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Dual Immune Check Point Blockade in *MGMT*-Unmethylated Newly Diagnosed Glioblastoma: NRG Oncology BN007, a Randomized Phase II/III Clinical Trial

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PURPOSE	New therapies for glioblastoma are needed, especially *MGMT*-unmethylated (u*MGMT*) disease. NRG Oncology BN002 (phase I) demonstrated safety and suggested efficacy of ipilimumab (ipi) with nivolumab (nivo) in newly diagnosed glioblastoma, leading to this phase II/III trial.
METHODS	Adults with newly diagnosed u*MGMT* glioblastoma and Karnofsky performance status (KPS) ≥70 were randomly assigned to radiotherapy with either immunotherapy (ipi and nivo) or temozolomide (TMZ), stratified by recursive partitioning analysis (RPA) class and intention to use tumor treating fields. With 95% power to detect a hazard ratio (HR) ≤0.58 for progression-free survival (PFS) at a one-sided significance level (*P*) of .15, superior PFS with immunotherapy in phase II would lead to phase III overall survival (OS) testing. Corticosteroids were disallowed when starting immunotherapy. Diagnosis, biomarkers, and PFS were centrally assessed.
RESULTS	One hundred fifty-nine participants were randomly assigned (79 immunotherapy and 80 TMZ). Arms were well balanced for age (median 60 years, range, 28-79), sex (male n = 105, 66%), KPS (90-100 n = 97, 61%), resection extent (gross total, n = 103, 65%), and RPA class (III, n = 16, 10%; IV, n = 116, 73%; V, n = 27, 17%). A preplanned analysis of phase II data conducted after 100 centrally determined PFS events showed no significant PFS improvement for ipi and nivo versus TMZ (median 7.7 months *v* 8.5 months, HR, 1.47 [70% CI, 1.19 to 1.83]; one-sided *P* = .96 [95% CI, 0.98 to 2.2]). OS is immature (>50% alive) but with no observed difference between arms (median approximately 13 months each, HR, 0.95 [95% CI, 0.61 to 1.49]; *P* = .36).
CONCLUSION	Ipi and nivo did not improve PFS among patients with newly diagnosed u*MGMT* glioblastoma versus TMZ. Accrual closed permanently; the trial will not proceed to phase III. No new safety signals were identified. Molecular correlative analyses and survival follow-up are ongoing.

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INTRODUCTION

The most common primary cancer of the brain in adults is glioblastoma. Prognosis remains poor despite aggressive multimodality first-line therapy,[1] typically cytoreductive surgery followed by radiotherapy and temozolomide (TMZ) chemotherapy, with or without tumor treating fields (TTFields).[2,3] New therapies are needed.

TMZ was demonstrated to prolong survival when added to radiotherapy 20 years ago.[1] Since then, most clinical trials

incorporated TMZ as the standard of care, and experimental agents have been added on to, rather than *in lieu* of, the radiochemotherapy backbone, including trials from National Cancer Institute (NCI) networks, such as Radiation Therapy Oncology Group (RTOG) 0525 (dose-dense TMZ),[4] RTOG 0825 (bevacizumab),[5] RTOG 3508 (EGFR-directed antibody drug conjugate),[6] and most recently Alliance A071102 (veliparib).[7] However, none of these approaches improved survival.

Immune checkpoint inhibitors (ICIs), first the T lymphocyte–associated protein-4 inhibitor ipilimumab (ipi) and later the

CONTEXT

Key Objective
Does dual immune checkpoint inhibition with the T lymphocyte–associated protein-4 inhibitor ipilimumab and the PD-1 pathway inhibitor nivolumab (without temozolomide [TMZ]) improve survival in newly diagnosed MGMT-unmethylated glioblastoma, when compared with TMZ, each with radiotherapy after maximal safe surgical resection?

Knowledge Generated
Progression-free survival (PFS) was not improved and was numerically shorter with dual immune checkpoint inhibition than with TMZ. Overall survival is immature also but without improvement at the time of analysis.

Relevance (R.G. Maki)
While hope continues that immunotherapy in one its manifestations will be useful for patients with glioblastoma, these data reaffirm the activity of TMZ with radiation for primary resected disease.*

*Relevance section written by *JCO* Associate Editor Robert G. Maki, MD, PhD, FACP, FASCO.

PD-1 pathway inhibitors such as nivolumab (nivo), revolutionized treatment of other cancers.[8,9] Dual ICI therapy has superior efficacy, with reasonable safety, over single agents in other solid tumors such as malignant skin (melanoma),[10] urothelial,[11] colorectal,[12] and ovarian cancers,[13] including those with brain metastases[14] and low PD-L1 expression[15] that typifies most glioblastomas.

Therefore, NRG Oncology first conducted a phase I clinical trial (BN002) in newly diagnosed glioblastoma, demonstrating both safety and a possible early efficacy signal (median survival 21 months, n = 19) with combined ipi and nivo, despite limited potential brain penetration of checkpoint inhibitors.[16] As a randomized trial was a logical next step, NRG Oncology designed the phase II/III BN007, especially as there were no other NCI- or industry-sponsored dual ICI trials for newly diagnosed glioblastoma ongoing or planned. To ensure appropriate resource utilization, the trial was designed with a go–no go strategy to proceed to the full randomized phase III effort after 100 initial progression of disease (PD) events in the randomized phase II.

Finally, TMZ is most effective in tumors demonstrating silencing of the alkylator resistance gene O⁶-methylguanine-DNA-methyltransferase (*MGMT*) through promoter methylation; conversely, tumors with an unmethylated *MGMT* promoter (u*MGMT*), representing >60% of all cases, are generally considered TMZ-insensitive.[17] As TMZ is neither curative nor innocuous, replacing TMZ with a potentially superior alternative is an attractive therapeutic strategy.[18] Therefore, we focused on the patients with u*MGMT* glioblastomas, omitting TMZ in an experimental immunotherapy (ipi plus nivo) arm, both to simplify the study design and to avoid potential toxicities of TMZ, including lymphopenia that could reduce ICI efficacy. In addition, u*MGMT* glioblastoma is more aggressive than methylated disease;

therefore, restricting eligibility to patients with u*MGMT* tumors would also abbreviate the trial.

METHODS

Eligibility

Adults with a Karnofsky performance status (KPS) ≥70[19] and newly diagnosed u*MGMT* glioblastoma were the patient population. Active autoimmune disease and immunosuppressive therapy were exclusionary. Systemic corticosteroids were disallowed within 3 days of random assignment (below).

All patients or their legally authorized representatives provided written informed consent before any study-specific procedures. The study was approved and overseen by the NCI–Central Institutional Review Board.

Biomarkers

Diagnosis (glioblastoma by K.D.A., M.S., and K.G.) and *MGMT* promoter methylation (E.P.S.) by *MGMT*-STP27[20] were confirmed centrally before random assignment using the Illumina EPIC v1 Array with previously reported protocols.[21] The WHO 2016 criteria[22] for the definition of glioblastoma were used as they were active during trial design. However, we (K.D.A.) were aware of and contributed to an emerging consensus[23] that isocitrate dehydrogenase (*IDH*) mutation would become mutually exclusive with a diagnosis of glioblastoma in the 2021 criteria, which were published after the trial launched.[24] Therefore, anticipating the evolving definition of glioblastoma, we required IDH testing (locally) by at least one standard method during screening, and *IDH* mutation was exclusionary. Although confirmatory *IDH*-specific gene sequencing was not conducted in all cases when IDH1 (R132H) immunohistochemistry did not detect an

IDH1 R132H mutant protein (which could fail to identify approximately 10% of all *IDH* mutations[25]), high-grade *IDH*-mutated gliomas and other glioblastoma histopathologic mimickers were excluded using the central nervous system tumor classifier as described previously.[26] Tissue and serum were also collected for molecular correlative analyses, such as PD-L1 expression and mutational burden, to be performed post hoc and reported separately.

Treatment

Radiotherapy

In all patients, radiotherapy was planned using a contrast-enhanced brain magnetic resonance imaging (MRI) performed within 3 days postoperatively to a total dose of 60 Gy in 30 fractions of 2 Gy each over approximately 6 weeks, using a shrinking-field approach, typical of all RTOG/NRG glioblastoma trials. In general, treatment was performed using a sequential boost technique based upon the postoperative contrast-enhanced and T2-weighted FLAIR (preferred over conventional T2) MRI—46 Gy in 2 Gy per fraction to the T2-weighted FLAIR abnormality including the surgical cavity (GTV_4600) followed by a boost of 14 Gy in 2 Gy per fraction to the contrast-enhancing T1 abnormality and surgical cavity (GTV_6000) to a total dose of 60 Gy. A 2 cm CTV margin was used, which may be reduced around natural barriers, as well as a 4-5 mm PTV margin. Dose constraints are specified in the protocol. Both intensity-modulated and 3-dimensional conformal approaches were permitted. Protons were disallowed.

Chemotherapy and Immunotherapy

Eligible patients were randomly assigned (1:1) to start treatment within 6 weeks after maximal safe surgical resection. Treatment consisted of radiotherapy with and followed by either TMZ (standard arm) or ipi and nivo without TMZ (experimental arm). Neither treating investigators nor patients were blinded to results of random assignment. TMZ was sourced commercially and administered at standard doses during radiotherapy and for six adjuvant 28-day cycles[1] with up to 12 adjuvant cycles allowed. In the experimental arm, no TMZ was given; ipi was dosed at 1 mg/kg once every 4 weeks (4 dose maximum); nivo was dosed at 3 mg/kg once every 2 weeks (or 240 mg flat dose after completion of ipi) and intended to continue until disease progression. Ipi and nivo were supplied by the NCI. Postprogression treatment was at the discretion of the treating investigator and was not collected. Crossover from TMZ to immunotherapy was not offered.

TTFields

As TTFields is an approved therapy in the United States for glioblastoma, we allowed TTFields on the standard arm (after radiotherapy) both to address ethical considerations and reduce dropout. However, TTFields were disallowed on the immunotherapy arm because of concerns about overlapping cutaneous toxicities. To balance these considerations, we followed the design of Alliance A071102, which stratified random assignment by intention to use TTFields.[7] Intention and actual TTF usage were classified as binary variables (yes or no), and we did not collect other details such as amount of time or duration the device was worn. TTFields was commercially sourced.

Supportive Care

Prophylaxis for Pneumocystis jirovecii (previously carinii) pneumonia during chemoradiotherapy was strongly recommended but not required.[1] Systemic corticosteroids, anticonvulsants, antiemetics, and other general neuro-oncology supportive care measures were unrestricted after treatment initiation on both arms. Immunotherapy-related adverse events were managed with dose delays and reductions and, if needed, corticosteroids according to typical algorithms associated with commercial ipi and nivo usage. Similarly, dose adjustments and delays for TMZ-associated toxicities followed standard-of-care guidance.

Follow-Up

Routine physical, neurologic, and laboratory evaluations were performed at baseline and before every 4-week cycle in all patients. Brain MRI scans were performed 4 weeks after radiotherapy (baseline as detailed below) and before every other cycle thereafter during treatment. Additional evaluations were performed in patients randomly assigned to the experimental arm to enhance the safety and monitoring for immunotherapy toxicities, including thyroid, chemistry, and hepatic function testing before every nivo dose. Patient-reported outcomes were collected and neurocognitive function evaluated at baseline and before every other cycle, intended on the same day as contrast-enhanced brain MRI scans to allow clinical and imaging correlations. No other anticancer therapy other than protocol treatment was permitted. Adverse events were graded according to CTCAE v5.0.

Response Criteria

PD was defined according to the 2010 Response-Assessment in Neuro-Oncology (RANO) criteria[27] except that the postradiotherapy MRI, rather than postoperative pre-radiotherapy MRI, was used as the baseline for patients continuing on protocol therapy,[28] the approach which has since become part of the RANO 2.0 criteria.[29] PD within 12 weeks after radiotherapy completion was defined as new contrast-enhancing tumor outside the radiation field (beyond the high-dose region or 80% isodose line) or unequivocally viable tumor on histopathologic analysis of a new surgical specimen. After 12 weeks from radiotherapy completion, PD was defined as an increase by ≥25% in cross-sectional area of enhancing disease (relative to the postradiotherapy baseline), or disease-related clinical deterioration. Assessment of PD for purposes of deciding whether to discontinue protocol therapy was made by the

treating investigator. Treatment was allowed to continue in ambiguous situations with reassessment for PD (imaging, clinical) after ≤2 additional cycles.

PD for calculating progression-free survival (PFS) was determined centrally by study modality chairs (led by V.G. with contributions from T.J.C.W.). To reduce the potential for real or perceived bias, central reviewers were blinded to treatment allocation, and the overall principal investigator (A.B.L.) was not involved.

Statistical Design

The primary end point for phase II was PFS, defined as the time from random assignment to centrally determined PD or death from any cause. The primary end point for phase III was overall survival (OS), defined as the time from random assignment to death from any cause.

There was a two-step registration process. In step 1, tissue from accrued patients was sent for central *MGMT* and diagnostic testing. Patients who met diagnostic, *MGMT*, and other eligibility criteria proceeded to step 2 and were randomly assigned 1:1 using the permuted-block randomization and stratified by intention to use TTFields (yes *v* no) as above, and by recursive partitioning analysis (RPA) class (III *v* IV *v* V), a composite encompassing the known prognostic variables of performance status, extent of resection, neurologic function, and age[30].

Phase II planned to randomly assign ≥150 patients; 100 PFS events (from both arms) would provide 95% statistical power to detect an improvement in median PFS from 5.7 months expected in the control arm to 9.7 months in the experimental arm, corresponding to a hazard reduction of 42% (hazard ratio [HR], 0.58) at one-sided significance level of 0.15. The definitive analysis for phase II would be conducted after 100 PFS events were observed and central reviews of progression completed. The analysis was performed on an intention-to-treat basis, including all randomly assigned patients with follow-up information. If the stratified log-rank test had a one-sided *P* value ≤.15, then continuation of accrual to phase III would occur to evaluate OS; otherwise, accrual would discontinue permanently after phase II. All analyses were performed using SAS version 9.4.

Secondary and exploratory end points to be reported separately included the effect of immunotherapy on patient-reported outcomes and on neurocognitive function, and biomarkers of potential predictive importance for immunotherapy such as PD-L1 expression and tumor mutational burden.

The full protocol contains additional methodological details (Data Supplement, online only).

RESULTS

Enrollment

The trial activated on August 6, 2020, and accrual was suspended on April 27, 2022; 374 patients were screened and 159 randomly assigned (Fig 1, Data Supplement). The
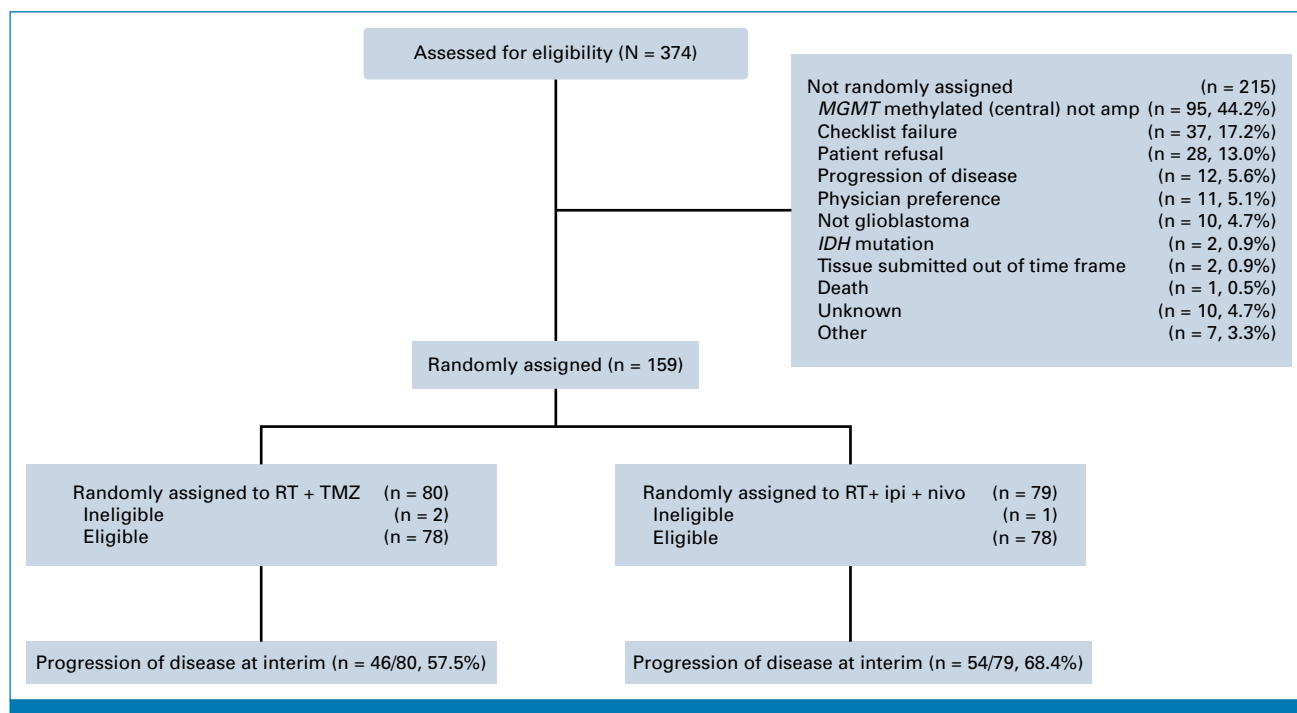

FIG 1. CONSORT diagram for patient enrollment. ipi, ipilimumab; nivo, nivolumab; RT, radiotherapy; TMZ, temozolomide.

TABLE 1. Baseline Characteristics Among Randomly Assigned Patients

Baseline Characteristic	RT + TMZ (n = 80)	RT + ipi + nivo (n = 79)	Total (N = 159)
Age, years, median (range)	59.5 (28-77)	61 (35-79)	60 (28-79)
Sex, No. (%)			
Male	54 (67.5)	51 (64.6)	105 (66.0)
Female	26 (32.5)	28 (35.4)	54 (34.0)
Race, No. (%)			
Asian	3 (3.8)	4 (5.1)	7 (4.4)
Black or African American	1 (1.3)	2 (2.5)	3 (1.9)
White	71 (88.8)	69 (87.3)	140 (88.1)
Unknown/not reported	5 (6.3)	4 (5.1)	9 (5.7)
Ethnicity, No. (%)			
Hispanic or Latino	7 (8.8)	9 (11.4)	16 (10.1)
Not Hispanic or Latino	73 (91.3)	69 (87.3)	142 (89.3)
Unknown	0 (0.0)	1 (1.3)	1 (0.6)
KPS, No. (%)			
70	10 (12.5)	6 (7.6)	16 (10.1)
80	24 (30.0)	22 (27.8)	46 (28.9)
90	37 (46.3)	36 (45.6)	73 (45.9)
100	9 (11.3)	15 (19.0)	24 (15.1)
Extent of resection, No. (%)			
Biopsy	1 (1.3)	0 (0.0)	1 (0.6)
Subtotal	28 (35.0)	27 (34.2)	55 (34.6)
Total (gross)	51 (63.8)	52 (65.8)	103 (64.8)
Neurologic function, No. (%)			
No symptoms	22 (27.5)	37 (46.8)	59 (37.1)
Minor symptoms	44 (55.0)	27 (34.2)	71 (44.7)
Moderate symptoms (fully active)	11 (13.8)	10 (12.7)	21 (13.2)
Moderate symptoms (required assistance)	3 (3.8)	5 (6.3)	8 (5.0)
RPA class,[a] No. (%)			
III	9 (11.3)	7 (8.9)	16 (10.1)
IV	58 (72.5)	58 (73.4)	116 (73.0)
V	13 (16.3)	14 (17.7)	27 (17.0)
Intention to use tumor treating fields,[a] No. (%)			
No	42 (52.5)	41 (51.9)	83 (52.2)
Yes	38 (47.5)	38 (48.1)	76 (47.8)

NOTE. RPA Class definitions: III: age <50 years, KPS ≥ 90; IV: age < 50 years, KPS < 90; OR age ≥ 50 years, KPS ≥ 70, EOR > biopsy, INF ≤ minor; V: age ≥ 50 years, KPS ≥ 70, EOR > Bx, INF > minor; OR age ≥ 50 years, KPS ≥ 70, EOR = biopsy.

Abbreviations: EOR, extent of resection; INF, impairment of neurologic function; ipi, ipilimumab; KPS, Karnofsky performance status; nivo, nivolumab; RPA, recursive partitioning analysis; RT, radiotherapy; TMZ, temozolomide.

[a]Stratification factor in random assignment.

most common reason that patients did not proceed to random assignment (n = 215, 57%) was *MGMT* promoter status (n = 95, 44.2%). Central analyses determined a diagnosis other than glioblastoma in 10 (4.7%) and detected an *IDH* mutation in two (<1%). Among randomly assigned patients, median age was 60 years (range, 28-79), and 105 (66.0%) were men. The arms were well balanced for age, KPS, extent of resection, RPA class, and TTFields intent (Table 1). Most patients were male, White (n = 140, 88.1%), and not Hispanic or Latino (n = 142,

89.3%). Three patients were randomly assigned despite ineligibility (two TMZ, one ICI), all because corticosteroids were taken within 3 days before step 2 registration; they are included in the intention-to-treat analyses of PFS and OS.

Treatment Delivery

On the standard and experimental arms, 93% and 98% of patients, respectively, received radiotherapy per protocol,

TABLE 2. All Reported Treatment-Related (definitely, probably, or possibly) Adverse Events

Treatment-Related AE	RT + TMZ (n = 74), No. (%)	RT + ipi + nivo (n = 78), No. (%)
Grade <3	46 (62.2)	46 (59.0)
Grade 3 to 5	28 (37.8)	32 (41.0)

NOTE. Seven patients received no study treatment (6 on the standard arm and 1 on the experimental arm) and were excluded from adverse event analyses, which were graded with CTCAE version 5.

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; ipi, ipilimumab; nivo, nivolumab; RT, radiotherapy; TMZ, temozolomide.

nearly always (97% and 95%) with IMRT. TMZ was given to 92% of patients on the standard arm (and 0% on the experimental arm) with a median of 4 (range, 1-10) adjuvant postradiotherapy cycles. Ipi and nivo were given to 99% of patients on the experimental arm (and 0% on the standard arm), with a median of 4 (range, 1-4) and 8 (range, 1-25) infusions each (Appendix Tables A1-A3, online only).
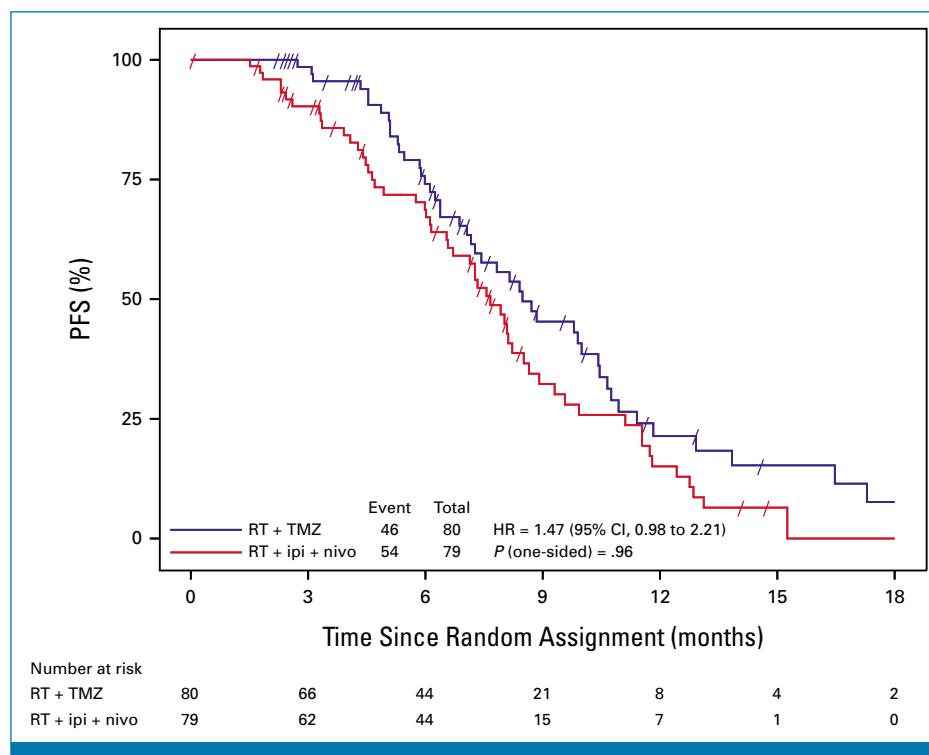
Adverse Events

Treatment-related (possibly, probably, or definitely) grade 3 to 4 (highest-grade) adverse events were reported in 22 (29.7%) and six (8.1%) patients on the TMZ arm compared with 26 (33.3%) and four (5.1%) on the immunotherapy arm. There were two treatment-related deaths on the immunotherapy arm: autoimmune disorder reported as probably related, and colitis reported as definitely related, 68 and 84 days after the last ipi/nivo infusion, respectively. There were nine (11.5%) patients with reported grade ≥3 GI disorders on the immunotherapy arm compared with two (2.7%) on the TMZ arm. However, there was no significant difference in the frequency of treatment-related adverse events between arms (n = 28, 37.8%, TMZ arm v n = 32, 41%, immunotherapy arm; P = .69 by chi-square Table 2 and Appendix Table A4).

Efficacy

Among 159 randomly assigned patients, PFS was not improved by combined ipi and nivo over TMZ (HR, 1.47 [70% CI, 1.19 to 1.83]; one-sided P = .96 [95% CI, 0.98 to 2.21]; Fig 2). Median PFS among patients randomly assigned to immunotherapy was 7.7 months (95% CI, 6.5 to 8.5) versus 8.5 months (95% CI, 7.1 to 10.4) among patients randomly assigned to TMZ after 12.9 months of median follow-up (95% CI, 8.6 to 14.7). As the threshold for likely superiority of immunotherapy over TMZ did not meet the prespecified goal (one-sided P = .96 > 0.15), accrual was discontinued permanently after phase II and will not reopen for phase III. At the time of the phase II primary analysis, a total of 34 PFS observations were

	Event	Total	
RT + TMZ	46	80	HR = 1.47 (95% CI, 0.98 to 2.21)
RT + ipi + nivo	54	79	P (one-sided) = .96

Number at risk
RT + TMZ	80	66	44	21	8	4	2
RT + ipi + nivo	79	62	44	15	7	1	0

FIG 2. PFS by treatment arm. HR, hazard ratio; ipi, ipilimumab; nivo, nivolumab; PFS, progression-free survival; RT, radiotherapy; TMZ, temozolomide.

censored within 6 months of random assignment; administrative censoring and consent withdrawal were the primary reasons for these early censored observations. There was also no obvious difference in OS between arms at the time of data analysis (HR, 0.95 [95% CI, 0.61 to 1.49]; $P = .36$), noting, however, that these data remain immature with 81 (51%) of randomly assigned patients alive (Appendix Fig A1). Among 78 patients who died, PD was the most common reported cause (TMZ: n = 41, 90.2%; ipi + nivo: n = 37, 78.4%).

TTFields

Before random assignment, 72 of 159 patients (45.3%) declared an intention to use TTFields if permitted. Among these, 38 were then randomly assigned to each arm, only four (11%) of whom actually used TTFields on the standard arm (after radiotherapy as permitted). None used TTFields on the experimental arm where it was disallowed per protocol (Appendix Table A5).

DISCUSSION

Ipi and nivo did not improve PFS for patients with newly diagnosed u*MGMT* glioblastoma in this NCI National Clinical Trials Network (NRG BN007) randomized phase II/III trial. There was no benefit from immunotherapy despite disallowing corticosteroids at the start of immunotherapy, which had emerged as possibly correlated with efficacy from ICIs from subset analyses in other studies.[31,32] In addition, although there was no limit on maximum tumor size for accrual, the requirement for a KPS of at least 70 and a complete tapering of corticosteroids at least 3 days before random assignment indirectly excluded patients with very large tumors with symptomatic surrounding cerebral edema. In this way, we also sought to exclude patients with tumors growing so rapidly that ICI therapy might not take effect before PD. Along these lines, 12 patients with rapidly growing tumors who suffered PD during screening were also excluded (Fig 1). As an additional mechanism to guard against accruing patients with minimally resected tumors, we required sufficient tissue for central *MGMT* and other biomarker analyses; in fact, all patients randomly assigned to ICIs underwent at least subtotal resection (Table 1).

Only four patients (11%) permitted to use TTFields actually did so, consistent with previous data suggesting limited uptake in the glioblastoma population.[33,34] Therefore, although we cannot exclude an imbalance of benefit from TTFields favoring the standard arm, the minimal use of TTFields suggests that there was no confounding effect on results in this exploratory analysis. Two NCI network trials (this trial and Alliance A071102) have now successfully incorporated intention to use TTFields as a stratification factor during random assignment to balance the ethical concerns with disallowing use of a US Food and Drug Administration–approved therapy against the potential confounding effect of its use on disease control, and future studies for glioblastoma may follow this lead.

Since this trial was designed, several other randomized studies for newly diagnosed[35,36] or recurrent[31] glioblastoma were completed. Although patients in these other trials were treated with single-agent PD-1 inhibitors rather than dual ICI therapy, none showed superiority of immunotherapy over standard of care. Therefore, NRG BN007 adds to the growing collection of data indicating ICIs are ineffective in glioblastoma, at least without molecular selection or other criteria to enrich accrual for those most likely to benefit.

In addition, an emerging theme surrounding omission of TMZ is concerning. For example, the phase III CheckMate 498 (ClinicalTrials.gov identifier: NCT02617589) randomly assigned 560 patients with newly diagnosed u*MGMT* glioblastoma to either standard TMZ or nivo.[36] There was no benefit from nivo over TMZ overall, or by baseline corticosteroid dose or PD-L1 expression. Moreover, survival was *significantly worse* among patients randomly assigned to nivo versus TMZ (median 13.4 *v* 14.9 months; HR, 1.31 [95% CI, 1.09 to 1.58]; $P = .0037$). Similarly, we found PFS was numerically shorter among patients randomly assigned to ipi and nivo versus TMZ.

Although it is plausible that ipi and nivo shortened survival, we believe that is unlikely, given the lack of a difference in moderate to severe adverse events between arms. Rather, as *MGMT* promoter status exists on a spectrum from methylated to unmethylated, our results and those from CheckMate 498 reinforce that TMZ accordingly has some antitumor activity in glioblastomas classified as u*MGMT*.[37] By extension, this means that, in designing future studies, replacing TMZ with the special sauce *du jour* may be reasonable, but the said sauce must demonstrate superiority not only to nothing, but also to the limited but nonzero benefit provided by TMZ in u*MGMT* cases. We relied on central *MGMT* analysis, rather than local results, to avoid enrolling patients with *MGMT*-promoter methylated disease because concordance between laboratories is poor.[38] However, it may have been prudent to require dual testing (with u*MGMT* results on both), an approach used by others.[39]

Finally, although we observed no difference in OS between arms at the time of the interim analysis, the data are immature (Appendix Fig A1). Follow-up continues and biomarker analyses are ongoing seeking a subset that may have benefited from dual ICI therapy.

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PRIOR PRESENTATION

The study was presented as an abstract at the European Association of Neuro-Oncology 2023 annual meeting (award-winning) in Rotterdam, the Netherlands, and as an *encore* at the Society for Neuro Oncology 2023 annual meeting in Vancouver, Canada.

SUPPORT

CLINICAL TRIAL INFORMATION

NCT04396860 (NRG-BN007)

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO-25-00618.

DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/JCO-25-00618.

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REFERENCES

1. Stupp R, Mason WP, van den Bent MJ, et al: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352:987-996, 2005
2. 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 318:2306-2316, 2017
3. 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 10:459-466, 2009
4. Gilbert MR, Wang M, Aldape KD, et al: Dose-dense temozolomide for newly diagnosed glioblastoma: A randomized phase III clinical trial. J Clin Oncol 31:4085-4091, 2013
5. Gilbert MR, Dignam JJ, Armstrong TS, et al: A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med 370:699-708, 2014
6. Lassman AB, Pugh SL, Wang TJC, et al: Depatuxizumab mafodotin in EGFR-amplified newly diagnosed glioblastoma: A phase III randomized clinical trial. Neuro Oncol 25:339-350, 2023
7. Sarkaria JN, Ballman KV, Kizilbash SH, et al: Efficacy of adding veliparib to temozolomide for patients with MGMT-methylated glioblastoma: A randomized clinical trial. JAMA Oncol 10:1637-1644, 2024
8. Wolchok J: Putting the immunologic brakes on cancer. Cell 175:1452-1454, 2018
9. Chang E, Pelosof L, Lemery S, et al: Systematic review of PD-1/PD-L1 inhibitors in oncology: From personalized medicine to public Health. Oncologist 26:e1786-e1799, 2021
10. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al: Long-term outcomes with nivolumab plus ipilimumab or nivolumab alone versus ipilimumab in patients with advanced melanoma. J Clin Oncol 40:127-137, 2022
11. Keegan NM, Funt SA, Kania BE, et al: Durable clinical benefit from combination ipilimumab (IPI) and nivolumab (NIVO) in anti-PD-1 therapy resistant, platinum resistant metastatic urothelial carcinoma (mUC). J Clin Oncol 37, 2019 (suppl 7; abstr 481)
12. André T, Lonardi S, Wong KYM, et al: Nivolumab plus low-dose ipilimumab in previously treated patients with microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: 4-year follow-up from CheckMate 142. Ann Oncol 33:1052-1060, 2022
13. Zamarin D, Burger RA, Sill MW, et al: Randomized phase II trial of nivolumab versus nivolumab and ipilimumab for recurrent or persistent ovarian cancer: An NRG oncology study. J Clin Oncol 38:1814-1823, 2020
14. Long GV, Atkinson V, Lo S, et al: Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: A multicentre randomised phase 2 study. Lancet Oncol 19:672-681, 2018
15. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al: Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 377:1345-1356, 2017
16. Sloan AE, Winter K, Gilbert MR, et al: NRG-BN002: Phase I study of ipilimumab, nivolumab, and the combination in patients with newly diagnosed glioblastoma. Neuro Oncol 26:1628-1637, 2024
17. Hegi ME, Diserens AC, Gorlia T, et al: MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 352:997-1003, 2005
18. Wick W, Weller M, van den Bent M, et al: MGMT testing—The challenges for biomarker-based glioma treatment. Nat Rev Neurol 10:372-385, 2014
19. Karnofsky DA, Abelmann WH, Craver LF, et al: The use of the nitrogen mustards in the palliative treatment of carcinoma. With particular reference to bronchogenic carcinoma. Cancer 1:634-656, 1948
20. Bady P, Delorenzi M, Hegi ME: Sensitivity analysis of the MGMT-STP27 model and impact of genetic and epigenetic context to predict the MGMT methylation status in gliomas and other tumors. J Mol Diagn 18:350-361, 2016
21. Serrano J, Snuderl M: Whole genome DNA methylation analysis of human glioblastoma using Illumina BeadArrays. Methods Mol Biol 1741:31-51, 2018
22. Louis DN, Perry A, Reifenberger G, et al: The 2016 World Health Organization classification of tumors of the central nervous system: A summary. Acta Neuropathol 131:803-820, 2016
23. Brat DJ, Aldape K, Colman H, et al: cIMPACT-NOW update 3: Recommended diagnostic criteria for "Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV". Acta Neuropathol 136:805-810, 2018
24. Louis DN, Giannini C, Perry A, et al: Glioblastoma, IDH-wildtype. in WHO Classification of Tumours Editorial Board (eds): Central Nervous System Tumours, Volume 6 (ed 5). Lyon, France, International Agency for Research on Cancer (IARC), 2021. https://tumourclassification.iarc.who.int/chapters/45
25. DeWitt JC, Jordan JT, Frosch MP, et al: Cost-effectiveness of IDH testing in diffuse gliomas according to the 2016 WHO classification of tumors of the central nervous system recommendations. Neuro Oncol 19:1640-1650, 2017
26. Galbraith K, Vasudevaraja V, Serrano J, et al: Clinical utility of whole-genome DNA methylation profiling as a primary molecular diagnostic assay for central nervous system tumors—A prospective study and guidelines for clinical testing. Neurooncol Adv 5:vdad076, 2023
27. 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 28:1963-1972, 2010
28. Ellingson BM, Wen PY, Cloughesy TF: Modified criteria for radiographic response assessment in glioblastoma clinical trials. Neurotherapeutics 14:307-320, 2017
29. Wen PY, van den Bent M, Youssef G, et al: RANO 2.0: Update to the response assessment in neuro-oncology criteria for high- and low-grade gliomas in adults. J Clin Oncol 41:5187-5199, 2023
30. Li J, Wang M, Won M, et al: Validation and simplification of the Radiation Therapy Oncology Group recursive partitioning analysis classification for glioblastoma. Int J Radiat Oncol Biol Phys 81:623-630, 2011
31. 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 6:1003-1010, 2020
32. Verheijden RJ, de Groot JS, Fabriek BO, et al: Corticosteroids for immune-related adverse events and checkpoint inhibitor efficacy: Analysis of six clinical trials. J Clin Oncol 42:3713-3724, 2024
33. Lassman AB, Joanta-Gomez AE, Pan PC, et al: Current usage of tumor treating fields for glioblastoma. Neurooncol Adv 2:vdaa069, 2020
34. Cloughesy TF, Lassman AB: NovoTTF: Where to go from here? Neuro Oncol 19:605-608, 2017
35. Lim M, Weller M, Idbaih A, et al: Phase III trial of chemoradiotherapy with temozolomide plus nivolumab or placebo for newly diagnosed glioblastoma with methylated MGMT promoter. Neuro Oncol 24:1935-1949, 2022
36. Omuro A, Brandes AA, Carpentier AF, et al: Radiotherapy combined with nivolumab or temozolomide for newly diagnosed glioblastoma with unmethylated MGMT promoter: An international randomized phase III trial. Neuro Oncol 25:123-134, 2023
37. 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 25:1809-1816, 2019
38. Lassman AB, Dimino C, Mansukhani M, et al: Concordance of EGFR and MGMT analyses between local and central laboratories: Implications for clinical trial design and precision medicine for depatuxizumab-mafodotin (ABT-414) in glioblastoma (GBM) [abstract ACTR-68]. Neurooncology 19:vi15, 2017
39. Wick W, Dettmer S, Berberich A, et al: N2M2 (NOA-20) phase I/II trial of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed non-MGMT hypermethylated glioblastoma. Neuro Oncol 21:95-105, 2019

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Dual Immune Check Point Blockade in *MGMT*-Unmethylated Newly Diagnosed Glioblastoma: NRG Oncology BN007, a Randomized Phase II/III Clinical Trial

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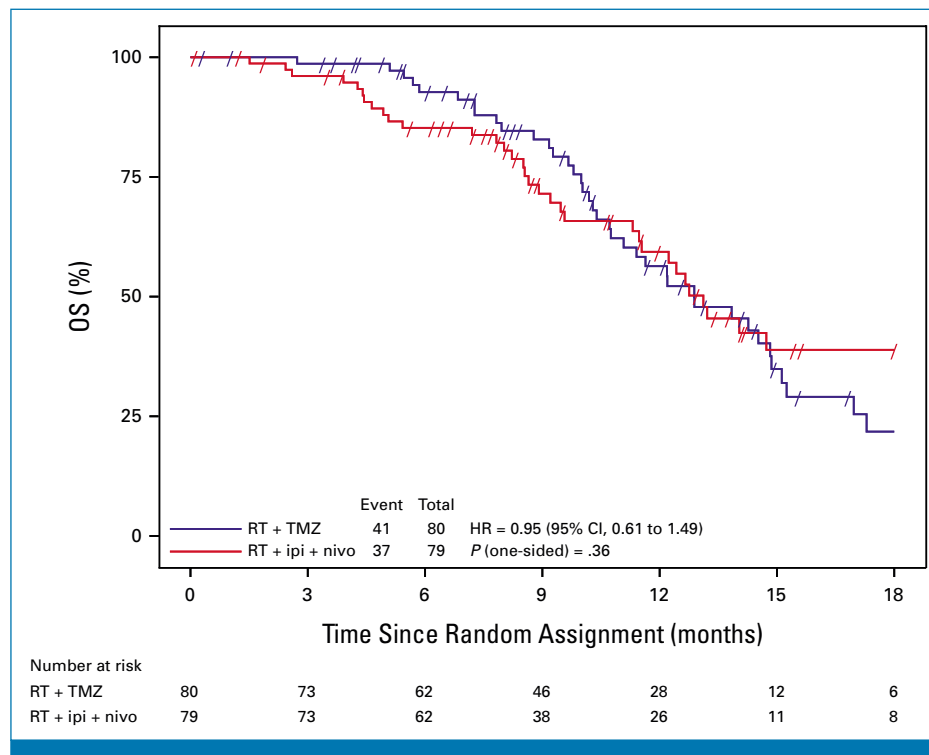
APPENDIX

FIG A1. OS by treatment arm. Median follow-up for survival was 13.7 months (95% CI, 11.9 to 14.9). HR, hazard ratio; ipi, ipilimumab; nivo, nivolumab; OS, overall survival; RT, radiotherapy; TMZ, temozolomide.

TABLE A1. Radiotherapy Delivery

Radiotherapy	Radiotherapy + Temozolomide (n = 80)	Radiotherapy + Ipilimumab+ Nivolumab (n = 79)
Radiotherapy given, No. (%)		
No	6 (7.5)	1 (1.3)
Yes	74 (92.5)	77 (97.5)
Not reported	0 (0.0)	1 (1.3)
Reasons radiotherapy not started or discontinued, No. (%)		
Completed	72 (90.0)	71 (89.9)
Adverse event	0 (0.0)	1 (1.3)
Physician decision	0 (0.0)	1 (1.3)
Progressive disease	1 (1.3)	1 (1.3)
Withdrawal by patient	5 (6.3)	2 (2.5)
Other	1 (1.3)	2 (2.5)
Unknown	1 (1.3)	0 (0.0)
Not reported	0 (0.0)	1 (1.3)
Radiotherapy technique, No. (%)	(n = 74)	(n = 77)
3-dimensional conformal radiotherapy	1 (1.4)	2 (2.6)
Intensity-modulated radiotherapy	72 (97.3)	73 (94.8)
Not reported	1 (1.4)	2 (2.6)

TABLE A2. Temozolomide Delivery

Chemotherapy	Control Arm (n = 80)
Temozolomide given, No. (%)	
Yes	74 (92.5)
No	6 (7.5)
Adjuvant cycles, No.	
Median (range)	4 (1-10)

TABLE A3. Immunotherapy (experimental arm only, n = 79)

Immunotherapy	Ipilimumab	Nivolumab
Immunotherapy given, No. (%)		
Yes	78 (98.7)	78 (98.7)
No	1 (1.3)	1 (1.3)
Infusions given, No.		
Median (range)	4 (1-4)	8 (1-25)

NOTE. Ipilimumab given once every 4 weeks for up to four doses, and nivolumab given once every 2 weeks.

TABLE A4. Highest-Grade Adverse Events Reported as Possibly, Probably, or Definitely Related to Protocol Treatment

System Organ Class	Radiotherapy + Temozolomide (n = 74)					Radiotherapy + Ipilimumab + Nivolumab (n = 78)				
	Patients by Grade, No. (%)					Patients by Grade, No. (%)				
	1	2	3	4	5	1	2	3	4	5
Overall highest grade	16 (21.6)	23 (31.1)	22 (29.7)	6 (8.1)	0 (0.0)	9 (11.5)	32 (41.0)	26 (33.3)	4 (5.1)	2 (2.6)
Blood and lymphatic system disorders	13 (17.6)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	11 (14.1)	1 (1.3)	1 (1.3)	0 (0.0)	0 (0.0)
Cardiac disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.8)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Endocrine disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (7.7)	7 (9.0)	2 (2.6)	0 (0.0)	0 (0.0)
Eye disorders	1 (1.4)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	8 (10.3)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
GI disorders	25 (33.8)	17 (23.0)	2 (2.7)	0 (0.0)	0 (0.0)	13 (16.7)	16 (20.5)	6 (7.7)	2 (2.6)	1 (1.3)
General disorders and administration site conditions	27 (36.5)	16 (21.6)	3 (4.1)	0 (0.0)	0 (0.0)	21 (26.9)	23 (29.5)	1 (1.3)	1 (1.3)	0 (0.0)
Immune system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	1 (1.3)
Infections and infestations	2 (2.7)	2 (2.7)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	5 (6.4)	2 (2.6)	1 (1.3)	0 (0.0)
Injury, poisoning, and procedural complications	5 (6.8)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	5 (6.4)	5 (6.4)	1 (1.3)	0 (0.0)	0 (0.0)
Investigations	9 (12.2)	16 (21.6)	15 (20.3)	5 (6.8)	0 (0.0)	18 (23.1)	12 (15.4)	8 (10.3)	2 (2.6)	0 (0.0)
Metabolism and nutrition disorders	15 (20.3)	9 (12.2)	0 (0.0)	0 (0.0)	0 (0.0)	17 (21.8)	6 (7.7)	4 (5.1)	1 (1.3)	0 (0.0)
Musculoskeletal and connective tissue disorders	6 (8.1)	0 (0.0)	2 (2.7)	0 (0.0)	0 (0.0)	8 (10.3)	8 (10.3)	5 (6.4)	0 (0.0)	0 (0.0)
Nervous system disorders	17 (23.0)	9 (12.2)	6 (8.1)	0 (0.0)	0 (0.0)	12 (15.4)	13 (16.7)	8 (10.3)	1 (1.3)	0 (0.0)
Psychiatric disorders	6 (8.1)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	4 (5.1)	5 (6.4)	1 (1.3)	0 (0.0)	0 (0.0)
Renal and urinary disorders	1 (1.4)	2 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	2 (2.7)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	8 (10.3)	3 (3.8)	2 (2.6)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	17 (23.0)	7 (9.5)	0 (0.0)	0 (0.0)	0 (0.0)	23 (29.5)	7 (9.0)	3 (3.8)	0 (0.0)	0 (0.0)
Vascular disorders	2 (2.7)	1 (1.4)	2 (2.7)	0 (0.0)	0 (0.0)	3 (3.8)	5 (6.4)	4 (5.1)	1 (1.3)	0 (0.0)

NOTE. Seven patients received no study treatment and are not included. Adverse events were graded with CTCAE, version 5.0.
Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events.

TABLE A5. Tumor Treating Fields, Intention to Use Versus Actually Used

Intent to Use Tumor Treating Fields	Tumor Treating Fields Not Used, No. (%)	Tumor Treating Fields Used, No. (%)	Total, No. (%)
Radiotherapy + temozolomide arm	(n = 76)	(n = 4)	(n = 80)
No	42 (55.3)	0 (0.0)	42 (52.5)
Yes	34 (44.7)	4 (100.0)	38 (47.5)
Radiotherapy + ipilimumab + nivolumab arm	(n = 79)	(n = 0)	(n = 79)
No	41 (51.9)	0 (0.0)	41 (51.9)
Yes	38 (48.1)	0 (0.0)	38 (48.1)