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NUTMEG: A randomized phase II study of nivolumab and temozolomide versus temozolomide alone in newly diagnosed older patients with glioblastoma

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Abstract

Background. There is an immunologic rationale to evaluate immunotherapy in the older glioblastoma population, who have been underrepresented in prior trials. The NUTMEG study evaluated the combination of nivolumab and temozolomide in patients with glioblastoma aged 65 years and older.

Methods. NUTMEG was a multicenter 2:1 randomized phase II trial for patients with newly diagnosed glioblastoma aged 65 years and older. The experimental arm consisted of hypofractionated chemoradiation with temozolomide, then adjuvant nivolumab and temozolomide. The standard arm consisted of hypofractionated chemoradiation with

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temozolomide, then adjuvant temozolomide. The primary objective was to improve overall survival (OS) in the experimental arm.

Results. A total of 103 participants were randomized, with 69 in the experimental arm and 34 in the standard arm. The median (range) age was 73 (65–88) years. After 37 months of follow-up, the median OS was 11.6 months (95% CI, 9.7–13.4) in the experimental arm and 11.8 months (95% CI, 8.3–14.8) in the standard arm. For the experimental arm relative to the standard arm, the OS hazard ratio was 0.85 (95% CI, 0.54–1.33). In the experimental arm, there were three grade 3 immune-related adverse events which resolved, with no unexpected serious adverse events.

Conclusions. Due to insufficient evidence of benefit with nivolumab, the decision was made not to transition to a phase III trial. No new safety signals were identified with nivolumab. This complements the existing series of immunotherapy trials. Research is needed to identify biomarkers and new strategies including combinations.

Key Points

- The addition of nivolumab to temozolomide did not improve survival in the older glioblastoma population.
- There were no safety concerns with the addition of nivolumab to temozolomide in the older glioblastoma population.

Importance of the Study

This was a randomized international multicenter phase II trial that assessed the activity of nivolumab in older patients with glioblastoma, which is an area of great unmet need. There was insufficient evidence of clinical benefit with nivolumab in this population, no new safety signals were identified, and more research is needed to identify biomarkers and better strategies including rational combinations.

Glioblastoma is the most common primary malignant brain tumor in adults, representing 50% of all primary malignant central nervous system (CNS) tumors.[1] Glioblastoma confers the worst prognosis of all primary brain tumors, with a median survival of approximately 15 months with standard-of-care treatment.[1–3]

A hallmark of cancer is immune evasion that can be mediated, in part, by the expression of programmed death-ligand 1 (PD-L1), which binds the programmed death 1 (PD-1) receptor expressed by T cells, B cells, dendritic cells, and natural killer cells.[4,5] Anti-PD-L1 (aPD-L1) and anti-PD-1 (aPD-1) monoclonal antibodies capable of binding these molecules and blocking their interaction have shown promising outcomes in several cancers.[6,7]

Glioblastoma has been shown to express modest levels of PD-L1, suggesting that this immunosuppressive signaling axis may be active.[8] Furthermore, PD-L1 positivity (defined as >5% expression) in glioblastoma is correlated with worse outcomes.[8] At the time this study was proposed, similar trials including CheckMate-498, which evaluated nivolumab for newly diagnosed *O*^{6}*-methylguanine-DNA methyltransferase (MGMT)*-unmethylated glioblastoma,[9] and CheckMate-548, which evaluated nivolumab for newly diagnosed *MGMT*-methylated glioblastoma,[10] were still actively enrolling participants.

There were multiple reasons to conduct this prospective trial in older glioblastoma patients. Survival is worse in older patients,[11] and many do not live more than 10 months past diagnosis.[12] Furthermore, older individuals comprise a significant proportion of the glioblastoma patient population, as the median age at diagnosis is 65 and the incidence increases with age, peaking at a rate of 15.17 per 100 000 in the 75–84 age range.[1] By targeting this patient group, NUTMEG aimed to address a significant unmet need within a population that is often overlooked. It is noteworthy that all participants in NUTMEG would be aged 65 years or older. In comparison, subsequently published phase III trials such as CheckMate-498 included 29% of participants aged 65 years or older, with only 5% falling within the age group of 70 years or older.[9] Similarly, CheckMate-548 included 33% of participants aged 65 years or older, with only 6% aged 70 years or older.[10]

From an immunologic perspective, we sought to prospectively assess the use of aPD-1/aPD-L1 in older glioblastoma patients specifically because an increase in mutations with age is well-documented both in glioblastoma, as well as cancers in general.[13,14] In some cancer types (eg, melanoma), a higher tumor mutational burden (TMB) may result in an increase in tumor antigens and, in turn, tumor immunogenicity.[15] Mutational load is thought to be a surrogate marker of neoantigen expression. Neoantigens are proteins entirely absent from the normal human genome that are formed by tumor-specific genomic alterations in DNA that result in the production of these novel proteins.

Recognition of neoantigens is a major factor contributing to anti-tumor immunity.[16] Importantly, there is a positive correlation between the frequency of tumor somatic mutations and overall response to aPD-1/aPD-L1.[15] Taken together, we wanted to examine if older glioblastoma patients, a group with higher TMB, might demonstrate an improvement in survival in response to aPD-1/aPD-L1 therapy.We conducted the trial in the newly diagnosed setting because tumor-driven immunosuppression is less pronounced.[17,18] Furthermore, there is evidence that radiation and TMZ may potentiate anti-tumor immune responses in preclinical glioma models.[19,20] Newly diagnosed glioblastomas, like most cancers, express neoantigens at baseline; however, TMZ treatment can increase tumor antigen load significantly due to its mutagenic properties.[21] Through the focused investigation of this crucial yet frequently underrepresented patient population, guided by a biologically relevant rationale and acknowledging the prevailing scientific consensus at the time, we conducted a signal-seeking phase II trial to explore the potential efficacy of TMZ, with or without nivolumab, in older patients with newly diagnosed glioblastoma.

Materials and Methods

Study Objectives

The primary objective of the NUTMEG study was to evaluate OS in participants with newly diagnosed glioblastoma who were aged 65 years or older. They received hypofractionated (40 Gy in 15 daily fractions over 3 weeks) chemoradiation followed by adjuvant TMZ, with or without nivolumab.[22]

Secondary objectives were to evaluate 6-month progression-free survival (PFS), toxicity, health-related quality of life (HRQL) and neurologic function. Tertiary objectives were to identify molecular and imaging biomarkers of treatment response.

Participant Eligibility

Eligible participants had newly diagnosed glioblastoma based on the 2016 World Health Organization Classification of Tumors of the Central Nervous System (2016 CNS WHO).[23] They were aged 65 years or older, and the treatment recommendation needed to be hypofractionated chemoradiation (40 Gy in 15 fractions)[22] rather than long-course chemoradiation (60 Gy in 30 fractions).[2] None had received prior treatment other than surgery, as tissue was required to determine *MGMT* promoter methylation status, which was a stratification factor. Other inclusion criteria were: Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; life expectancy of >12 weeks; adequate bone marrow function (neutrophils > 1.5×10^9/l and platelets > 100×10^9/l); adequate liver function (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] < 1.5 times the upper limit of normal); and adequate renal function (creatinine clearance > 30 ml/min based on the Cockroft–Gault equation).

Participants were excluded if they required >4 mg/day of dexamethasone (or an equivalent dose of steroids) for glioblastoma symptoms, or >2 mg/day of dexamethasone (or steroid equivalent) for other conditions. Other exclusion criteria were: prior chemotherapy or cranial radiation within 2 years; other malignancy within 2 years (except for adequately treated carcinoma-in situ, basal cell carcinoma of the skin, squamous cell carcinoma of the skin or superficial transitional cell carcinoma of the bladder); significant infection; autoimmune disease (except for endocrine conditions requiring hormone replacement only or skin conditions requiring topical treatment only); and any other comorbidities that might compromise study procedures.

Study Oversight

The NUTMEG study was an investigator-led multicenter trial conducted in Australia and the United States. Study oversight was provided by the Cooperative Trials Group for Neuro-Oncology (COGNO) at the National Health and Medical Research Council (NHMRC) Clinical Trials Centre (CTC), University of Sydney. The Trial Management Committee (TMC) offered oversight of trial conduct and the Independent Safety and Data Monitoring Committee (ISDMC) performed an independent assessment of participant safety and trial progress. Funding was provided by NHMRC Project Grant APP1125204. Bristol-Myers Squibb supplied nivolumab but was not involved in any aspects of trial conduct or reporting. Centralized ethics approval was provided by the Northern Sydney Local Health District Human Research Ethics Committee (2019/ETH08586). The trial was prospectively registered on ClinicalTrials.gov (NCT04195139) and the Australia New Zealand Clinical Trials Register (ACTRN12617000267358).

Study Design and Treatment

This study was a randomized, parallel-design, open-label, phase II clinical trial (Figure 1). Participants gave their written informed consent before commencing study procedures. They were randomly assigned in a 2:1 ratio to the experimental or standard treatment arms. The 2:1 ratio was intended to encourage study enrollment.

Randomization was stratified by ECOG performance status (0 versus 1–2), age (65–69 versus ≥70), *MGMT* promoter methylation status (methylated versus unmethylated) and surgery type (gross total resection versus subtotal resection or biopsy) using the method of minimization. Allocation concealment was achieved by using computer-generated central randomization via a web-based interface. Randomization was initiated prior to hypofractionated chemoradiation to improve the generalizability of findings. This ensured that the study population would not have a significantly better prognosis than historical controls, which might otherwise result from excluding participants who drop out due to early disease progression or deterioration due to other reasons. In response to *MGMT* testing delays, a protocol amendment subsequently allowed participants to commence

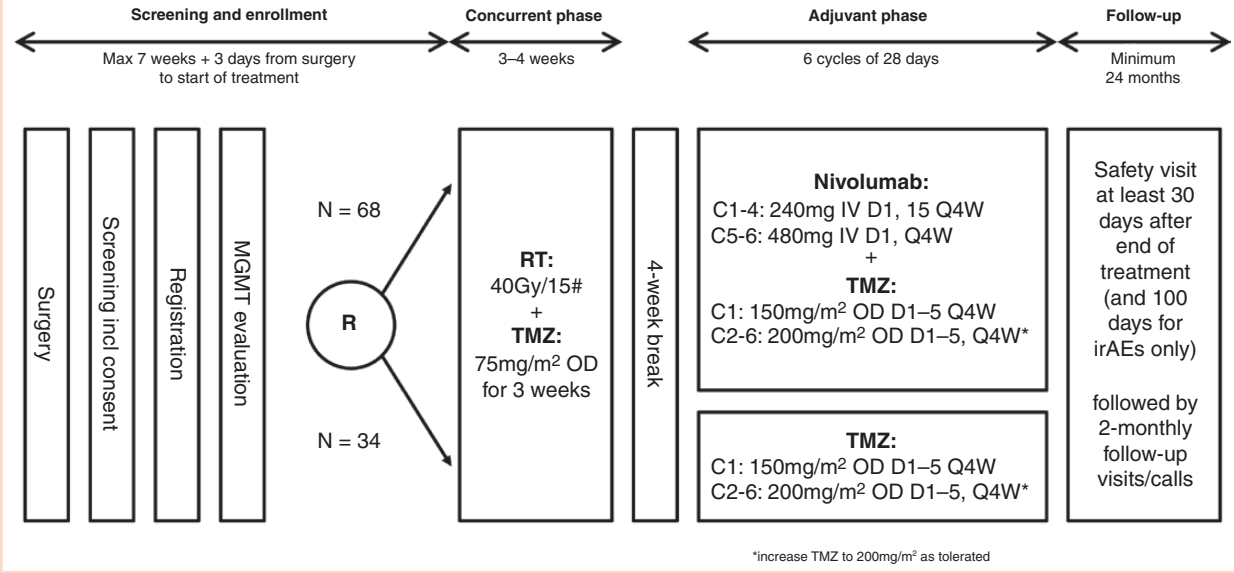

Figure 1. NUTMEG study schema. Abbreviations: irAEs = immune-related adverse events; *MGMT* = O^6-methylguanine-DNA-methyltransferase promoter methylation status; OD = once daily; RT = radiotherapy; TMZ = temozolomide.

hypofractionated chemoradiation while awaiting their *MGMT* results, to be randomized within 4 calendar days once available.

The experimental arm involved hypofractionated chemoradiation, followed by a 4-week treatment break, followed by up to 6 cycles of adjuvant nivolumab combined with TMZ. The standard arm involved hypofractionated chemoradiation, followed by a 4-week treatment break, followed by up to 6 cycles of adjuvant TMZ. Hypofractionated chemoradiation consisted of 40 Gy over 15 fractions with concurrent TMZ 75 mg/m^2 once daily. All sites underwent quality assurance in radiotherapy. Adjuvant TMZ was dosed at 150 mg/m^2 once daily on Days 1–5 every 28 days for Cycle 1, then escalated to 200 mg/m^2 once daily on Days 1–5 every 28 days for Cycles 2–6 if well-tolerated. If necessary due to toxicity, the TMZ dose was decremented to 150 mg/m^2, then 100 mg/m^2, then 75 mg/m^2, and then discontinued. Adjuvant nivolumab was dosed at 240 mg once daily on Days 1 and 15 every 28 days for Cycles 1–4, then 480 mg once daily on Day 1 and every 28 days for Cycles 5–6. There were no nivolumab dose reductions.

Treatment was continued until regimen completion, progressive disease, death, unacceptable toxicity, or consent withdrawal. Throughout the study, steroid use was to be minimized at the lowest safe dose possible. Concomitant investigational or anticancer treatments, including bevacizumab, were not permitted.

Assessments

The primary endpoint of the NUTMEG study was OS in all randomized participants. OS was defined as the interval from the date of randomization to the date of death from any cause. Participants who were alive at their last follow-up were censored at that date.

Secondary endpoints included 6-month PFS in all randomized participants, which was calculated by the Kaplan–Meier method as the proportion without a PFS event at 6 months postrandomization. PFS was defined as the interval from the date of randomization to the date of disease progression or death from any cause. Participants who were alive and progression-free at their last follow-up were censored at that date. Disease progression was determined by investigators using the modified Response Assessment in Neuro-Oncology (mRANO) criteria that were introduced into neuro-oncology practice in 2017.[24] mRANO provides clear definitions of pseudoprogression and pseudoresponse, and has been recommended as an outcome measure in neuro-oncology trials for both antiangiogenic and immunotherapy agents. As per mRANO, the first MRI scan after completion of hypofractionated chemoradiation was used as the baseline reference. In addition, due to potential pseudoprogression, participants were allowed to continue treatment beyond initial radiographic progression until this was confirmed. If the tumor showed a continual increase in size on 2 sequential scans, disease progression was documented as the date at which potential progression was first identified. If the tumor exhibited pseudoprogression, as indicated by a transient increase in size followed by stability or shrinkage, disease progression was documented as the date of subsequent radiographic progression after pseudoprogression. MRI scans were performed every 8 weeks until disease progression or death. Independent central radiographic review will be retrospectively performed by trained neuroradiologists at the University of California, Los Angeles (UCLA) Brain Tumor Imaging Laboratory.

Toxicity was evaluated by investigators using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. Clinical

assessments and blood tests were performed prior to hypofractionated chemoradiation and at the start of each adjuvant treatment cycle. In addition, there was a safety follow-up visit 30 days after the end of treatment, and 100 days after the last dose of nivolumab for immune-related adverse events.

HRQL was reported by participants using the EORTC core quality of life questionnaire (QLQ-C30),[25] the EORTC brain tumor module (QLQ-BN20)[26] and the EuroQol Group multi-attribute utility instrument (EQ-5D-5L).[27] They were collected prior to hypofractionated chemoradiation, at the start of each adjuvant treatment cycle, and every 8 weeks thereafter. The following HRQL domains were prespecified as being of key interest: global health status, physical functioning, social functioning, motor dysfunction, and communication deficit. This was based on their clinical relevance to glioblastoma to limit the number of statistical comparisons and maintain consistency with prior neuro-oncology trials.[28–30]

Neurologic function was evaluated by investigators using the Neurologic Assessment in Neuro-Oncology (NANO) scales and response criteria.[31] NANO was performed alongside each MRI scan to assist with the mRANO assessment.

MGMT promoter methylation testing was conducted by bisulfite modification of tumor DNA and pyrosequencing, utilizing the Qiagen therascreen® *MGMT* Pyro Kit (cat. 971061). This process was performed centrally and prospectively at the primary Australian neuropathology testing center located at the Brain and Mind Centre, University of Sydney. The testing methodology has been previously published[32] and used in prior randomized prospective trials.[30] Additionally, the test has received accreditation from the National Association of Testing Authorities (NATA). Tumor samples were also submitted to the Brain and Mind Centre, University of Sydney for retrospective central neuropathology review.

Statistical Analysis

The target sample size was 102 participants (68 participants in the experimental arm and 34 participants in the standard arm, based on the 2:1 randomization ratio). This was based on a one-sided 5% significance level and a 10% drop-out rate. Median OS in the standard arm was expected to be approximately 9 months, based on the analogous study population in the CCTG CE6 trial who received hypofractionated chemoradiation followed by adjuvant TMZ.[22] Study accrual was scheduled over 18 months and the minimum follow-up interval was 24 months. This would enable estimation of the OS hazard ratio (HR) for the experimental arm versus the standard arm, with 90% power to detect an HR of 0.5, 72% power to detect an HR of 0.6 and 50% power to detect an HR of 0.7. As this would be underpowered to detect a modest effect, additional information related to the observed HR such as HRQL and other outcomes would be used to decide whether to transition to a larger phase III trial.

Statistical analyses were conducted in SAS 9.4 on Microsoft Windows. Descriptive statistics were used to summarize the participant characteristics and treatment delivery. As per the intention-to-treat principle, all randomized participants were analyzed for OS, PFS, HRQL and neurologic function, based on the treatment allocated. All participants who commenced a treatment regimen were analyzed for toxicity, based on the treatment received. As part of a prespecified safety lead-in, the ISDMC reviewed toxicity data from the initial 10 participants who received the experimental arm and the initial 5 participants who received the standard arm; there were no other interim analyses.

Survival outcomes were estimated using the Kaplan–Meier method. Participants who did not experience progression and/or death were censored at the date they were last known to be event-free. HRs for OS and PFS were estimated using Cox proportional hazards regression models, with the treatment arm as the independent predictor. These results were presented with confidence intervals describing differences between groups but formal statistical comparisons were not intended for this phase II trial. In addition, adjusted HRs for OS and PFS were estimated using Cox proportional hazards regression models, with treatment arm, ECOG performance status, age, *MGMT* promoter methylation status, and surgery type as the independent predictors. First-order interaction variables were used to check the consistency of treatment effects across subgroups.

For toxicity, each adverse event was characterized within each participant by the worst grade across all study visits after baseline. For neurologic function, NANO response was described at the first adjuvant follow-up visit by treatment arm and overall. Median follow-up was computed using the reverse Kaplan–Meier estimator.

Results

Participants and Treatment

From March 2018 through June 2021, 103 participants were enrolled in the NUTMEG study, 69 of whom were allocated to the experimental arm and 34 to the standard arm (Figure 2). All participants received their allocated treatment; there were no exclusions or crossovers. Participants were recruited across 15 hospital sites in Australia and 1 hospital site in the United States. Baseline characteristics were similar in both treatment arms (Table 1). Overall, the median age of participants was 73 years (range, 65 to 88), 64% were male ($n = 66/103$), 88% had ECOG performance status of 0–1 ($n = 91/103$) and 51% underwent gross total resection ($n = 53/103$). Regarding *MGMT* status, the tumor was unmethylated in 55% of participants in the experimental arm ($n = 38/69$) compared to 62% in the standard arm ($n = 21/34$). *Isocitrate dehydrogenase (IDH)* mutation status was available via immunohistochemistry for 101 of the 103 participants; all had negative *IDH* staining. Baseline dexamethasone use was recorded for 52% ($n = 36/69$) of participants in the experimental arm, with a mean dose of 2.6 mg, and 59% ($n = 20/34$) of participants in the standard arm, with a mean dose of 2.5 mg. The mean baseline absolute lymphocyte count was 1.7×10^9/l in the experimental arm and 1.8×10^9/l in the standard arm.

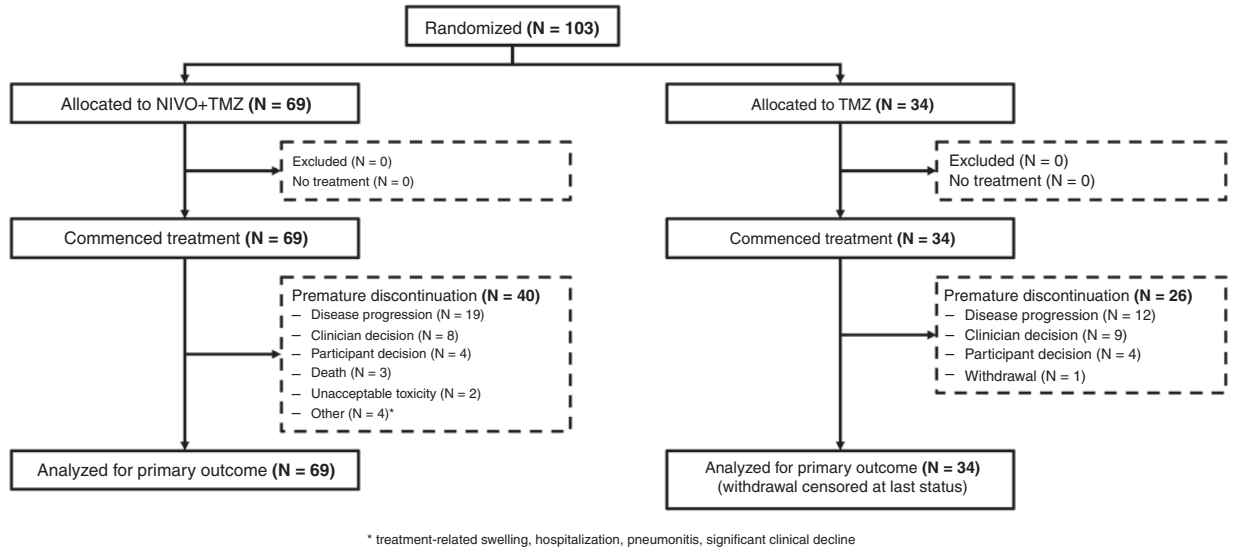

Figure 2. CONSORT diagram. Abbreviations: NIVO = nivolumab; TMZ = temozolomide.

Table 1. Baseline characteristics in the NUTMEG study

		Nivolumab + temozolomide	Temozolomide	Overall
		(*N* = 69)	(*N* = 34)	(*N* = 103)
Age	Median (range) in years	73 (65–88)	73 (66–84)	73 (65–88)
Gender	Female	26 (38%)	11 (32%)	37 (36%)
	Male	43 (62%)	23 (68%)	66 (64%)
ECOG	0	24 (35%)	13 (38%)	37 (36%)
	1	37 (54%)	17 (50%)	54 (52%)
	2	8 (12%)	4 (12%)	12 (12%)
Surgery	GTR	36 (52%)	17 (50%)	53 (51%)
	STR	12 (17%)	6 (18%)	18 (17%)
	Biopsy only	21 (30%)	11 (32%)	32 (31%)
MGMT	Methylated	31 (45%)	13 (38%)	44 (43%)
	Unmethylated	38 (55%)	21 (62%)	59 (57%)
Baseline	None/unknown	33 (48%)	14 (41%)	47 (46%)
dexamethasone	<3 mg/day	25 (36%)	14 (41%)	39 (38%)
	≥3 mg/day	11 (16%)	6 (18%)	17 (17%)
	Mean (range) in mg	2.6 (0.5–8)	2.5 (0.5–6)	2.5 (0.5–8)
Baseline	Mean (range) in 10^9/L	1.7 (0.3–5.4)	1.8 (0.6–4.2)	1.7 (0.3–5.4)
lymphocytes				

Abbreviations: ECOG = Eastern Cooperative Oncology Group performance status; GTR = gross total resection; *MGMT* = O^6-methylguanine-DNA-methyltransferase promoter methylation status; STR = subtotal resection.

Following a protocol amendment in June 2020, participants were allowed to commence hypofractionated chemoradiation while awaiting their *MGMT* results. In the experimental arm, the average time from randomization to the start of radiotherapy was + 1 day (range, –33 to +11); in the standard arm, the average time was +2 days (range, –11 to + 10). For the experimental and standard arms, hypofractionated chemoradiation was completed in 96% (*n* = 66/69) and 94% (*n* = 32/34) of participants, respectively. All planned study treatments were completed

in 42% ($n = 29/69$) and 24% ($n = 8/34$) of participants. TMZ dose intensity was 88% and 86% of delivered cycles, and 61% and 49% of all planned cycles. The most common reasons for treatment discontinuation were disease progression (28% [$n = 19/69$] and 35% [$n = 12/34$]), investigator preference (12% [$n = 8/69$] and 26% [$n = 9/34$]) and participant preference (6% [$n = 4/69$] and 12% [$n = 4/34$]). In addition, there was 1 participant in the standard arm who received hypofractionated chemoradiation and approximately 2 cycles of adjuvant TMZ, then declined further follow-up.

Efficacy

At the data cutoff on October 27, 2022, the median (quartile 1–quartile 3) follow-up was 37 (18–44) months. Of the 103 participants, there were 84 participants who had died, and 91 participants who had either progression or death reported.

Median OS was 11.6 months (95% CI, 9.7–13.4) in the experimental arm and 11.8 months (95% CI, 8.3–14.8) in the standard arm (Figure 3a). The 9-month OS rate was 65% (95% CI, 52–75; 43 alive, 24 deaths, 2 censored) in the experimental arm and 54% (95% CI, 36–69; 17 alive, 15 deaths, 2 censored) in the standard arm. For the experimental arm relative to the standard arm, the OS HR was 0.85 (95% CI, 0.54–1.33). Accounting for ECOG performance status, age, *MGMT* promoter methylation status and surgery type, the adjusted OS HR was 1.01 (95% CI, 0.64–1.59). Median PFS was 7.4 months (95% CI, 6.3–8.7) in the experimental arm and 5.9 months (95% CI, 3.6–8.2) in the standard arm (Figure 3b). The 6-month PFS rate was 64% (95% CI, 51–74; 44 alive and progression-free, 25 events) in the experimental arm and 49% (95% CI, 31–64; 16 alive and progression-free, 17 events, 1 censored) in the standard arm. For the experimental arm relative to the standard arm, the PFS HR was 0.77 (95% CI, 0.49–1.19). Accounting for ECOG performance status, age, MGMT promoter methylation status, and surgery type, the adjusted PFS HR was 0.86 (95% CI, 0.55–1.34). For OS and PFS, there was no evidence of interactions between the treatment arm and ECOG performance status, age, *MGMT* promoter methylation status, or surgery type (Supplementary Table 1).

Toxicity

As part of a prespecified safety lead-in, the ISDMC reviewed toxicity data in October 2019 and the study was continued without change. The most common adverse events in the experimental arm were fatigue (58% [$n = 40/69$]), nausea (29% [$n = 20/69$]), thrombocytopenia (26% [$n = 18/69$]), headache (25% [$n = 17/69$]), anorexia (17% [$n = 12/69$]) and muscle weakness (17% [$n = 12/69$]); in the standard arm, fatigue (38% [$n = 13/34$]), nausea (26% [$n = 9/34$]), headache (21% [$n = 7/34$]), constipation (18% [$n = 6/34$]), thrombocytopenia (15% [$n = 5/34$]), anorexia (15% [$n = 5/34$]), and seizure (15% [$n = 5/34$]) (Table 2). Other adverse events that were grade 3 or higher in the experimental arm included lung infection (7% [$n = 5/69$]), sepsis (4% [$n = 3/69$]), gait disturbance (3% [$n = 2/69$]), elevated ALT (3% [$n = 2/69$]), elevated AST (3% [$n = 2/69$]), pneumonitis (3% [$n = 2/69$]), maculopapular rash (3% [$n = 2/69$]), cognitive disturbance (3% [$n = 2/69$]), cerebral edema (1% [$n = 1/69$]) and fall (1% [$n = 1/69$]); in the standard arm, gait disturbance (3% [$n = 1/34$]), cerebral edema (3% [$n = 1/34$]), and fall (3% [$n = 1/34$]). Cumulatively, grade 3 or higher adverse events were reported in 46% of participants in the experimental arm ($n = 32/69$) compared to 29% of participants in the standard arm ($n = 10/34$). Three participants in the experimental arm experienced immune-related adverse events; namely, grade 3 pneumonitis ($n = 1$), grade 3 lung infection with possible pneumonitis ($n = 1$) and grade 3 extraocular muscle paresis ($n = 1$), which subsequently resolved. There were no treatment-related deaths or suspected unexpected serious adverse reactions (SUSARs) attributable to either TMZ or nivolumab.

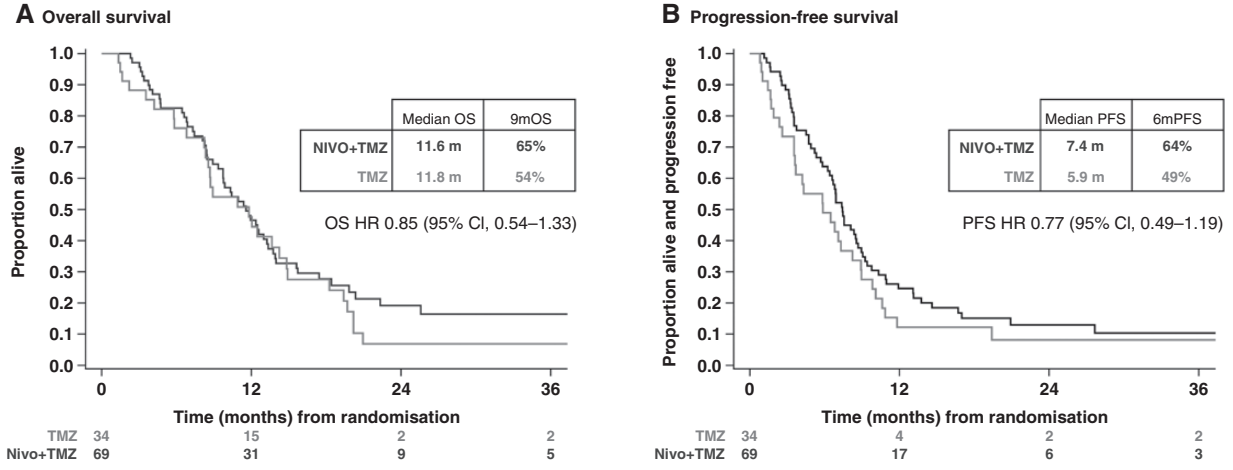

Figure 3: Efficacy Kaplan–Meier curves: (a) overall survival; (b) progression-free survival. Abbreviations: HR (95% CI) = hazard ratio with 95% CI; NIVO = nivolumab; OS = overall survival; PFS = progression-free survival; TMZ = temozolomide.

Table 2. Adverse events occurring in ≥10% of participants in the NUTMEG study

	Nivolumab + temozolomide (*N* = 69)						Temozolomide (*N* = 34)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any
Fatigue	22 (32%)	14 (20%)	4 (6%)	–	–	40 (58%)	5 (15%)	5 (15%)	3 (9%)	–	–	13 (38%)
Nausea	16 (23%)	4 (6%)	–	–	–	20 (29%)	7 (21%)	2 (6%)	–	–	–	9 (26%)
Headache	14 (20%)	3 (4%)	–	–	–	17 (25%)	7 (21%)	–	–	–	–	7 (21%)
Thrombocytopenia	9 (13%)	6 (9%)	3 (4%)	–	–	18 (26%)	2 (6%)	2 (6%)	1 (3%)	–	–	5 (15%)
Anorexia	9 (13%)	3 (4%)	–	–	–	12 (17%)	4 (12%)	1 (3%)	–	–	–	5 (15%)
Constipation	6 (9%)	3 (4%)	–	–	–	9 (13%)	4 (12%)	2 (6%)	–	–	–	6 (18%)
Muscle weakness	3 (4%)	4 (6%)	5 (7%)	–	–	12 (17%)	1 (3%)	1 (3%)	–	–	–	2 (6%)
Seizure	1 (1%)	3 (4%)	2 (3%)	–	1 (1%)	7 (10%)	2 (6%)	1 (3%)	2 (6%)	–	–	5 (15%)
Thromboembolism	–	3 (4%)	5 (7%)	–	–	8 (12%)	1 (3%)	1 (3%)	2 (6%)	–	–	4 (12%)
Vomiting	3 (4%)	3 (4%)	2 (3%)	–	–	8 (12%)	2 (6%)	–	1 (3%)	–	–	3 (9%)
Confusion	3 (4%)	3 (4%)	1 (1%)	–	–	7 (10%)	2 (6%)	1 (3%)	1 (3%)	–	–	4 (12%)

Health-Related Quality of Life

The HRQL questionnaire completion rate was 91% prior to short-course chemoradiation ($n = 94/103$), 80% prior to adjuvant treatment ($n = 82/103$) and 50% by the end-of-treatment visit ($n = 52/103$). The principal reasons cited for noncompletion were that participants were too unwell or declined.

There were no discernible differences between the treatment arms for the mean change in global health status from baseline (Figure 4).

Neurologic Function

Neurologic function was documented during the initial post-treatment follow-up, with reference to the preradiotherapy baseline. By then, NANO scales were available from 53 participants in the experimental arm and 22 participants in the standard arm. In the experimental arm, there were neurologic responses in 8% of participants ($n = 4/53$), neurologic stability in 81% of participants ($n = 43/53$) and neurologic progression in 2% of participants ($n = 1/53$); the overall response was non evaluable in 1 participant and not completed in 4 participants. In the standard arm, there were neurologic responses in 23% of participants ($n = 5/22$), neurologic stability in 55% of participants ($n = 12/22$) and neurologic progression in 9% of participants ($n = 2/22$); overall response was not completed in three participants.

Discussion

In the NUTMEG study, there was insufficient evidence of clinical benefit. The observed differences in survival outcomes were not considered meaningful. Median OS favored the standard arm by 0.2 months and median PFS favored the experimental arm by 1.5 months. The addition of nivolumab appeared to be safe and tolerable. Nivolumab did not contribute to excess TMZ dose reductions and there were no new safety signals identified. There were no discernible differences in HRQL outcomes, and the majority of participants experienced neurologic stability, but with greater variability in outcomes in the standard arm. Given these findings, the decision was made collectively not to transition to a larger phase III trial.

Importantly, the NUTMEG study addressed a pertinent research question regarding immune checkpoint inhibition in older patients with glioblastoma, a large subset that has historically been understudied. In NUTMEG, the median age at enrollment was 73 years, with all participants meeting the eligibility requirement of being 65 years of age or older. In comparison to preceding trials, the proportion of participants aged 65 years or older was 19% in CheckMate-143,[33] 29% in CheckMate-498[9] and 33% in CheckMate-548.[10] Secondly, the NUTMEG study randomized participants prior to the initiation of hypofractionated chemoradiation. This broadened the generalizability of findings, by using a comparable time point to other trials. Thirdly, assumptions about the standard arm of NUTMEG were based on the CCTG CE6 study, which involved a similar study population.[22] Despite this, the median OS in the

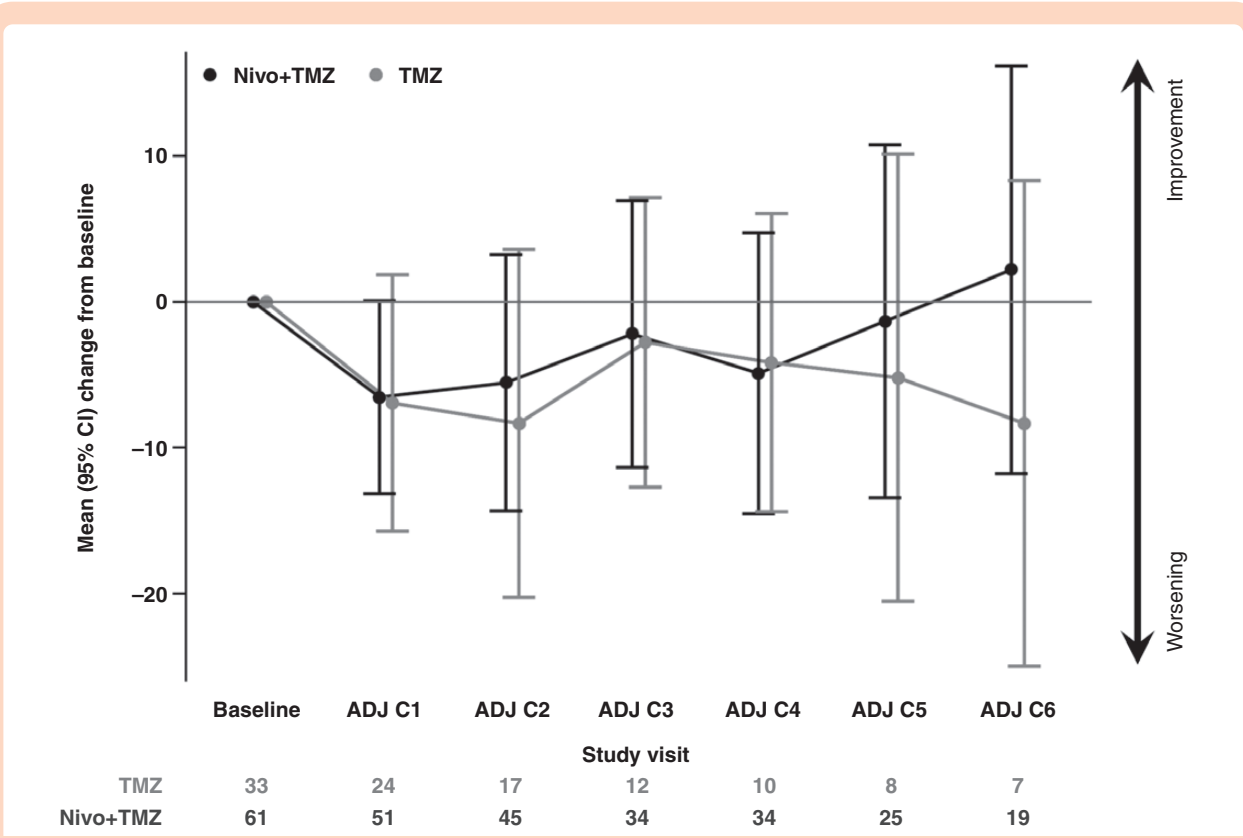

Figure 4: Mean change in EORTC QLQ-C30 global health status compared to baseline. Abbreviations: ADJ = adjuvant chemotherapy; NIVO = nivolumab; TMZ = temozolomide.

standard arm of NUTMEG was closer to 12 months, compared to the prior estimate of 9 months. Finally, we have collected serum and plasma from patients at baseline, end of treatment and at the time of recurrence, baseline tumor and also tumor from all patients who underwent tumor re-resection at the time of recurrence. Future analysis of collected biospecimens and linkage of molecular, imaging and clinical data may identify biomarkers and mechanisms of resistance and response.

A challenge in the NUTMEG study was evaluating response in the first-line setting for glioblastoma, where there is potential for pseudoprogression and pseudoresponse. This is relevant to an open-label trial, where this may have contributed to the higher rates of investigator and participant discontinuation in the standard arm. Retrospective central review of MRI imaging may delineate this further. To address limitations associated with the trial design, we focused on the objective primary endpoint of OS. Another challenge was the determination of *MGMT* promoter methylation status. A growing body of evidence suggests that *MGMT* status may be better categorized into multiple groups, including an intermediate category of partial methylation.[34] In NUTMEG, equivocal results were regarded as being *MGMT*-methylated, which is consistent with the observation that partial methylation is associated with better outcomes than *MGMT*-unmethylated disease. Finally, NUTMEG was designed as a signal-seeking phase II trial, utilizing a modest sample size within a vulnerable population. The intention was to assess the potential for a sufficiently promising effect size before proceeding to a phase III trial. As previously mentioned, the study had 90% power to detect an HR of 0.5, 72% power to detect an HR of 0.6 and 50% power to detect an HR of 0.7. Evidently, NUTMEG could not reliably exclude effect sizes of HR 0.7 or higher for the primary endpoint of OS.

This is the latest in a series of clinical trials examining the impact of adjuvant nivolumab in glioblastoma that have failed to demonstrate a clinical benefit.[9,10,35] While there is now recent evidence of limited success with nivolumab in the neoadjuvant context, it is clear that nivolumab, and potentially immune checkpoint blockade more broadly, has failed to revolutionize care in glioblastoma in the same way as other extracranial malignancies.[36] Studies examining the factors underlying a successful response to aPD-1/aPD-L1 therapy across cancer types are continuously generating new insights[37–40]; however, we do not yet fully understand what combination of tumoral, immunologic, and patient features are required to result in an impactful anti-tumor immune response.

Glioblastoma presents many obstacles to the success of immunotherapy, both tumor-intrinsic and as a result of its intracranial locale. Findings in extracranial solid tumors have not been recapitulated in glioblastoma, including, seemingly, the correlation between increased TMB and response to immunotherapy. There is a myriad of potential contributing factors complicating this relationship in glioblastoma, including the low mutational burden

as compared to other tumor types[41]; highly immunosuppressive tumor microenvironment[42,43]; prior/concurrent therapies administered, especially dexamethasone for the management of symptomatic cerebral edema[44–46]; and systemic immune dysfunction.[47–50] Indeed, we know now that the relationship between TMB and response to immunotherapy is rather complex. Paradoxically, patients with glioblastoma who have tumors with a low TMB at recurrence appear to be more responsive to immunotherapy.[51,52] A possible explanation for the apparent inverse relationship between TMB and response to immunotherapy in patients with glioblastoma is that neoantigen depletion via immunoediting is more likely in patients with glioblastoma and low TMB.[52]

Prospective studies are undoubtedly needed to test the utility of low TMB in predicting immunotherapy response in glioma patients. An increasing body of evidence indicates that high TMB is not a biomarker for response to immunotherapy in glioma despite pan-cancer guidance from the FDA supporting the use of immune checkpoint blockade in high TMB tumors.[53–55] More research is needed to understand why gliomas are refractory to cancer immunotherapies, and why a higher neoantigen burden does not translate to immunotherapy success in gliomas.

In older patients, there are likely to be additional challenges when considering immune-based therapies. Global immune function declines markedly with age, due to a host of factors. Impaired lymphopoiesis and thymic involution result in decreased lymphocyte numbers, thereby reducing the overall capacity of the adaptive immune system to mount an anti-tumor response.[56,57] Senescence also leads to skewing of the immune landscape and dysregulation of immune cell function, which contributes to impaired immune function.[58–61] It stands to reason that these immune features could potentially have profound consequences for the efficacy of immunotherapy in older patients.

Ultimately, there are a host of unique factors that must be addressed either prior to or concurrently when employing immunotherapy in glioblastoma. It is possible that the failure of PD-1/PD-L1 blockade observed to date in glioblastoma could be reversed by removing some or all of these additional obstacles. Further preclinical and clinical research is needed to expand on the findings of the NUTMEG study, in order to investigate novel and combinatorial immunotherapy approaches and to tailor treatment to aging populations who represent the mainstay of those with glioblastoma yet remain underrepresented in clinical trials.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (https://academic.oup.com/neuro-oncology)

Keywords

clinical trials | glioblastoma | immunotherapy | older cancer patients | systemic therapy.

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Conflict of interest statement

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Data availability statement

The original data are presented in the study manuscript and included in the supplementary Material. Further inquiries can be directed to the corresponding authors.

Authorship statement

Designing research studies: E.H.B., S.Y., E.S.K., D.M.A., R.V., A.B.H., M.A.R., E.J.H., B.M.E., K.L.M., C.G., J.R.S., Z.L., M.K. Patient accrual: H.W.S., E.S.K., R.J., E.J.H., A.T., H.W., M.B., A.L., K.C., S.B., C.G., A.M., H.L., M.O.J., J.R.S., Z.L., M.K. Analyzing data: H.W.S., E.H.B., S.Y., E.S.K., M.K. Writing manuscript: H.W.S., L.W., M.K. Reviewing and editing of manuscript: All authors

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