug toxicity (NIVO + RT,  $n = 26$  [9.4%]; TMZ + RT,  $n = 20$  [7.3%]) (Figure 1). In the TMZ + RT arm, 76 patients (27.6%) completed treatment.

### Efficacy

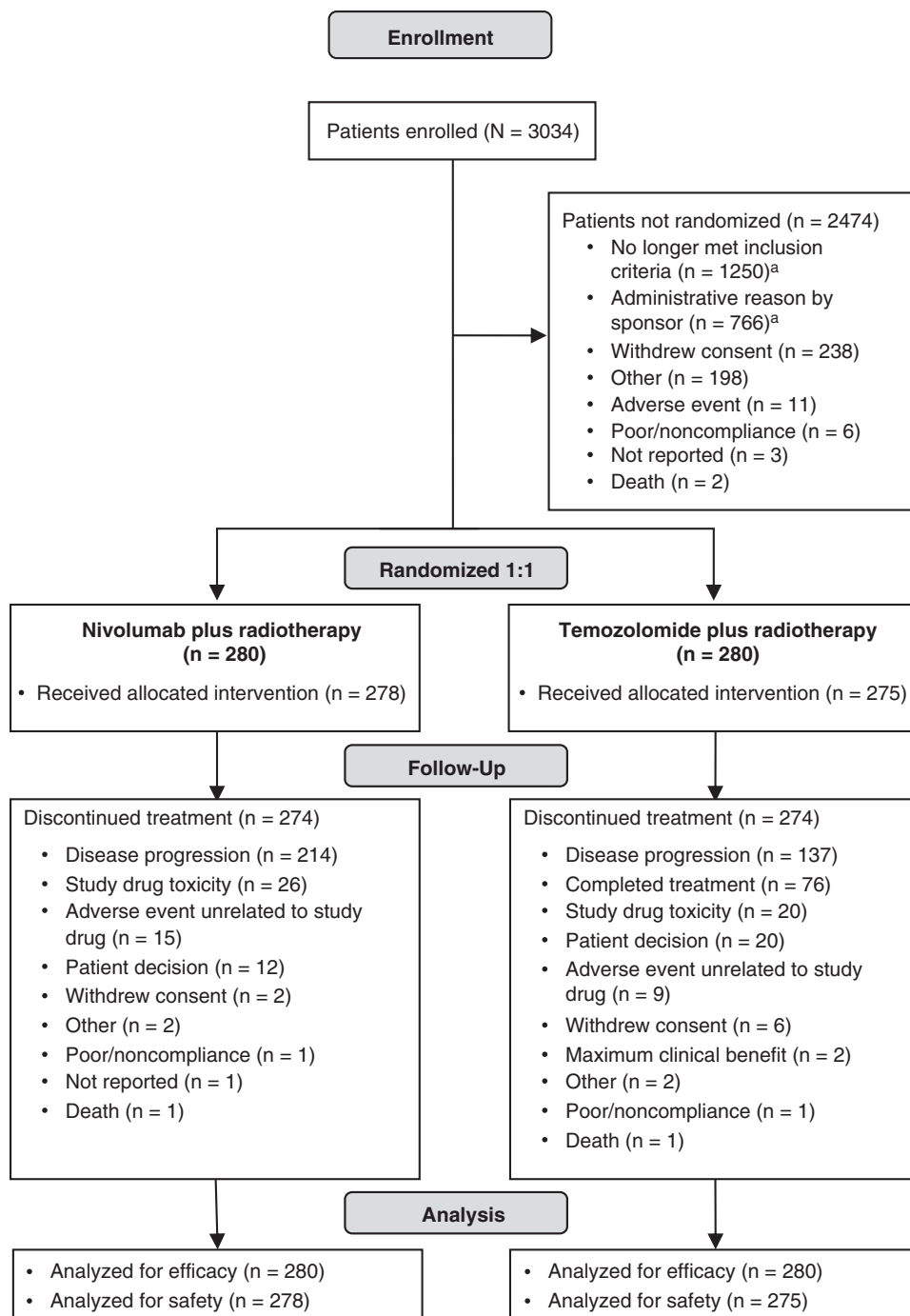
At data cutoff (March 21, 2019), the median follow-up time for OS was 13.0 months (range, 0.6–32.4) in the NIVO + RT arm and 14.2 months (range, 0–32.6) in the TMZ + RT arm. The final analysis was performed after 462 OS events had occurred. The median OS (mOS) was 13.4 months (95% CI, 12.6 to 14.3) in the NIVO + RT arm and 14.9 months (95% CI, 13.3 to 16.1) in the TMZ + RT arm (HR, 1.31; 95% CI, 1.09 to 1.58;  $P = .0037$ ) (Table 2 and Figure 2A). The 24-month OS rates were 10.3% (95% CI, 6.8 to 4.6) in the NIVO + RT arm and 21.2% (95% CI, 16.4 to 26.5) in the TMZ + RT arm.

Among patients with baseline PD-L1 expression  $\geq 1\%$ , mOS was 12.6 months ( $n = 104$ ; 95% CI, 11.3 to 14.2) in the NIVO + RT arm and 15.5 months ( $n = 125$ ; 95% CI, 13.2 to 17.2) in the TMZ + RT arm (HR, 1.4; 95% CI, 1.1 to 1.9) (Supplemental Figure S1A). The mOS in patients with PD-L1  $< 1\%$  was 13.8 months ( $n = 171$ ; 95% CI, 13.0 to 14.6) in the NIVO + RT arm and 14.7 months ( $n = 155$ ; 95% CI, 12.6 to 16.0) in the TMZ + RT arm (HR, 1.2; 95% CI, 0.9 to 1.5) (Supplemental Figure S1B). OS data by baseline PD-L1 expression  $\geq 5\%$  are shown in Supplemental Figures S1C and S1D. The results were consistent across several subgroup analyses, including complete tumor resection (Figure 3).

Exploratory analyses (not protocol defined) showed balanced distributions of *MGMT* scores across both arms. Median PFS was 6.0 months (95% CI, 5.7 to 6.2) with NIVO + RT versus 6.2 months (95% CI, 5.9 to 6.7) with TMZ + RT (HR, 1.38; 95% CI, 1.15 to 1.65) (Table 2; Figure 2B). The 12-month PFS rate was 5.7% (95% CI, 3.2 to 9.1) with NIVO + RT and 17.7% (95% CI, 13.3 to 22.7) with TMZ + RT.

The investigator-assessed objective response rate per RANO criteria was 7.8% (9/116; 95% CI, 3.6 to 14.2) in the NIVO + RT arm and 7.2% (8/111; 95% CI, 3.2 to 13.7) in the TMZ + RT arm (Supplemental Table S2). Duration of





**Fig. 1** Trial profile. <sup>a</sup>The majority of the nonrandomized population was excluded due to methylation status (cutoff, ratio of the gene copy numbers of methylated *MGMT* to control ( $\beta$ -actin)  $\times 1000 < 2$ ).

response data are presented in [Supplemental Table S2](#). Demographic and disease characteristics of responders are presented in [Supplemental Table S3](#).

Subsequent cancer therapy (any therapy) was received by 63.6% and 53.6% of patients in the NIVO + RT and TMZ + RT groups, respectively, of which 52.9% and 46.1%, respectively, received subsequent systemic cancer therapy ([Supplemental Table S4](#)). In the NIVO + RT group, 41.1% of

patients received subsequent treatment with alkylating agent (including 38.9% receiving TMZ therapy), and 27.5% received vascular endothelial growth factor antibody. In the TMZ + RT group, 30.7% of patients received alkylating agent, and 28.9% received vascular endothelial growth factor antibody. Three patients (1.1%) in the NIVO + RT arm and 7 (2.5%) in the TMZ + RT arm received subsequent immunotherapy ([Supplemental Table S4](#)).

**Table 1.** Patient Demographics and Baseline Characteristics

	Nivolumab plus radiotherapy (n = 280)	Temozolomide plus radiotherapy (n = 280)
Age, years		
Median	59.5	56.0
Range	18–83	23–81
Age, no. (%)		
< 65 years	190 (67.9)	207 (73.9)
≥ 65 to < 75 years	76 (27.1)	61 (21.8)
≥ 75 years	14 (5.0)	12 (4.3)
Sex, no. (%)		
Male	190 (67.9)	175 (62.5)
Female	90 (32.1)	105 (37.5)
Histopathologic diagnosis, no. (%)		
Glioblastoma	272 (97.1)	270 (96.4)
Gliosarcoma	8 (2.9)	10 (3.6)
RPA class, no. (%) <sup>a</sup>		
III	20 (7.1)	42 (15.0)
IV	219 (78.2)	202 (72.1)
V	41 (14.6)	36 (12.9)
Other	0	0
Extent of surgery, no. (%) <sup>b</sup>		
Complete resection	151 (53.9)	144 (51.4)
Partial resection	129 (46.1)	136 (48.6)
KPS, no. (%)		
100	76 (27.1)	91 (32.5)
90	122 (43.6)	118 (42.1)
80	54 (19.3)	47 (16.8)
70	28 (10.0)	20 (7.1)
Not reported	0	4 (1.4)
Time from diagnosis to randomization, weeks		
Median	4.93	5.14
Range	(4.1–5.6)	(4.3–5.9)
Patients with evaluable PD-L1 expression, no. (%)		
PD-L1 expression level, no. (%) <sup>c</sup>		
< 1%	171 (62.2)	155 (55.4)
≥ 1%	104 (37.8)	125 (44.6)
Not quantifiable	1 (0.4)	0
Corticosteroid use, no. (%) <sup>d</sup>		
Yes		
≤ 3 mg/day	62 (22.1)	73 (26.1)
> 3 mg/day	16 (5.7)	22 (7.9)
No		
	202 (72.1)	185 (66.1)

KPS, Karnofsky Performance Scale; PD-L1, programmed cell death ligand 1; RPA, recursive-partitioning analysis.

<sup>a</sup>The RPA classes were as follows: class III, age < 50 years and KPS ≥ 90 (on a scale of 0–100, with higher scores indicating better function); class IV, < 50 years and KPS < 90 (or ≥ 50 years, KPS ≥ 70, complete or partial tumor resection, and ability to work); class V, ≥ 50 years, KPS ≥ 70, complete or partial tumor resection, and inability to work (or ≥ 50 years, KPS ≥ 70, and tumor-biopsy specimen only; or ≥ 50 years and KPS < 70).<sup>35</sup>

<sup>b</sup>This characteristic was used as a stratification factor as recorded in the interactive voice response system at time of randomization. Information presented as collected in the case report form.

<sup>c</sup>Percentages were based on the number of patients with evaluable PD-L1 expression.

<sup>d</sup>Based on average corticosteroid use 5 days before start of dosing or randomization date for patients not treated (in dexamethasone equivalent). Patients enrolled at doses > 3 mg/day were tapered off; treatment did not commence until the dose was ≤ 3 mg/day.

**Table 2.** Overall Survival and Progression-Free Survival Rates Per Investigator Assessment

	Nivolumab plus radiotherapy (n = 280)	Temozolomide plus radiotherapy (n = 280)
Overall survival, months		
Median (95% CI)	13.4 (12.6 to 14.3)	14.9 (13.3 to 16.1)
Overall survival rate, (95% CI) %		
6 months	88.5 (84.1 to 91.7)	88.7 (84.4 to 91.9)
12 months	58.3 (52.2 to 63.9)	62.3 (56.3 to 67.8)
18 months	28.5 (23.3 to 34.0)	36.4 (30.7 to 42.2)
24 months	10.3 (6.8 to 14.6)	21.2 (16.4 to 26.5)
Progression-free survival, months		
Median (95% CI)	6.0 (5.7 to 6.2)	6.2 (5.9 to 6.7)
Progression-free survival rate, (95% CI) %		
6 months	50.5 (44.3 to 56.3)	54.6 (48.4 to 60.4)
9 months	14.8 (10.7 to 19.4)	30.9 (25.3 to 36.6)
12 months	5.7 (3.2 to 9.1)	17.7 (13.3 to 22.7)
18 months	3.0 (1.3 to 5.8)	8.1 (5.1 to 11.9)

## Safety

Any-grade treatment-related AEs (TRAEs) were reported in 72.7% of patients treated with NIVO + RT and 75.6% of patients treated with TMZ + RT. The most frequent TRAE was fatigue (any grade, 19.1%) in the NIVO + RT arm and nausea (any grade, 29.1%) in the TMZ + RT arm (Table 3; Supplemental Table S5). Rates of grade 3/4 TRAEs were 22.0% with NIVO + RT and 25.1% with TMZ + RT. Three treatment-related deaths were reported in the NIVO + RT arm: vasogenic cerebral edema, sudden death, and respiratory failure (1 each), after receiving 10, 7, and 10 infusions of NIVO, respectively. The patient who died from sudden death had previously experienced hyperglycemia and grade 3 rash and had been treated with insulin and corticosteroids. No deaths attributed to treatment were reported in the TMZ + RT arm. Neurological TRAEs occurred in 16.5% (grade 3/4, 1.8%) of patients treated with NIVO + RT and 9.5% (grade 3/4, 0%) of patients treated with TMZ + RT. Any-grade serious TRAEs occurred in 17.3% (NIVO + RT) and 7.6% (TMZ + RT) of patients. Any-grade TRAEs leading to discontinuation occurred in 24 patients (8.6%) in the NIVO + RT arm and 16 patients (5.8%) in the TMZ + RT arm. Treatment-related, immune-mediated AEs reported by category are shown in Supplemental Table S6. Most patients were not receiving corticosteroids at baseline (NIVO + RT = 200/278 [71.9%]; TMZ + RT = 180/275 [65.5%]). The median dose of corticosteroid was 0 mg/day (dexamethasone equivalents) in the NIVO + RT arm throughout the study treatment, except at weeks 11–18 and 91–98 when median corticosteroid use was 0.21 and 0.44 mg/day, respectively. Similarly, in the TMZ + RT arm, median dose of corticosteroid was 0 mg/day except at weeks 1–6 and 11–18 when median corticosteroid use was 0.24 and 0.66 mg/day, respectively.

## PROs

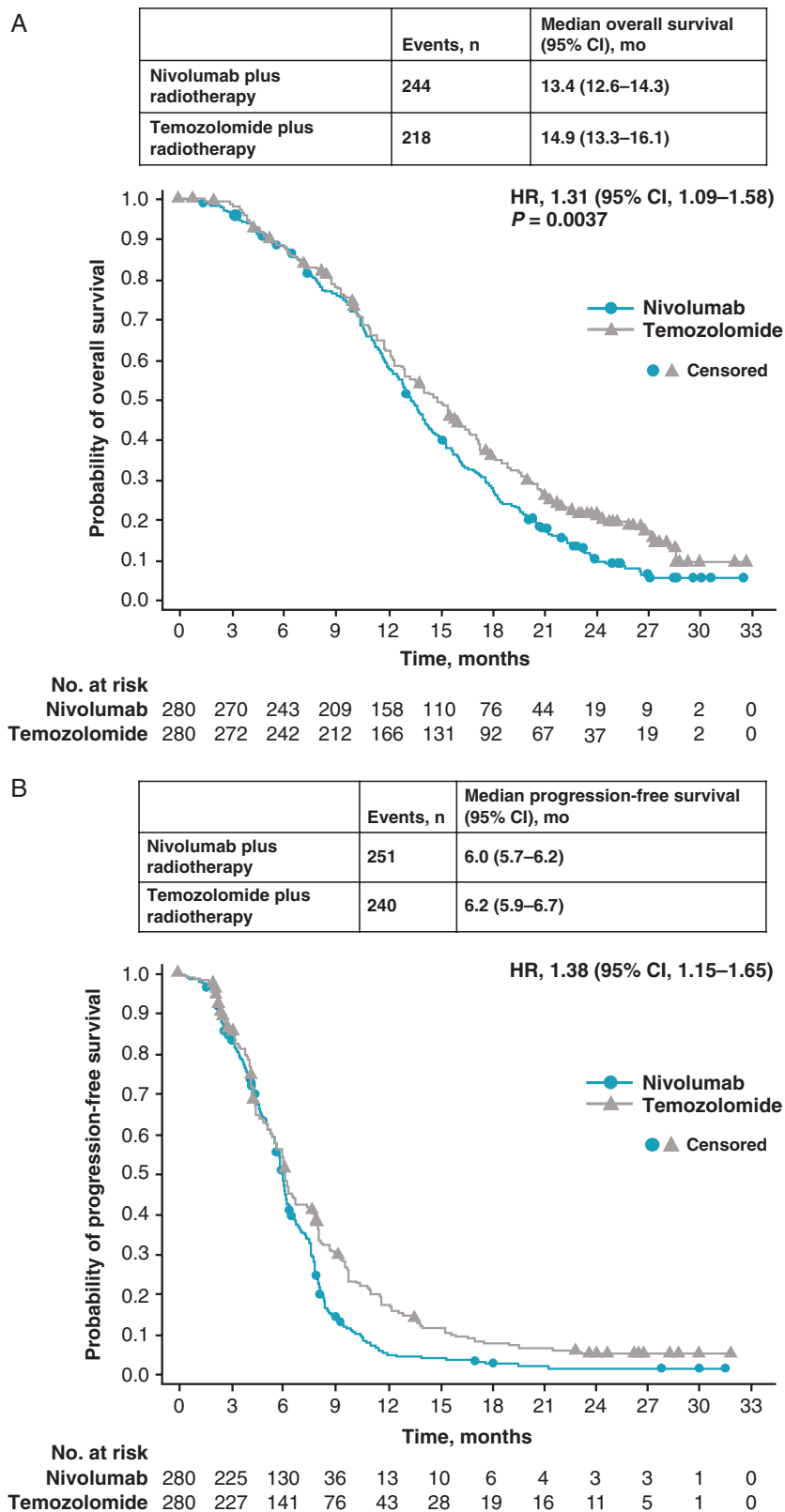
In all randomized patients, median time to deterioration of HRQoL scores was 4.6 months with NIVO + RT and

3.1 months with TMZ + RT (HR, 0.76; 95% CI, 0.59 to 0.99;  $P = .039$ ). A trend of delayed time to deterioration was observed in the NIVO + RT arm compared with the TMZ + RT arm for most domains of HRQoL and similarly for general health utilities (EQ-5D-3L index and visual analog scale; Supplemental Figure S2). However, these results for time to deterioration were affected by heavy censoring and should be interpreted with caution.

## Discussion

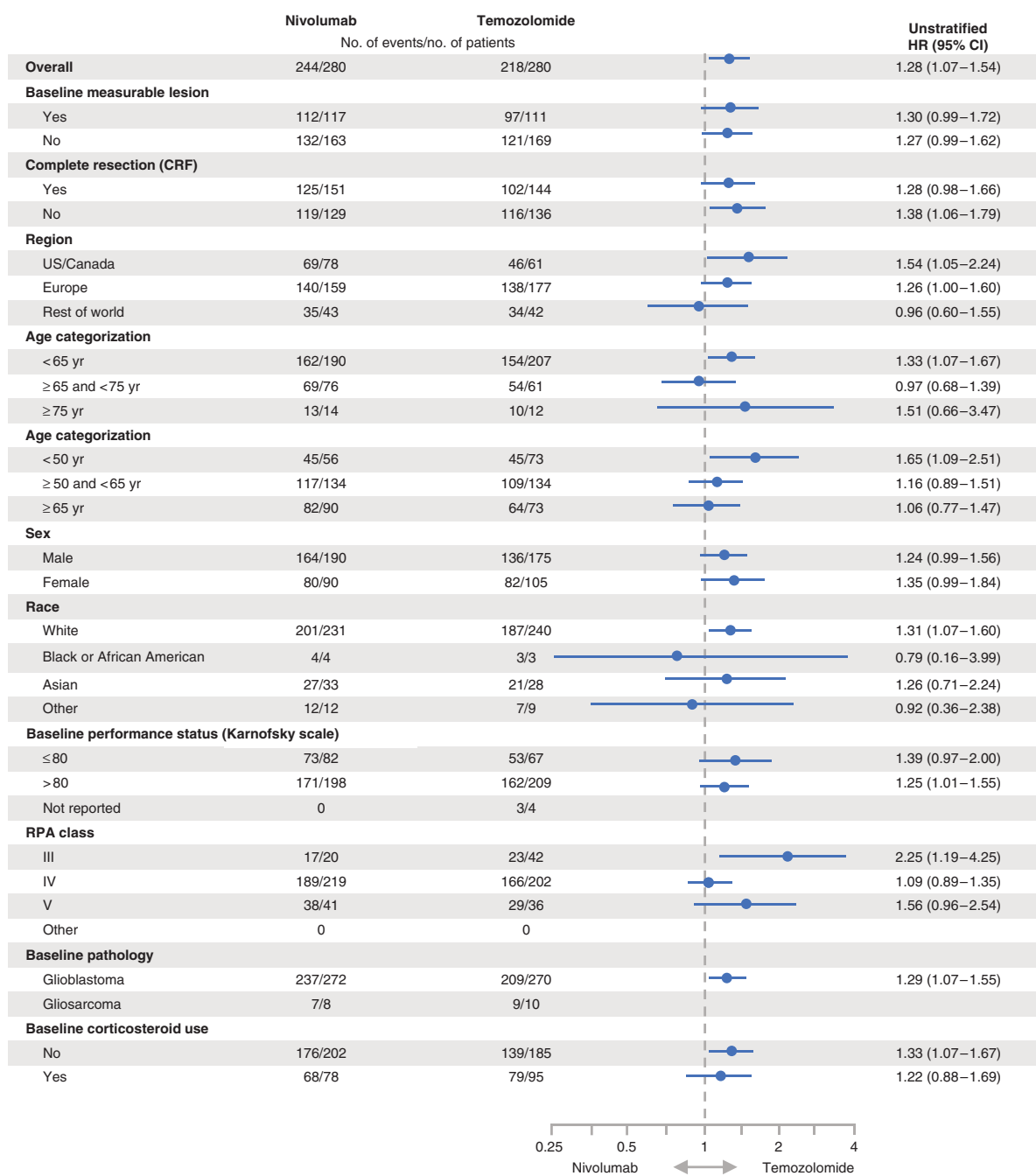
CheckMate 498 is a randomized phase III study investigating the efficacy of NIVO + RT compared with conventional TMZ + RT chemoradiation in patients with newly diagnosed GBM with unmethylated *MGMT* promoter. Although patients in both arms fared better than historical controls, the primary endpoint was not met. TMZ + RT was associated with superior OS compared with NIVO + RT (mOS, 14.9 vs. 13.4 months), suggesting that NIVO is not a substitute for TMZ in this patient population.

Although NIVO has shown notable efficacy in several other cancer types, it did not demonstrate a survival benefit in patients with newly diagnosed GBM with unmethylated *MGMT* promoter compared with TMZ. Likewise, in a subgroup analysis of the CheckMate 143 phase III study, NIVO did not demonstrate a survival benefit versus bevacizumab in patients with recurrent GBM with unmethylated *MGMT* promoter.<sup>27,28</sup> PD-L1 expression in this study ( $\approx 41\%$  of all patients expressed PD-L1  $\geq 1\%$ ) was similar to that observed in other GBM studies.<sup>18</sup> However, it did not predict survival benefit with NIVO, suggesting that other factors may hinder successful immune responses in this tumor type. Notably, recent results from the CheckMate 548 study (NCT02667587) in newly diagnosed GBM with methylated *MGMT* have also shown the addition of NIVO to TMZ + RT does not prolong PFS or OS compared with TMZ + RT alone.<sup>29</sup> Taken together, these results clearly highlight



**Fig. 2** OS and PFS in all patients. (A) Shows the number of events, median OS, and the Kaplan-Meier curve for OS in all patients treated with nivolumab plus radiotherapy or temozolomide plus radiotherapy. (B) Shows the number of events, median PFS, and the Kaplan-Meier curve for PFS per investigator assessment in patients treated with nivolumab plus radiotherapy or temozolomide plus radiotherapy. Symbols indicate censored observations. Hazard ratios and 95% CIs were estimated using a Cox proportional hazards model. OS, overall survival; PFS, progression-free survival.





**Fig. 3** Overall survival in prespecified patient subgroups defined by baseline clinical characteristics. This figure shows a forest plot of unstratified hazard ratios for death in the analysis of treatment effect in prespecified patient subgroups according to baseline characteristics.

a need for better understanding the mechanisms of immune evasion in GBM to improve the efficacy of immunotherapies. In addition to PD-L1 expression, multiple factors have been implicated in the maintenance of an immunosuppressive microenvironment in gliomas. These include both tumor- and brain-specific mechanisms (eg, low tumor mutational burden, recruitment of other immune checkpoints, decreased T-cell responsiveness, inhibitory cytokine production, interactions between CNS microenvironment

and microglia, predominance of myeloid cells, and paucity of lymphocytes in TME), in addition to frequent corticosteroid use.<sup>30-33</sup>

A key limitation of our study was the lack of immune-predictive biomarkers and comprehensive genomic characterization due to limited availability of tumor samples; therefore, novel biomarkers remain to be further explored. In addition, this study did not consider potential effects of the timing of PD-1 blockade relative to RT administration,

**Table 3.** Treatment-Related Adverse Events<sup>a</sup>

	Nivolumab plus radiotherapy (n = 278)		Temozolomide plus radiotherapy (n = 275)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any treatment-related adverse event, no. (%) <sup>b</sup>	202 (72.7)	61 (21.9)	208 (75.6)	69 (25.1)
Fatigue	53 (19.1)	1 (0.4)	77 (28.0)	3 (1.1)
Pyrexia	15 (5.4)	4 (1.4)	2 (0.7)	0
Alopecia	31 (11.2)	0	48 (17.5)	1 (0.4)
Rash	28 (10.1)	5 (1.8)	6 (2.2)	1 (0.4)
Pruritus	20 (7.2)	1 (0.4)	11 (4.0)	0
Diarrhea	22 (7.9)	2 (0.7)	8 (2.9)	0
Nausea	18 (6.5)	0	80 (29.1)	2 (0.7)
Headache	16 (5.8)	0	11 (4.0)	0
Radiation skin injury	21 (7.6)	0	17 (6.2)	0
Hypothyroidism/autoimmune hypothyroidism	16 (5.8)	2 (0.8)	0	0
Decreased appetite	15 (5.4)	0	34 (12.4)	0
Lymphocyte count decreased/lymphopenia	12 (4.3)	4 (1.5)	51 (18.6)	28 (10.2)
Asthenia	10 (3.6)	0	17 (6.2)	1 (0.4)
Vomiting	8 (2.9)	0	39 (14.2)	0
Constipation	7 (2.5)	0	40 (14.5)	0
Neutrophil count decreased/neutropenia	4 (1.4)	3 (1.1)	28 (10.2)	12 (4.4)
Platelet count decreased/thrombocytopenia	3 (1.1)	1 (0.4)	66 (24.0)	30 (10.9)
Treatment-related adverse event leading to discontinuation, no. (%)	24 (8.6)	20 (7.2)	16 (5.8)	12 (4.4)

<sup>a</sup>Data are based on a March 21, 2019, database lock. The safety analysis included all patients who received  $\geq 1$  dose of study drug. Some patients had  $> 1$  adverse event. Includes events reported between first dose and 30 days after last dose of study therapy. Three treatment-related deaths were reported in the nivolumab arm due to vasogenic cerebral edema, sudden death, and respiratory failure (1 each); no treatment-related deaths were reported in the temozolomide arm.

<sup>b</sup>These treatment-related adverse events were reported in  $\geq 5\%$  of the patients in either study arm. The full-length treatment-related adverse events table is included in [Supplement Table S5](#).

which has subsequently been demonstrated to be of possible consequence in some preclinical, non-GBM settings.<sup>34</sup>

The overall safety profile with NIVO + RT in this study was similar to that reported in CheckMate 143 for NIVO alone, with no new safety signals observed.<sup>28</sup> However, in some AE categories, as expected, more AEs were reported in the NIVO + RT arm than in the TMZ + RT arm. One of the reasons for the omission of TMZ in the NIVO + RT arm was to manage lymphopenia and immunosuppression; indeed, lymphopenia was more frequent in the TMZ + RT arm than in the NIVO + RT arm. Interestingly, HRQoL deteriorated numerically more rapidly in the TMZ + RT arm than in the NIVO + RT arm, consistent with expected effects of chemotherapy. However, time to deterioration results were affected by heavy censoring and should be interpreted with caution.

Our study found a statistically significant survival benefit with TMZ + RT over NIVO + RT despite tumor *MGMT* unmethylated status. mOS was 14.9 months (95% CI, 13.3 to 16.1) with TMZ + RT and 13.4 months (95% CI, 12.6 to 14.3) with NIVO + RT. These results were similar to those of previous studies, including the study conducted by Gilbert et al.,<sup>35</sup> which reported an mOS of 14.6 months (95% CI, 13.2 to 16.5) with TMZ + RT. The study conducted by Hegi et al.<sup>8</sup> also produced similar results: an mOS of 12.7 months (95% CI, 11.6 to 14.4) with TMZ + RT and 11.8 months (95% CI, 9.7 to 14.1)

with RT alone. Several potential differences in studies exist, including patient selection, study design, and patient management. However, one caveat is that NIVO was compared with TMZ, and any potential benefit of combining NIVO with TMZ was not evaluated to fully assess the effects of NIVO.

In summary, we report on the largest phase III study conducted to date in patients with GBM molecularly selected for unmethylated *MGMT* promoter and the first to prospectively examine the omission of TMZ in this population. Overall, our results indicate that immunotherapy with NIVO is not a suitable replacement for chemotherapy with TMZ despite the chemoresistance of this difficult-to-treat patient population. Further immunotherapy efforts in GBM include alternative immune checkpoint inhibitors, vaccines, oncolytic viruses, and cell therapies. Additionally, immune checkpoint inhibitors combined with each other or with vaccines may also be explored.

## Supplementary Material

Supplementary material is available at *Neuro-Oncology* online.

## Keywords

newly diagnosed glioblastoma | nivolumab | radiotherapy | temozolomide | unmethylated *MGMT*

## Funding

This work was supported by Bristol Myers Squibb, Princeton, NJ.

## Acknowledgments

We thank the patients and their families who made this study possible; Corina Taitt for her contribution to study development and design; investigators and research staff at all study sites; ONO Pharmaceutical Company Ltd. (Osaka, Japan); and the staff of Dako, an Agilent Technologies, Inc., company, for collaborative development of the PD-L1 IHC 28-8 pharmDx assay. Editorial assistance was provided by Bridget Sackey-Aboagye, PhD, Judith Matray-Devoti, PhD, and Larra Yuelling, PhD, of SciMentum, Inc, a Nucleus Holding Ltd company, and was funded by Bristol Myers Squibb.

**Conflict of interest statement.** A.O. has served as a consultant on ad hoc advisory boards for Bristol Myers Squibb, AstraZeneca, Inovio, Merck, Stemline, Novocure, Alexion, and KIYATEC and has received grant funding from Arcus Biosciences. A.A.B. has nothing to disclose. A.F.C. received personal fees from Bristol Myers Squibb. A.I. received grants and other funding from Carthera, Transgene, Sanofi, Air Liquide, and Leo Pharma. D.A.R. received other funding from Acerta Pharma, Agenus, Celldex, EMD Serono, Incyte, Inovio, Midatech, Omnio, and Tragara and personal fees from AbbVie, Advantagene, Agenus, Amgen, Bayer, Bristol Myers Squibb, Celldex, DelMar, EMD Serono, Genentech/Roche, Inovio, Merck, Merck KGaA, Monteris, Novocure, Oncorus, Oxigene, Regeneron, Stemline, and Taiho Oncology, Inc. T.C. received personal fees from Roche, Bayer, Amgen, Chimerix, Novocure, Novartis, Jubilant, Immvira, Gan & Lee, Brainstorm, Tyme, SDP, Inovio, Sapience, DNATrix, QED, DelMar, Tocagen, Karyopharm, GW Pharma, KIYATEC, AbbVie, Boehringer Ingelheim, VBI, Deciphera, VBL, Agios, Merck, Bristol Myers Squibb, and Cortice; is a co-founder, with milestone royalties, stock and stock options, consultant, scientific advisory board to Katmai; has stock, milestones and royalties from Chimerix, and is a member of the board for the 501(c)(3) nonprofit Global Coalition for Adaptive Research and SAB for Break Through Cancer. A.S. has nothing to disclose. J.B. has served as a consultant for Bristol Myers Squibb. M.V.D.B. received personal fees from Bristol Myers Squibb, Carthera, Nerviano, AbbVie, Bayer, Boehringer Ingelheim, Agios, and Genenta. O.B. has received personal fees from medac Pharma and Novocure. G.L. received personal fees from Bayer Italy S.p.A., AbbVie, Orbus, and Brainfarm. P.M. has nothing to disclose. G.T. received personal fees from AbbVie, Bayer, Bristol Myers Squibb, medac Pharma, and Novocure and grants from Bristol Myers Squibb, medac Pharma, Roche Diagnostics, and Novocure. U.L. received grant funding from Bristol Myers Squibb. J.M.S. received grant funding from Pfizer, other fees from Astellas, and personal fees from AbbVie and Celgene, a Bristol-Myers Squibb company.

M.K. received grant funding from Bristol Myers Squibb and AbbVie and personal fees from Roche, Ipsen, Novartis, Pfizer, and AbbVie. E.V. has nothing to disclose. Y.M. received grant funding from MSD, Chugai Pharma, Otsuka, Tsumura, and Hitachi and personal fees from Novocure, AbbVie, Ono Pharmaceutical, Daiichi Sankyo, MSD, Chugai Pharma, Otsuka, Eisai, and Novartis. A.M.D.G. received other funding from Bristol Myers Squibb, Pierre Fabre, MSD, Inscyte, and GSK. N.B. has nothing to disclose. P.R. received other funding from Bristol Myers Squibb and personal fees from Bristol Myers Squibb, Debiopharm, medac Pharma, Merck, QED, Roche, MSD, Virometix, and Novocure and grant funding from MSD and Novocure. X.Q. was an employee of Bristol Myers Squibb and received stocks from Bristol Myers Squibb. A.Z.F. was an employee of Bristol Myers Squibb. Y.L. was an employee of Bristol Myers Squibb. V.P. was an employee of Bristol Myers Squibb. A.-G.C. is an employee of and has received stocks from Bristol Myers Squibb. K.T. was an employee of Bristol Myers Squibb. M.L. received grants from Arbor Pharmaceuticals, Accuray, DNATrix, Biohaven, Bristol Myers Squibb, Kyowa Kirin, and UroGen; received personal fees from VBI, Stryker, Bristol Myers Squibb, Tocagen, InCephalo Therapeutics, Pyramid Bio, Merck, Insightec, Biohaven, Sanianoia, Hemispherian, Black Diamond Therapeutics, and Novocure; and has a patent. M.W. received other funding from Bristol Myers Squibb; grants from MSD, Merck (EMD), Novocure, and Quercis; and personal fees from Bristol Myers Squibb, AbbVie, MSD, Merck (EMD), Orbus, and Y-mAbs.

**Authorship statement.** A.O., D.A.R., M.L., and M.W. participated in the initial study design; A.-G.C. participated in the statistical analysis of the data; A.O., A.A.B., A.F.C., A.I., D.A.R., T.C., A.S., J.B., M.V.D.B., O.B., G.L., P.M., G.T., U.L., J.M.S., M.K., E.V., Y.M., A.M.D.G., N.B., P.R., M.L., and M.W. participated in acquisition of the data; all authors provided critical review or revision of the manuscript; and all authors approved to submit the manuscript for publication.

## Data Availability

The data sets presented in this article are not readily available because requestors must complete a data request on the BMS investigator portal. Requests to access the data sets should be directed to <https://fastrack-bms.force.com/Login>. Bristol Myers Squibb's policy on data sharing may be found at <https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html>.

## References

- Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2011–2015. *Neuro Oncol*. 2018; 20(suppl\_4):iv1–iv86.
- Preusser M, Lim M, Hafler DA, Reardon DA, Sampson JH. Prospects of immune checkpoint modulators in the treatment of glioblastoma. *Nat Rev Neurol*. 2015;11(9):504–514.
- Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy

- alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol.* 2009;10(5):459–466.
4. Wen PY, Weller M, Lee EQ, et al. Glioblastoma in adults: a Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions. *Neuro Oncol.* 2020;22(8):1073–1113.
  5. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med.* 2005;352(10):987–996.
  6. Weller M, van den Bent M, Preusser M, et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. *Nat Rev Clin Oncol.* 2021;18(3):170–186.
  7. Gerson SL. *MGMT*: its role in cancer aetiology and cancer therapeutics. *Nat Rev Cancer.* 2004;4(4):296–307.
  8. 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.
  9. Esteller M, Garcia-Foncillas J, Andion E, et al. Inactivation of the DNA-repair gene MGMT and the clinical response of gliomas to alkylating agents. *N Engl J Med.* 2000;343(19):1350–1354.
  10. Weller M, Stupp R, Reifenberger G, et al. MGMT promoter methylation in malignant gliomas: ready for personalized medicine? *Nat Rev Neurol.* 2010;6(1):39–51.
  11. Hegi ME, Diserens AC, Godard S, et al. Clinical trial substantiates the predictive value of O-6-methylguanine-DNA methyltransferase promoter methylation in glioblastoma patients treated with temozolomide. *Clin Cancer Res.* 2004;10(6):1871–1874.
  12. 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.
  13. Weller M. Where does O<sup>6</sup>-methylguanine DNA methyltransferase promoter methylation assessment place temozolomide in the future standards of care for glioblastoma? *Cancer.* 2018;124(7):1316–1318.
  14. *Opdivo™ (Nivolumab) US Prescribing Information.* Princeton, NJ: Bristol-Myers Squibb; 2019.
  15. Lauko A, Thapa B, Jia X, Ahluwalia MS. Efficacy of immune checkpoint inhibitors in patients with brain metastasis from NSCLC, RCC, and melanoma. *J Clin Oncol.* 2018;36(5):214–214.
  16. Tawbi HA, Forsyth PA, Algazi A, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *N Engl J Med.* 2018;379(8):722–730.
  17. Berghoff AS, Kiesel B, Widhalm G, et al. Programmed death ligand 1 expression and tumor-infiltrating lymphocytes in glioblastoma. *Neuro Oncol.* 2015;17(8):1064–1075.
  18. Nduom EK, Wei J, Yaghi NK, et al. PD-L1 expression and prognostic impact in glioblastoma. *Neuro Oncol.* 2016;18(2):195–205.
  19. Zeng J, See AP, Phallen J, et al. Anti-PD-1 blockade and stereotactic radiation produce long-term survival in mice with intracranial gliomas. *Int J Radiat Oncol Biol Phys.* 2013;86(2):343–349.
  20. Lugade AA, Moran JP, Gerber SA, et al. Local radiation therapy of B16 melanoma tumors increases the generation of tumor antigen-specific effector cells that traffic to the tumor. *J Immunol.* 2005;174(12):7516–7523.
  21. Golden EB, Apetoh L. Radiotherapy and immunogenic cell death. *Semin Radiat Oncol.* 2015;25(1):11–17.
  22. Lhuillier C, Rudqvist N-P, Elemento O, Formenti SC, Demaria S. Radiation therapy and anti-tumor immunity: exposing immunogenic mutations to the immune system. *Genome Med.* 2019;11(1):40.
  23. *TEMODAR® (Temozolomide) US Prescribing Information.* Whitehouse Station, NJ: Merck; 2017.
  24. 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.
  25. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol.* 2010;28(11):1963–1972.
  26. Cocks K, King MT, Velikova G, et al. Evidence-based guidelines for interpreting change scores for the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. *Eur J Cancer.* 2012;48(11):1713–1721.
  27. Weller M, Reardon D, Brandes A, et al. Nivolumab vs bevacizumab in patients with recurrent glioblastoma: exploratory analysis of MGMT methylation status and baseline corticosteroid use. *Neuro Oncol.* 2019; 21(suppl\_6):vi12.
  28. Reardon DA, Brandes AA, Omuro A, et al. Effect of nivolumab vs bevacizumab in patients with recurrent glioblastoma: the CheckMate 143 phase 3 randomized clinical trial. *JAMA Oncol.* 2020;6(7):1003–1010.
  29. Weller M, Lim M, Idhahbi A, et al. A randomized phase 3 study of nivolumab or placebo combined with radiotherapy plus temozolomide in patients with newly diagnosed glioblastoma with methylated MGMT promoter: CheckMate 548. *Neuro Oncol.* 2021; 23(suppl\_6):vi55–vi56.
  30. Chongsathidkiet P, Jackson C, Koyama S, et al. Sequestration of T cells in bone marrow in the setting of glioblastoma and other intracranial tumors. *Nat Med.* 2018;24(9):1459–1468.
  31. Hodges TR, Ott M, Xiu J, et al. Mutational burden, immune checkpoint expression, and mismatch repair in glioma: implications for immune checkpoint immunotherapy. *Neuro Oncol.* 2017;19(8):1047–1057.
  32. Mangani D, Weller M, Roth P. The network of immunosuppressive pathways in glioblastoma. *Biochem Pharmacol.* 2017;130:1–9.
  33. Wong ET, Lok E, Gautam S, Swanson KD. Dexamethasone exerts profound immunologic interference on treatment efficacy for recurrent glioblastoma. *Br J Cancer.* 2015;113(2):232–241.
  34. Wei J, Montalvo-Ortiz W, Yu L, et al. Sequence of  $\alpha$ PD-1 relative to local tumor irradiation determines the induction of abscopal antitumor immune responses. *Sci Immunol.* 2021;6(58):eabg0117.
  35. 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.