original reports

NRG Oncology/RTOG1205: A Randomized Phase II Trial of Concurrent Bevacizumab and Reirradiation Versus Bevacizumab Alone as Treatment for Recurrent Glioblastoma

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abstract

PURPOSE To assess whether reirradiation (re-RT) and concurrent bevacizumab (BEV) improve overall survival (OS) and/or progression-free survival (PFS), compared with BEV alone in recurrent glioblastoma (GBM). The primary objective was OS, and secondary objectives included PFS, response rate, and treatment adverse events (AEs) including delayed CNS toxicities.

METHODS NRG Oncology/RTOG1205 is a prospective, phase II, randomized trial of re-RT and BEV versus BEV alone. Stratification factors included age, resection, and Karnofsky performance status (KPS). Patients with recurrent GBM with imaging evidence of tumor progression ≥ 6 months from completion of prior chemo-RT were eligible. Patients were randomly assigned 1:1 to re-RT, 35 Gy in 10 fractions, with concurrent BEV IV 10 mg/kg once in every 2 weeks or BEV alone until progression.

RESULTS From December 2012 to April 2016, 182 patients were randomly assigned, of whom 170 were eligible. Patient characteristics were well balanced between arms. The median follow-up for censored patients was 12.8 months. There was no improvement in OS for BEV + RT, hazard ratio, 0.98; 80% CI, 0.79 to 1.23; $P = .46$; the median survival time was 10.1 versus 9.7 months for BEV + RT versus BEV alone. The median PFS for BEV + RT was 7.1 versus 3.8 months for BEV, hazard ratio, 0.73; 95% CI, 0.53 to 1.0; $P = .05$. The 6-month PFS rate improved from 29.1% (95% CI, 19.1 to 39.1) for BEV to 54.3% (95% CI, 43.5 to 65.1) for BEV + RT, $P = .001$. Treatment was well tolerated. There were a 5% rate of acute grade 3+ treatment-related AEs and no delayed high-grade AEs. Most patients died of recurrent GBM.

CONCLUSION To our knowledge, NRG Oncology/RTOG1205 is the first prospective, randomized multi-institutional study to evaluate the safety and efficacy of re-RT in recurrent GBM using modern RT techniques. Overall, re-RT was shown to be safe and well tolerated. BEV + RT demonstrated a clinically meaningful improvement in PFS, specifically the 6-month PFS rate but no difference in OS.

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ASSOCIATED CONTENT

See accompanying Oncology Grand Rounds on page 1183

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Glioblastoma (GBM) is the most common primary brain tumor in adults.[1] Despite optimal treatment with surgery, chemotherapy, and radiation (RT), the median survival remains approximately 12-16 months. Nearly all patients relapse at a median of 8 months with frequently devastating neurologic consequences.[1] Management of recurrent gliomas is particularly challenging given the paucity of effective treatment options. The absence of clear evidence of survival benefit has led to diverse treatment strategies.

Radiation significantly improves overall survival (OS) in newly diagnosed GBM.[2] With limited treatment options, reirradiation (re-RT) is increasingly offered to select patients with localized recurrence. Retrospective data suggest that re-RT is safe and well-tolerated and provides improved disease control. re-RT may delay disease progression, thereby reducing chronic steroid use and potentially decreasing neurologic symptoms. Several retrospective studies have also shown safety and putatively improved outcomes in select patients.[3-6] Despite careful patient selection, the benefit of re-RT remains unclear. Given the heterogeneous nature of recurrent GBM, the impact of meta-analyses on establishing benefit is limited. Therefore, a prospective, randomized multi-institutional study was conducted to address this important clinical question.

Vascular proliferation is a notable feature of GBM, and several trials targeting the vascular endothelial growth

CONTEXT

Key Objective

What is the role of reirradiation in recurrent glioblastoma (GBM)?

Knowledge Generated

To our knowledge, NRG Oncology/RTOG1205 is the first prospective, randomized multi-institutional study to evaluate the safety and efficacy of reirradiation added to the standard of care bevacizumab (BEV) in recurrent GBM. The addition of RT to BEV did not demonstrate a benefit in overall survival compared with the control arm but did show statistically significant improvement in the predefined secondary end point of 6-month progression-free survival.

Relevance *(I.K. Mellinghoff)*

Radiation plays an important role in the initial treatment of brain tumors. The current study shows that a second course of radiation with concurrent BEV is well tolerated and prolongs progression-free survival in patients with recurrent GBM. Although this treatment did not prolong overall survival, local disease control remains an important goal in this disease with limited treatment options.*

*Relevance section written by *JCO* Associate Editor Ingo K. Mellinghoff, MD.

factor (VEGF) have been conducted.[7] Anti-VEGF therapy has been shown to inhibit new vessel growth causing vascular regression and normalization.[8] Antiangiogenic therapies rapidly normalize leaky abnormal tumor vessels, decreasing vasogenic edema. Reduced dependence on corticosteroids may significantly improve a patient's quality of life (QOL).[9] In 2009, bevacizumab (BEV), a humanized monoclonal antibody that targets VEGF, gained US Food and Drug Administration approval, on the basis of progression-free survival (PFS) improvement, without categorical improvement in OS.[10] Several trials have evaluated the safety and efficacy of BEV alone or in combination with chemotherapy. A single-institution phase II trial demonstrated increased response and prolonged 6-month PFS.[11,12] The median OS of patients with GBM was 9.2 months. Phase II trials have evaluated BEV in combination with chemotherapy agents, including temozolomide, irinotecan, and nitrosoureas without improved efficacy.[9-18]

The clinical rationale for combining BEV with re-RT is several-fold. Preclinical studies have demonstrated that antiangiogenic agents may target radioresistant and highly tumorigenic cancer stem cells by disrupting vascular niches harboring cancer stem cells.[19,20] Vascular normalization can decrease tumor hypoxia, which is one possible mechanism for radioresistance. Addition of BEV may reduce the toxicity associated with re-RT by reducing the risk of radiation necrosis.[21] A single prospective trial suggested increased efficacy with BEV and re-RT with durable disease control and improved OS.[22] Several retrospective series have reported on the safety of this approach.[23,24] Thus, the combination of BEV and RT in recurrent GBM may increase the therapeutic ratio through enhancement of the RT response, increase the anti-VEGF effect of BEV using RT to target resistant glioma stem-cell–like cells, and lower the incidence of radiation necrosis and CNS toxicity.

To our knowledge, NRG Oncology/RTOG1205 was designed as the first prospective, multi-institutional phase II randomized study to evaluate the role of re-RT in recurrent GBM using modern RT techniques. The primary objective of NRG Oncology/RTOG1205 was to determine if re-RT in combination with BEV improved OS compared with BEV alone. Secondary end points included PFS, 6-month PFS, objective response, and acute and late treatment-related toxicity rates (Common Terminology Criteria for Adverse Events version 4 [CTCAE v4]).

METHODS

Study Schema

NRG Oncology/RTOG1205 was a randomized phase II trial as proposed by Rubinstein et al[25] to determine whether BEV + re-RT (experimental arm) would improve OS compared with BEV alone (control arm). Patients were randomly assigned 1:1 using permuted block, after stratification by age ($<$ 50 years *v* $\geq$ 50 years), Karnofsky performance status (KPS; 60 *v* 70-80 *v* 90-100), and recent re-resection (yes *v* no/biopsy only).[26]

Eligibility Criteria

Eligibility criteria included recurrent GBM with histopathologically confirmed or unequivocal imaging evidence of tumor progression within 21 days of study registration. Prior cranial RT was completed at least 6 months before study entry unless one or more of the following criteria was met: (1) histologic evidence of tumor progression; (2) new areas of recurrent tumor outside the original RT fields; or (3) advanced imaging including positron emission tomography, magnetic resonance (MR) spectroscopy, or MR

perfusion imaging consistent with true progression, obtained ≥ 90 days from RT completion and ≤ 28 days of study entry.

Inclusion criteria were modified after slower-than-anticipated patient accrual to allow for patient enrollment with up to three relapses, a KPS of ≥ 60, and recurrent tumors ≤ 6 cm. Multifocal recurrence was no longer excluded, provided that the composite tumor volume was ≤ 6 cm. All patients provided written informed consent and received protocol-specified care and follow-up at a member site (see the Protocol [online only] for additional details).

Treatment

Radiation. re-RT dose was 35 Gy in 10 fractions, using 3D conformal RT, intensity-modulated RT, or protons. Gross target volume (GTV) was defined as enhancing tumor using computed tomography and/or magnetic resonance imaging images or postoperative resection cavity if no residual enhancing tumor was noted. A planning target volume (PTV) expansion of at least 3 mm was used. PTV margins of ≤ 5 mm required the treating institution to obtain prior image-guided RT credentialing and daily image-guided RT. Details regarding specific dose limits are described.

BEV. BEV was administered at a dose of 10 mg/kg once in every 2 weeks until disease progression. The initial cycle of BEV was initiated within 14 days of registration. Patients randomly assigned to the BEV and re-RT arm received an initial induction BEV dose (day 1) followed by concurrent BEV and re-RT at the next dose (day 14), and then once every 14 days until disease progression.

Outcomes

The primary end point was OS, defined as the interval from random assignment to death because of any cause. Secondary end points were objective response, PFS, defined as the interval from random assignment to progression or death, whichever occurred first, 6-month PFS, treatment-related adverse events (AEs), and evidence of grade 3 or greater acute or delayed CNS toxicity.

Statistical Methods

The primary objective was to determine whether BEV + re-RT improves OS compared with BEV alone. The null hypothesis is that the OS for both arms is 9 months, on the basis of NRG/RTOG 0625.[11,27]

The alternative hypothesis is that the BEV + re-RT arm will have an improvement in OS of 13 months.[22] With 160 eligible participants, there is an 80% power to detect a 31% reduction in the hazard ratio (HR) to 0.69 at the significance level of 0.10 (one-sided), as this was a randomized phase II signal-seeking trial. Analysis was to be performed when 135 events (deaths) had been reported. Guarding against an ineligibility rate of ≤ 10%, the target accrual was 178 participants. The study included an interim toxicity and interim futility analysis.

OS and PFS rates were estimated using the Kaplan-Meier method, with patients censored at their last known follow-up time, and differences between treatment arms were tested using the log-rank test.[28,29] Progression was ascertained by the local investigator on the basis of the MacDonald criteria. Multivariable analyses using stepwise selection were performed using the Cox proportional hazard model with the stratification variables as covariates to assess the adjusted treatment effect on OS and PFS.[30] Interactions between the treatment arm and stratification factors were run, and if significant ($P < .20$), subgroup analyses were conducted. CIs presented are 80% to match the type I error in the study design. Acute (occurring within 90 days from the end of treatment) and delayed (occurring after 90 days from the end of treatment) CNS toxicities, graded with CTCAE v4, were assessed. Differences in observed severities of toxicities and objective responses between treatment arms were tested using chi-square tests. For secondary end points, two-sided tests with a significance level of 0.05 were used.

RESULTS

Between December 20, 2012, and April 28, 2016, 182 patients from 90 institutions were randomly assigned. Twelve patients were subsequently found to be ineligible (Fig 1). Of the remaining 170 patients, 84 were randomly assigned to the control arm and 86 to the experimental arm. Eleven patients (6.5%) received no protocol treatment (eight on the control arm and three on the experimental arm) mainly because of disease progression or patient refusal (Fig 1). Pretreatment characteristics including KPS 60 (eight *v* three patients), moderate/severe neurologic symptoms (11 *v* 6 patients), and treatment at second/third relapse (22 *v* 11 patients) were higher in the BEV + RT arm (Table 1). MGMT methylation status from the primary tumor was available in 81 patients, with methylation rates of 30% in the BEV arm and 38% in the BEV + RT arm.

Primary Outcome

The median OS for the control arm was 9.7 months (80% CI, 9.0 to 11.2) and 10.1 months (95% CI, 9.5 to 11.3) for the experimental arm (HR, 0.98; 80% CI, 0.79 to 1.23, one-sided P value = .46), Figure 2. Thirty-five (20.6%) eligible and randomly assigned patients were censored at the time of this analysis. The median follow-up is 12.8 (min-max: 0.03-52.8) months. Recurrent GBM was the cause of death (approximately 85%). Twelve patients on the BEV arm received re-RT as salvage therapy. Multivariable Cox models revealed that older age (HR, 1.51; 80% CI, 1.13 to 2.01; $P = .065$) and lower KPS (60 *v* 90-100: HR, 3.97; 80% CI, 2.37 to 6.66; $P < .001$ and 70-80 *v* 90-100: HR, 1.70; 80% CI, 1.33 to 2.18; $P = .005$) were associated with worse OS (Table 2A and Appendix Table A1A, online only).

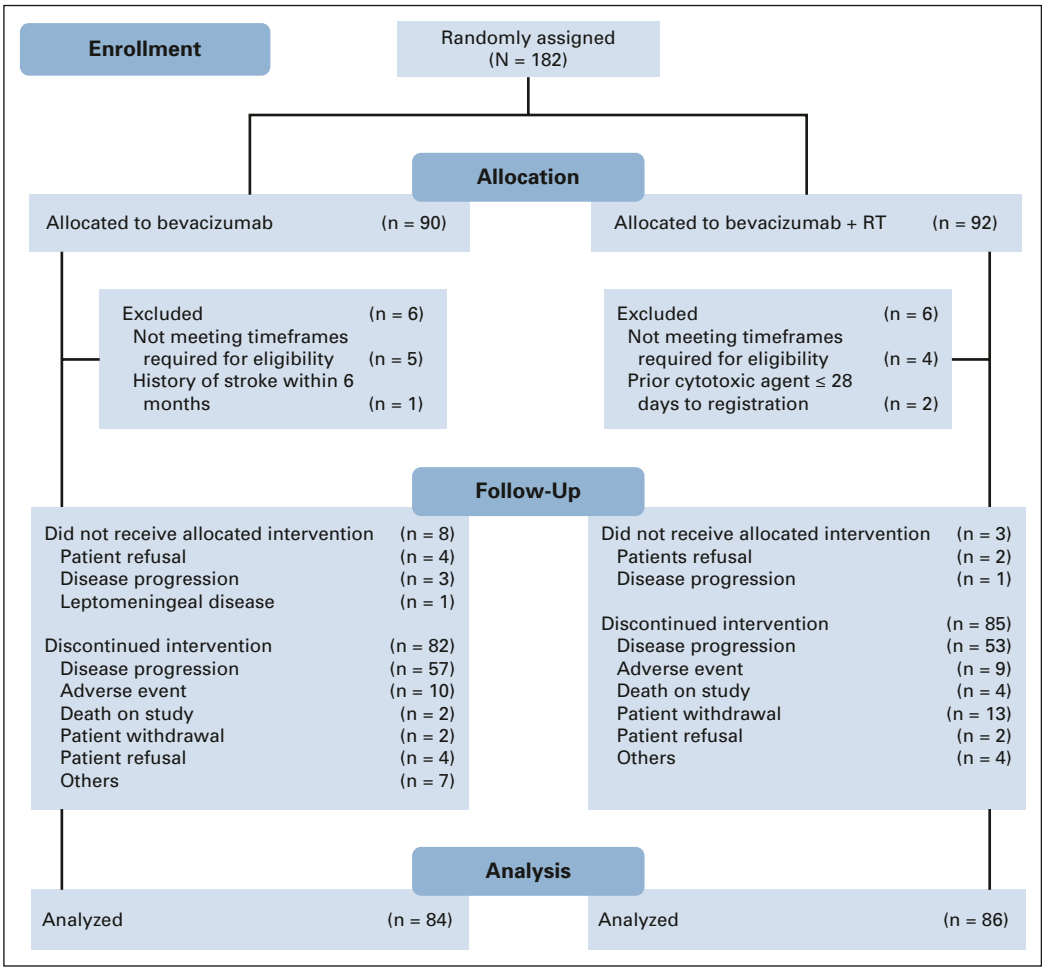

FIG 1. CONSORT diagram. RT, radiation therapy.

Significant tests for interaction were noted for KPS and surgery. The only significant difference between arms was noted for the KPS 90-100 subgroup, in which the BEV + RT arm showed improved survival (HR = 0.67; 95% CI, 0.40 to 1.13; $P = .13$). Multivariable models were performed for patients with available primary tumor MGMT promoter methylation status. Prognostic factors associated with worse OS included unmethylated promoter methylation status (HR, 2.51; 80% CI, 1.68 to 3.76; $P = .003$) and lower KPS (60-80 *v* 90-100: HR, 2.23; 80% CI, 1.58 to 3.14; $P = .003$; Table 2B and Appendix Tables A1B and A2C, online only).

Secondary End Points

Best objective responses by the treatment arm were based on both Macdonald[31] and Response Assessment Neuro-Oncology (RANO)[32] criteria (Appendix Table A2). Radiographic response relied on investigator assessment. Using the MacDonald criteria, the median PFS for the control versus experimental arms was 3.8 versus 7.1 months, respectively (HR, 0.73; 95% CI, 0.53 to 1.00; $P = .05$). The 6-month PFS was 29.1% (95% CI, 19.1 to 39.1) versus 54.3% (95% CI, 43.5 to 65.1; $P = .001$) in favor of BEV + RT. Analysis using RANO criteria revealed similar results.

Treatment AEs

AEs were scored using CTCAE v4. In eligible patients who received protocol treatment there were four patients (5.3%) in the control arm and eight (9.6%) in the experimental arm with reported grade 5 AEs all but two patients were deemed to be either unrelated or unlikely related to protocol treatment (Appendix Tables A3-A5, online only). One death was related to intratumoral hemorrhage in the BEV + RT arm reported as possibly related to protocol treatment, and the other was death not otherwise specified reported as probably related to protocol treatment. All four patients (4.8%) in the experimental arm reported acute grade 3+ treatment-related CNS AEs, whereas no patient had reported delayed grade 3+ treatment-related CNS AEs.

Centralized Protocol Review

Centralized review was undertaken to ascertain protocol compliance (Appendix Table A6, online only). The median number of BEV cycles completed in the experimental arm

TABLE 1. Patient and Tumor Characteristics for All Eligible Patients

Patient and Tumor Characteristic	BEV (n = 84)	BEV + RT (n = 86)	Total (n = 170)
Age, years[a]			
Median	57	60	59
Min-max	25-87	28-81	25-87
Q1-Q3	52-63.5	51-67	51-66
≤ 49, No. (%)	14 (16.7)	21 (24.4)	35 (20.6)
50-59, No. (%)	35 (41.7)	19 (22.1)	54 (31.8)
60-69, No. (%)	26 (31.0)	36 (41.9)	62 (36.5)
≥ 70, No. (%)	9 (10.7)	10 (11.6)	19 (11.2)
Sex, No. (%)			
Male	46 (54.8)	43 (50.0)	89 (52.4)
Female	38 (45.2)	43 (50.0)	81 (47.6)
Race, No. (%)			
American Indian/Alaska Native	4 (4.8)	0 (0.0)	4 (2.4)
Asian	6 (7.1)	2 (2.3)	8 (4.7)
Black or African American	3 (3.6)	2 (2.3)	5 (2.9)
White	66 (78.6)	75 (87.2)	141 (82.9)
Unknown or not reported	5 (6.0)	7 (8.1)	12 (7.1)
Ethnicity, No. (%)			
Hispanic or Latino	8 (9.5)	3 (3.5)	11 (6.5)
Not Hispanic or Latino	72 (85.7)	81 (94.2)	153 (90.0)
Unknown (individuals not reporting ethnicity)	4 (4.8)	2 (2.3)	6 (3.5)
Karnofsky performance status, No. (%)[a]			
60	3 (3.6)	8 (9.3)	11 (6.5)
70-80	42 (50.0)	41 (47.7)	83 (48.8)
90-100	39 (46.4)	37 (43.0)	76 (44.7)
Neurologic function, No. (%)			
No symptoms	21 (25.0)	24 (27.9)	45 (26.5)
Minor symptoms	40 (47.6)	36 (41.9)	76 (44.7)
Moderate symptoms (fully active)	17 (20.2)	15 (17.4)	32 (18.8)
Moderate symptoms (required assistance)	6 (7.1)	9 (10.5)	15 (8.8)
Severe symptoms	0 (0.0)	2 (2.3)	2 (1.2)
Surgery (initial brain tumor), No. (%)			
Biopsy only	8 (9.5)	7 (8.1)	15 (8.8)
Subtotal resection	20 (23.8)	25 (29.1)	45 (26.5)
Gross total resection	56 (66.7)	52 (60.5)	108 (63.5)
Others	0 (0.0)	2 (2.3)	2 (1.2)
Recent resection, No. (%)[a]			
No/biopsy only	49 (58.3)	57 (66.3)	106 (62.4)
Yes	35 (41.7)	29 (33.7)	64 (37.6)
Histologic tumor type, No. (%)			
GBM (WHO grade IV)	79 (94.0)	82 (95.3)	161 (94.7)
Gliosarcoma	2 (2.4)	2 (2.3)	4 (2.4)
Others	3 (3.6)	2 (2.3)	5 (2.9)

(continued on following page)

TABLE 1. Patient and Tumor Characteristics for All Eligible Patients (continued)

Patient and Tumor Characteristic	BEV (n = 84)	BEV + RT (n = 86)	Total (n = 170)
No. of relapses, No. (%)			
1	73 (86.9)	64 (74.4)	137 (80.6)
2	8 (9.5)	22 (25.6)	30 (17.6)
3	3 (3.6)	0 (0.0)	3 (1.8)
Type of radiation therapy administered, No. (%)			
3D-CRT		5 (5.8)	
IMRT		74 (86.0)	
Protons		2 (2.3)	
Unknown/missing		5 (5.8)	
MGMT status, No. (%)			
Methylated	12 (14.3)	18 (20.9)	30 (17.6)
Unmethylated	24 (28.6)	27 (31.4)	51 (30.0)
Invalid	4 (4.8)	2 (2.3)	6 (3.5)
Unknown/missing	44 (52.4)	39 (45.3)	83 (48.8)

Abbreviations: BEV, bevacizumab; GBM, glioblastoma; IMRT, intensity-modulated RT; Q1, first quartile; Q3, third quartile; RT, radiation therapy.
[a]Stratification factor.

was three (range, 1-16) and two (range, 1-17) in the control arm. Approximately 10% of the patients discontinued BEV because of an AE, side effects, or complications.

Detailed information on RT planning reviews revealed that 76 of 81 (93.8%) met the minimum quality standard, 60.5% followed the, and 33.3% had an acceptable deviation (Appendix Table A7, online only). The median gross target volume for the re-RT arm was 18 cc (min-max: 0.5-208 cc). The median PTV was 54 cc (min-max: 4-412 cc). Protocol shortcomings included the following: tumor size > 6 cm, evidence of multifocal disease, leptomeningeal or subependymal tumor spread, and RT plans with considerable underdosage of the tumor because of its location near critical structures. Of note, treatment planning MR imaging revealed recurrent, enhancing tumor in nine (36%) cases, despite reported GTR.

DISCUSSION

Few effective salvage treatment options for recurrent glioma exist, and no well-defined standard of care is universally accepted. BEV represents one relatively recently approved approach, and although it yields meaningful PFS improvement, OS improvement remains elusive.[33]

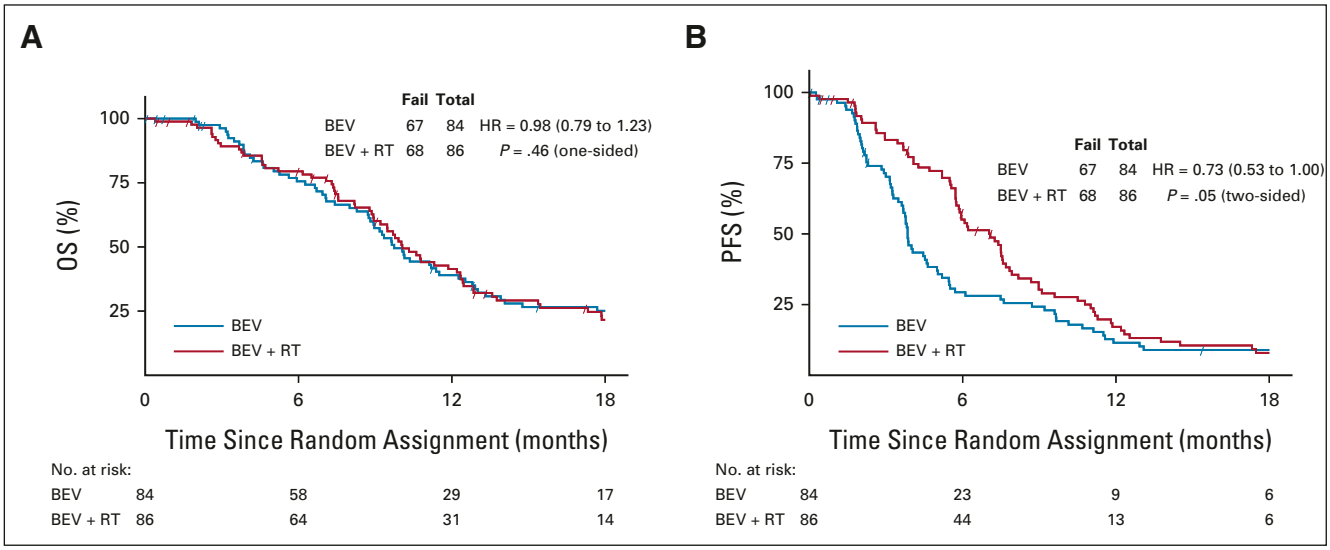

FIG 2. (A) OS and (B) PFS by treatment arm. CIs for OS are 80% and 95% for PFS. BEV, bevacizumab; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RT, radiation therapy.

TABLE 2. Cox Proportional Hazards Model for Overall Survival

Variable	HR (80% CI)	*P*
All patients (n = 170)		
Assigned treatment (BEV + RT *v* **BEV**)	—	.260
Age (50+ years *v* **< 50 years**)	1.51 (1.13 to 2.01)	.065
KPS		
60 *v* **90-100**	3.97 (2.37 to 6.66)	< .001
70-80 *v* **90-100**	1.70 (1.33 to 2.18)	.005
Months from the initial RT end to on-study (continuous)	0.99 (0.99 to 1.00)	.169
No. of relapses (2-3 *v.* **1**)	—	.069
Treatment × No. of relapses	—	.022
BEV + RT *v* **BEV** with 1 relapse	0.79 (0.61 to 1.03)	—
BEV + RT *v* **BEV** with 2-3 relapses	2.29 (1.34 to 3.92)	—
Patients with MGMT available (n = 81)		
Assigned treatment (BEV + RT *v* **BEV**)	0.87 (0.63 to 1.22)	.605
MGMT (unmethylated *v* **methylated**)	2.51 (1.68 to 3.76)	.003
KPS (60-80 *v* **90-100**)	2.23 (1.58 to 3.14)	.003
Months from the initial RT end to on-study (continuous)	0.98 (0.97 to 1.00)	.083
Patients with PTV available (n = 120)		
Assigned treatment (BEV + RT *v* **BEV**)	0.73 (0.54 to 0.98)	.178
KPS		
60 *v* **90-100**	3.63 (2.09 to 6.32)	.003
70-80 *v* **90-100**	1.98 (1.48 to 2.65)	.003
Months from the initial RT end to on-study (continuous)	0.99 (0.98 to 1.00)	.078
PTV (cc)	1.00 (1.00 to 1.01)	.102
No. of relapses (2-3 *v.***1**)	1.63 (1.16 to 2.30)	.066

NOTE. Reference level is given in bold. Covariates considered in all models: treatment arm (BEV + RT *v* BEV), MGMT (unmethylated *v* methylated), sex (male *v* female), age (≥ 50 years *v* < 50 years), KPS (60-80 *v* 90-100), recent resection (yes *v* no/biopsy), tumor area, months from the initial RT end to the date of random assignment, number of relapses (1 *v* 2-3), and interaction between the treatment arm and the number of relapses. Full models are given in the Supplement.

Abbreviations: BEV, bevacizumab; HR, hazard ratio; KPS, Karnofsky performance status; PTV, planning target volume; RT, radiation therapy.

re-RT has long been proposed as a safe and effective therapy.[3,34-37] Advances in RT techniques including fractionated stereotactic radiotherapy, heavy particles, and intensity-modulated RT have enabled increasingly conformal treatment, reducing the likelihood of acute and late CNS toxicity.[4-6,38-40] A recent meta-analysis of re-RT revealed a 12-month OS rate of 36% (95% CI, 32 to 40) and a 6-month PFS rate of 43% (95% CI, 35 to 50).[41] Previous studies have reported improved 6-month functional status and reduction or discontinuation of corticosteroid usage.[3,35,42-46] Consensus around treatment guidelines for recurrent glioma has proved to be elusive in part because of a lack of randomized, prospective trials and retrospective studies published without an established control group.[46,47]

NRG Oncology/RTOG1205 was a prospective, multiinstitutional randomized trial undertaken to confirm the safety of concurrent BEV and re-RT 35 Gy in 10 fractions. The primary objective was to evaluate OS with BEV alone versus concomitant BEV and re-RT in BEV-naïve recurrent GBM. To this end, the study failed to establish a significant survival benefit. Results demonstrated a median OS of 10.1 months for the experimental arm and 9.7 months for the control arm. Multivariable analysis revealed that younger age, improved KPS, and methylated MGMT promoter status were associated with better OS.

NRG Oncology/RTOG1205 confirmed improvement in PFS and 6-month PFS rates for the concomitant BEV + re-RT arm compared with BEV alone. The median PFS was 7.1 and 3.8 months, respectively. The 6-month PFS rate remains an important end point for recurrent GBM, whereas no prior therapeutic trials have demonstrated an OS benefit. Disease progression remains a key event in driving QOL deterioration. Preserving neurologic function and QOL without the need for chronic steroid use remains highly relevant. The historic assumption from multiple recurrent GBM trials is that the 6-month PFS is consistently around

15%. Many trials are powered to detect an approximately 13%-15% improvement on this baseline (28%-30%).[48,49] In 2017, BEV was granted regular approval, following results of EORTC trial 26101, a randomized study of 432 patients with recurrent GBM comparing lomustine versus lomustine plus BEV.[33] No difference in OS was noted between BEV + lomustine versus lomustine-alone arms. Patient characteristics were similar with a median age of 57 years (59 years in NRG Oncology/RTOG1205), 44% had a WHO performance status of 0 (KPS, 90-100 in 45% of NRG Oncology/RTOG1205), and 56% had a largest tumor diameter of ≤ 40 mm. Median PFS was improved in the BEV + lomustine arm (4.2 *v* 1.5 months; HR, 0.52; 95% CI, 0.41 to 0.64). Again, the median PFS in NRG Oncology/RTOG1205 was 3.8 months on the BEV arm and 7.1 months for BEV + re-RT.

Secondary analyses of salvage therapies for recurrent GBM have revealed trends toward better survival in those receiving salvage therapy compared with those who did not.[50] re-RT combined with systemic therapy was reported in 10% of patients (64 patients). The median OS was 9.7 months (range, 6.5-14.6). In multivariable analysis, KPS ≥ 70% ($P < .01$), re-RT for first recurrence ($P = .02$), longer time interval to re-RT ($P < .01$), and smaller PTVs ($P < .05$) were significant prognostic factors. Retrospective analyses provide similar confirmation that re-RT remains a safe, reasonable, and effective treatment option for patients with recurrent GBM with excellent KPS and limited volume recurrence.[3,4,34,36,37,41,46,47]

Strategies for salvage treatment of recurrent glioma have evolved largely without consensus. Poor outcomes, significant patient heterogeneity including genetically diverse subclones within the tumor, and a complex glioma tumor microenvironment capable of sustaining stem cell-like tumor cells that are frequently RT-resistant may provide some explanation for this pattern.[51] The blood brain barrier remains an ever-present obstacle to the delivery of potentially effective drug therapy. Despite randomized chemotherapy studies including novel targeted agents, no systemic therapy has shown significant improvement in OS for recurrent GBM (Table 3). Novel therapies such as a targeted immunotherapeutic approach with rindopepimut, an antiepidermal growth factor (EGFRvIII) cancer vaccine, in combination with BEV in recurrent GBM demonstrated a disappointing 6-month PFS of 28%.[52] Several studies evaluating BEV and re-RT including fractionated stereotactic radiotherapy and stereotactic radiosurgery (SRS) studies suggested promising efficacy (Table 3).[22,53-55]

re-RT using modern, SRS techniques delivers higher doses of RT to a considerably more precise target volume, in one to five fractions, and with a steep dose gradient beyond the tumor. A retrospective study of 49 patients with recurrent GBM receiving SRS and concurrent BEV reported a median OS of 10 months. Smaller treatment volume correlated with improved outcomes.[55] Future studies will determine the role of re-RT using SRS techniques in combination with novel agents including checkpoint inhibitors to prevent recurrence by eliciting a more durable immune response.[56]

Rethinking re-RT treatment target volumes combined with new approaches to RT delivery is another potential avenue. Fractionated SRT schedules (using ≤ 3.5 Gy/fraction) allow treatment of larger tumor volumes particularly near critical eloquent structures. Prospective studies evaluating targeting FLAIR should be considered.[57] re-RT strategies that target only enhancing tumor regions need to better account for the diffuse, infiltrative, and often nonenhancing pattern of recurrent GBM growth.[58]

NRG Oncology/RTOG1205 revealed key challenges in demonstrating an OS benefit in a prospective, randomized multi-institutional trial in the salvage setting. Selection of appropriate patients for re-RT remains crucial.[5,6,58-60] In response to low accrual, NRG Oncology/RTOG1205 was

TABLE 3. Summary of Other Trial Results

Author	No. of Patients	Treatment	Median OS (months) (95% CI)	Median GTV (cc) (min-max)	RT Dose Gy/Fractions (min-max)
Friedman et al[27]	85	BEV	9.2 (8.2 to 10.7)	NA	
Tsien 2021	86	BEV + FSRT	10.1 (8.9 to 12.3)	18 (0.5-208)	35 Gy in 10 fx
Gutin et al[22]	20	BEV + FSRT	12.5 (6.9 to 22.5)	34 (2-62)	30 Gy in 5 fx
Minniti et al[48]	26	BEV + FSRT	11 1-year OS 30% (19 to 41)	11.9 (2.1-38.5)	25 Gy in 5 fx
Cuneo et al[55]	49	BEV + SRS	11.2 1-year OS 50%	4.8	15 Gy (12.5-25)
Wick et al[33]	211	BEV + CCNU	9.1 (8.1 to 10.1)	NA	NA
Friedman et al[27]	82	BEV + CPT-11	8.7 (7.8 to 10.9)	NA	NA
Reardon et al[49]	40	BEV/CPT-11 + Carbo	8.3 (5.9 to 10.7)	NA	NA
Reardon et al[52]	36	BEV + Rindo	2-Year OS 20% (9 to 35)	7.9 (1.2-27.7)	NA

Abbreviations: BEV, bevacizumab; Carbo, carboplatin; CCNU, cyclohexyl-chloroethyl-nitrosourea; CPT, camptothecin; FSRT, fractionated stereotactic radiotherapy; fx, fractions; GTV, gross tumor volume; OS, overall survival; Rindo, rindopepimut; SRS, stereotactic radiosurgery.

amended to broaden eligibility, resulting in the inclusion of a significant number of patients less likely to benefit from focal, re-RT because of extensive disease burden. With limited third-line and fourth-line salvage options available, several patients on the control arm ultimately received salvage re-RT. Additional molecular markers including MGMT methylation and IDH mutation status should be considered as potential stratification factors.

In conclusion, optimal treatment for patients with recurrent GBM remains controversial. Although the combination of re-RT and BEV did not significantly improve OS for patients with BEV-naive recurrent GBM, NRG Oncology/RTOG1205 confirmed meaningful improvement in PFS, including the 6-month PFS rate, with concurrent re-RT and BEV compared with BEV alone, which most patients consider clinically beneficial. This is especially true when considering that treatment was safe and well-tolerated with no delayed CNS treatment–related toxicities. re-RT remains a reasonable option for patients with small volume of recurrence, methylated MGMT promoter status, and good KPS. re-RT should not be withheld on the basis of age as treatment remains safe and results in comparable outcomes. Future cooperative group studies should consider prospectively evaluating the neurocognitive, symptom burden and QOL benefit of salvage interventions in this patient population.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

NRG Oncology/RTOG1205: A Randomized Phase II Trial of Concurrent Bevacizumab and Reirradiation Versus Bevacizumab Alone as Treatment for Recurrent Glioblastoma

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APPENDIX

TABLE A1. Cox Proportional Hazards Model (full) for Overall Survival

Variable	HR (80% CI)	*P*
All patients (n = 170)		
Assigned treatment (BEV + RT *v* **BEV**)	—	.251
Sex (male *v* **female**)	1.15 (0.91 to 1.45)	.434
Age (50+ years *v* **< 5**0 years)	1.52 (1.14 to 2.03)	.063
KPS	3.93 (2.32 to 6.67)	< .001
60 *v* **90-100**		
70-80 *v* **90-100**	1.71 (1.33 to 2.19)	.006
Recent resection (yes *v* **no/biopsy**)	1.08 (0.84 to 1.39)	.692
Tumor area (continuous)	1.00 (1.00 to 1.00)	.054
Months from the initial RT end to on-study (continuous)	0.99 (0.99 to 1.00)	.179
No. of relapses	—	.249
Treatment × No. of relapses	—	.014
BEV + RT *v* BEV at 1 relapse	1.27 (0.97 to 1.65)	
BEV + RT *v* BEV at 2-3 relapses	0.40 (0.23 to 0.69)	
Patients with MGMT available (n = 81)		
Assigned treatment (BEV + RT *v* BEV)	—	.262
MGMT (unmethylated *v* methylated)	2.35 (1.53 to 3.63)	.011
KPS (60-80 *v* 90-100)	2.34 (1.64 to 3.32)	.002
Age (50+ years *v* < 50 years)	1.41 (0.95 to 2.11)	.270
Months from the initial RT end to on-study (continuous)	0.99 (0.97 to 1.00)	.196
No. of relapses	—	.649
Treatment × No. of relapses	—	.328
BEV + RT *v* BEV at 1 relapse	0.71 (0.48 to 1.05)	
BEV + RT *v* BEV at 2-3 relapses	1.37 (0.65 to 2.90)	

NOTE. Reference level is given in bold.
Abbreviations: BEV, bevacizumab; HR, hazard ratio; KPS, Karnofsky performance status.

TABLE A2. Best Objective Response Rate

Best Objective Response Rate	BEV (n = 78), No. (%)	BEV + RT (n = 77), No. (%)	Chi-Square *P*
Best response by Macdonald criteria			
CR/PR	16 (20.5)	23 (29.9)	.12
SD/PD/insufficient evaluation	62 (79.5)	54 (70.1)	
Best response by response assessment neuro-oncology (RANO) criteria			
CR/PR	14 (17.9)	22 (28.6)	.12
SD/PD/insufficient evaluation	64 (82.1)	55 (71.4)	

Abbreviations: BEV, bevacizumab; CR, complete response; PR, partial response; RT, radiation therapy; SD, stable disease.

TABLE A3. Distribution of Patients by Highest-Grade Adverse Events by System Organ Class For All Reported Adverse Events Without Regard to Attribution

	BEV (n = 76), No. of Patients by Grade (%)					BEV + RT (n = 83), No. of Patients by Grade (%)				
System Organ Class	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Overall highest grade	5 (6.6)	25 (32.9)	36 (47.4)	3 (3.9)	4 (5.3)	7 (8.4)	30 (36.1)	32 (38.6)	4 (4.8)	8 (9.6)
Blood and lymphatic system disorders	16 (21.1)	1 (1.3)	2 (2.6)	0 (0.0)	0 (0.0)	6 (7.2)	1 (1.2)	3 (3.6)	0 (0.0)	0 (0.0)
Cardiac disorders	3 (3.9)	3 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)	3 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	5 (6.6)	2 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.6)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Endocrine disorders	2 (2.6)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorders	11 (14.5)	4 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	15 (18.1)	1 (1.2)	1 (1.2)	0 (0.0)	0 (0.0)
GI disorders	24 (31.6)	11 (14.5)	5 (6.6)	0 (0.0)	0 (0.0)	25 (30.1)	12 (14.5)	5 (6.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	23 (30.3)	20 (26.3)	9 (11.8)	0 (0.0)	1 (1.3)	23 (27.7)	28 (33.7)	8 (9.6)	0 (0.0)	5 (6.0)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
Infections and infestations	2 (2.6)	8 (10.5)	6 (7.9)	2 (2.6)	0 (0.0)	3 (3.6)	15 (18.1)	7 (8.4)	2 (2.4)	1 (1.2)
Injury, poisoning, and procedural complications	8 (10.5)	3 (3.9)	1 (1.3)	0 (0.0)	0 (0.0)	6 (7.2)	7 (8.4)	1 (1.2)	0 (0.0)	0 (0.0)
Investigations	17 (22.4)	10 (13.2)	5 (6.6)	1 (1.3)	0 (0.0)	21 (25.3)	13 (15.7)	4 (4.8)	1 (1.2)	0 (0.0)
Metabolism and nutrition disorders	11 (14.5)	6 (7.9)	10 (13.2)	0 (0.0)	0 (0.0)	17 (20.5)	10 (12.0)	5 (6.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	14 (18.4)	12 (15.8)	13 (17.1)	0 (0.0)	0 (0.0)	16 (19.3)	14 (16.9)	8 (9.6)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Nervous system disorders	18 (23.7)	20 (26.3)	20 (26.3)	0 (0.0)	1 (1.3)	17 (20.5)	31 (37.3)	13 (15.7)	1 (1.2)	0 (0.0)
Psychiatric disorders	13 (17.1)	13 (17.1)	3 (3.9)	0 (0.0)	0 (0.0)	17 (20.5)	10 (12.0)	4 (4.8)	0 (0.0)	0 (0.0)
Renal and urinary disorders	14 (18.4)	12 (15.8)	2 (2.6)	0 (0.0)	0 (0.0)	14 (16.9)	11 (13.3)	3 (3.6)	0 (0.0)	0 (0.0)
Reproductive system and breast disorders	3 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	14 (18.4)	7 (9.2)	1 (1.3)	0 (0.0)	0 (0.0)	25 (30.1)	9 (10.8)	2 (2.4)	1 (1.2)	0 (0.0)
Skin and subcutaneous tissue disorders	16 (21.1)	3 (3.9)	1 (1.3)	0 (0.0)	0 (0.0)	18 (21.7)	6 (7.2)	1 (1.2)	0 (0.0)	0 (0.0)
Social circumstances	2 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Surgical and medical procedures	1 (1.3)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	4 (5.3)	20 (26.3)	16 (21.1)	2 (2.6)	0 (0.0)	8 (9.6)	17 (20.5)	10 (12.0)	0 (0.0)	1 (1.2)

NOTE. Adverse events were graded using Common Terminology Criteria for Adverse Events version 4.
Abbreviations: BEV, bevacizumab; RT, radiation therapy.

TABLE A4. Distribution of Patients by Highest-Grade Adverse Events By System Organ Class For All Reported Adverse Events Without Regard to Attribution For Commonly Reported Adverse Events

	BEV (n = 76), No.		BEV + RT (n = 83), No.	
System Organ Class	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Overall highest grade	73	43	81	44
Blood and lymphatic system disorders	19	2	10	3
Eye disorders	15	0	17	1
GI disorders	40	5	42	5
General disorders and administration site conditions	53	10	106	13
Infections and infestations	18	8	28	10
Investigations	33	6	39	5
Metabolism and nutrition disorders	27	10	32	5
Nervous system disorders	59	21	62	14
Psychiatric disorders	29	3	31	4
Respiratory, thoracic, and mediastinal disorders	22	1	37	3
Skin and subcutaneous tissue disorders	20	1	25	1
Vascular disorders	42	18	36	11

Abbreviations: BEV, bevacizumab; RT, radiation therapy.

TABLE A5. Distribution of Patients by Highest-Grade Adverse Events by System Organ Class Definitely, Probably, or Possibly Related to Protocol Treatment

	BEV (n = 76), No. of Patients by Grade (%)					BEV + RT (n = 83), No. of Patients by Grade (%)				
System Organ Class	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Overall highest grade	11 (14.5)	27 (35.5)	20 (26.3)	0 (0.0)	0 (0.0)	18 (21.7)	33 (39.8)	17 (20.5)	3 (3.6)	2 (2.4)
Blood and lymphatic system disorders	8 (10.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)	0 (0.0)	3 (3.6)	0 (0.0)	0 (0.0)
Cardiac disorders	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	3 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	2 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorders	0 (0.0)	2 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.6)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
GI disorders	9 (11.8)	4 (5.3)	1 (1.3)	0 (0.0)	0 (0.0)	13 (15.7)	7 (8.4)	2 (2.4)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	14 (18.4)	9 (11.8)	2 (2.6)	0 (0.0)	0 (0.0)	18 (21.7)	25 (30.1)	5 (6.0)	0 (0.0)	1 (1.2)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)
Infections and infestations	0 (0.0)	2 (2.6)	3 (3.9)	0 (0.0)	0 (0.0)	3 (3.6)	4 (4.8)	1 (1.2)	1 (1.2)	0 (0.0)
Injury, poisoning, and procedural complications	2 (2.6)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	3 (3.6)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	12 (15.8)	5 (6.6)	2 (2.6)	0 (0.0)	0 (0.0)	17 (20.5)	6 (7.2)	2 (2.4)	1 (1.2)	0 (0.0)
Metabolism and nutrition disorders	8 (10.5)	2 (2.6)	1 (1.3)	0 (0.0)	0 (0.0)	7 (8.4)	5 (6.0)	3 (3.6)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	8 (10.5)	4 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	8 (9.6)	4 (4.8)	1 (1.2)	0 (0.0)	0 (0.0)
Nervous system disorders	12 (15.8)	6 (7.9)	4 (5.3)	0 (0.0)	0 (0.0)	18 (21.7)	9 (10.8)	3 (3.6)	1 (1.2)	0 (0.0)
Psychiatric disorders	6 (7.9)	4 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	6 (7.2)	3 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)
Renal and urinary disorders	9 (11.8)	8 (10.5)	2 (2.6)	0 (0.0)	0 (0.0)	13 (15.7)	6 (7.2)	3 (3.6)	0 (0.0)	0 (0.0)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	5 (6.6)	2 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	10 (12.0)	3 (3.6)	1 (1.2)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	8 (10.5)	2 (2.6)	1 (1.3)	0 (0.0)	0 (0.0)	8 (9.6)	3 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	3 (3.9)	16 (21.1)	14 (18.4)	0 (0.0)	0 (0.0)	6 (7.2)	15 (18.1)	9 (10.8)	0 (0.0)	1 (1.2)

NOTE. Adverse events were graded using Common Terminology Criteria for Adverse Events version 4.
Abbreviations: BEV, bevacizumab; RT, radiation therapy.

TABLE A6. Chemotherapy Review

Chemotherapy Review	BEV (n = 84), No. (%)	BEV + RT (n = 86), No. (%)
BEV		
Overall review		
Per protocol	71 (84.5)	70 (81.4)
Acceptable variation	6 (7.1)	2 (2.3)
Unacceptable deviation	6 (7.1)	12 (14.0)
Not evaluable[a]	1 (1.2)	2 (2.3)
Dose		
85%-115%	56 (66.7)	59 (68.6)
< 85%, because of protocol-specified reasons	17 (20.2)	13 (15.1)
70% to < 85%, because of nonprotocol-specified reasons	1 (1.2)	2 (2.3)
< 70%, because of nonprotocol-specified reasons	7 (8.3)	10 (11.6)
> 115%	2 (2.4)	0 (0.0)
Not evaluable[a]	1 (1.2)	2 (2.3)
Treatment delays		
No delays	66 (78.6)	67 (77.9)
≤ 1 week	10 (11.9)	9 (10.5)
> 1 week, because of protocol-specified reasons	3 (3.6)	5 (5.8)
> 1- to ≤ 2-week delay, because of nonprotocol-specified reasons	4 (4.8)	0 (0.0)
> 2 weeks, because of nonprotocol-specified reasons	0 (0.0)	3 (3.5)
Not evaluable[a]	1 (1.2)	2 (2.3)

Abbreviations: BEV, bevacizumab; RT, radiation therapy

[a]Of the three not evaluable cases, two did not receive protocol treatment and one had incomplete data.

TABLE A7. Radiation Therapy Quality Review

Radiation Therapy Quality Review	Scenario 1[a] (n = 65), No. (%)	Scenario 2[b] (n = 16), No. (%)	Total (n = 81), No. (%)
Plan quality score			
Per protocol	54 (83.1)	14 (87.5)	68 (84.0)
Variation acceptable	5 (7.7)	2 (12.5)	7 (8.6)
Deviation unacceptable	6 (9.2)	0 (0.0)	6 (7.4)
Overall protocol score (plan quality + DVA)			
Per protocol	38 (58.5)	11 (68.8)	49 (60.5)
Variation acceptable	23 (35.4)	4 (25.0)	27 (33.3)
Deviation unacceptable	4 (6.2)	1 (6.3)	5 (6.2)

Abbreviation: DVA, dose volume analysis.

[a]Scenario 1: previous radiation to the local area including critical organs at risk.

[b]Scenario 2: no previous radiation to the local area or critical organs at risk.