Evaluation of Regorafenib in Newly Diagnosed and Recurrent Glioblastoma: GBM AGILE Phase II/III Bayesian Randomized Platform Trial

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ABSTRACT

PURPOSE GBM AGILE (ClinicalTrials.gov identifier: NCT03970447) is a phase II/III Bayesian adaptive platform registration trial testing multiple arms against a common control; the primary end point is overall survival (OS). Regorafenib, a multikinase inhibitor, showed OS benefit in recurrent (RD) glioblastoma in the phase II REGOMA trial and entered GBM AGILE as the first investigational arm.

METHODS Patient subtypes included in the regorafenib arm of GBM AGILE were newly diagnosed unmethylated (NDU) and RD glioblastoma. Prospective defined sets of subtypes, or arm signatures, were NDU, RD, and all (NDU + RD). As the first investigational arm in GBM AGILE, regorafenib was equally randomized to the control arm. Treatment in the control arm is temozolomide + radiotherapy (in newly diagnosed) or lomustine (in RD). Efficacy was assessed by OS hazard ratio (HR), arm/control, and demonstrated when the Bayesian probability of benefit (HR <1.00) was ≥98%. Analysis was performed monthly for limited efficacy, which occurs when the Bayesian predictive power is <25% for all signatures, and determines stopping enrollment. Follow-up continued for 12 months after accrual stopped.

RESULTS When the predictive power was <25% in all predefined signatures for regorafenib, accrual stopped for limited efficacy. The final analysis did not demonstrate OS improvement in the regorafenib arm in RD nor NDU glioblastoma. Median HRs were 1.05 (NDU), 1.07 (RD), and 1.07 (all) with final probabilities of benefit (HR <1.00) of 0.421 (NDU), 0.312 (RD), and 0.296 (all). Regorafenib was associated with increased toxicity relative to control.

CONCLUSION GBM AGILE did not show superiority of regorafenib over control in RD (lomustine) or NDU (temozolomide + radiotherapy) glioblastoma, yet caused increased toxicities. Regorafenib has been removed from National Comprehensive Cancer Network guidelines as a treatment option for RD.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

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INTRODUCTION

Glioblastoma accounts for most primary malignant brain tumors and carries a poor prognosis, with a 5-year survival rate of <7%.[1] Standard therapy is maximal safe surgical resection followed by radiotherapy with temozolomide chemotherapy. However, benefit from temozolomide is largely limited to patients with tumors with O^6-methylguanine DNA methyltransferase (*MGMT*) promoter methylation.[2] The use of tumor treating fields (TTF) for patients with newly diagnosed glioblastoma also improved overall survival (OS) in randomized phase III trials[2]; however, adoption of this therapy has been limited.[3,4] Relapse occurs in nearly all patients with glioblastoma, and outcomes after therapy in patients with recurrent disease are poor, with median OS of 6-10 months.[5]

Novel therapy development for glioblastoma has been historically slow and of limited success. Although glioblastoma is a highly vascularized tumor, previous trials with various

CONTEXT

Key Objective

To evaluate regorafenib in newly diagnosed and recurrent glioblastoma as the first investigational arm of the phase II/III Bayesian adaptive platform registration trial, GBM AGILE.

Knowledge Generated

GBM AGILE demonstrated that regorafenib did not improve overall survival compared with controls in recurrent (lomustine) or newly diagnosed (temozolomide + radiotherapy) glioblastoma. Additionally, regorafenib was associated with increased toxicity relative to control. The regorafenib arm, although failing to demonstrate superior efficacy, demonstrated the utility of the adaptive platform structure of GBM AGILE.

Relevance *(R.G. Maki)*

While a negative study, this study refuted use of regorafenib in primary therapy or recurrence of glioblastoma over existing standards of care. The ongoing nature of the novel trial design will hopefully allow for vetting of new agents or combinations more rapidly than individual trials.*

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

antiangiogenic drugs, such as bevacizumab, failed to demonstrate improvements in OS, although these therapies provided prolongation of progression-free survival (PFS) and preservation of neurologic function.[6,7]

Regorafenib is an oral small molecule inhibitor of multiple kinases.[8-10] In animal models of glioblastoma and other tumor types, regorafenib demonstrated antiangiogenic activity and inhibition of tumor growth, because of its dual targeted VEGFR2-TIE2 tyrosine kinase inhibition.[8,11-15]

In the phase II randomized trial, REGOMA,[16] OS was significantly longer with regorafenib than lomustine (median overall survival [mOS] 7.4 months [95% CI, 5.8 to 12.0], n = 59 *v* 5.6 months [4.7-7.3], hazard ratio [HR], 0.50 [95% CI, 0.33 to 0.75], n = 60; log-rank $P < .001$). As a result, regorafenib was listed in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines)[17] as a treatment option for recurrent glioblastoma. However, the efficacy of regorafenib has not been confirmed, and its toxicity can be significant. In addition, among other concerns,[18] the mOS for the lomustine control arm in REGOMA (5.6 months) was particularly poor relative to experience in other studies, in which mOS was consistently 7-10 months.[7,19,20] Thus, performing a sufficiently powered study to confirm or refute the potential benefit of regorafenib was needed to verify the REGOMA findings in recurrent disease and evaluate its efficacy in newly diagnosed glioblastoma.

Glioblastoma Adaptive, Global, Innovative Learning Environment (GBM AGILE) is a biomarker-based, multiarm, international, seamless phase II/III platform trial open to participants with newly diagnosed (ND) and recurrent (RD) glioblastoma.[21] The aim of the trial is to identify effective therapies for glioblastoma, matching these therapies with patient subtypes, with data generated to support regulatory filing for new drug applications.[21] Bayesian response adaptive randomization is used within patient subtypes of the disease to assign participants to investigational arms based on their performance. The primary end point is OS. Subtypes are prospectively identified patient subpopulations and are therapy-specific. Subtypes can include newly diagnosed methylated, newly diagnosed unmethylated (NDU), and recurrent (RD). A therapy with an enrichment biomarker also includes subtypes defined by that biomarker. Signatures are prospectively defined sets of patient subtypes that will be used to determine each investigational arm's indication. The trial is being conducted under a master protocol, allowing multiple investigational drugs/drug combinations to be evaluated simultaneously and/or over time.

Regorafenib entered GBM AGILE as the first investigational arm in June 2019, in which it was evaluated for efficacy and safety in newly diagnosed participants with *MGMT* promoter unmethylated glioblastoma, as well as participants with recurrent disease. We report the results of this investigational arm.

METHODS

Study Design

GBM AGILE is an ongoing, international, multicenter, adaptively randomized platform trial[21,22] designed to evaluate multiple investigational drugs concurrently against a common internal control. A master protocol[23] governs general conduct, overarching eligibility criteria, and statistical considerations. Each arm has its own arm-specific appendix to the master protocol, allowing for arm-specific

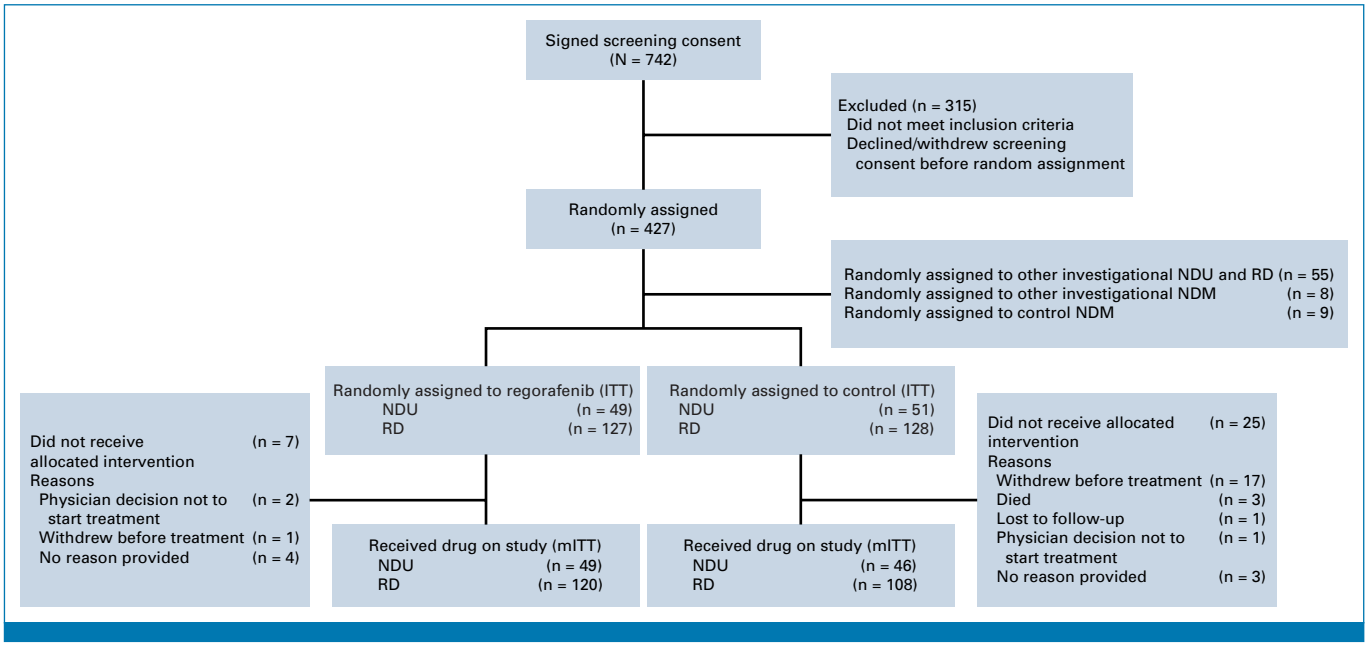


FIG 1. CONSORT diagram. ITT, intention-to-treat; mITT, modified ITT; NDM, newly diagnosed methylated; NDU, newly diagnosed unmethylated; RD, recurrent.

customizations that override the master protocol requirements. These customizations may include more (but not less) restrictive eligibility requirements, additional secondary and exploratory objectives, and arm-specific statistical considerations and sample sizes.

Per the GBM AGILE master protocol, the evaluation of each investigational arm proceeds in two possible stages. An investigational arm's stage 1 is an adaptively randomized screening stage for evaluating the arm within patient signatures compared against a common control arm. For an arm continuing to stage 2, there is a fixed randomization expansion cohort in the signature that has met the Bayesian predictive power of >80%.

The primary analysis of a regimen's effect on OS uses all patients in both its stages and all control patients in the trial in the signature continuing to stage 2, suitably adjusted for any possible time trends,[24] for investigational arms entering GBM AGILE after the first arm (regorafenib).

Participants

Participants in this study were randomly assigned at 38 centers in the United States and Canada. Key eligibility criteria were age 18 years and older at glioblastoma diagnosis (WHO 2016), no known isocitrate dehydrogenase mutation, either newly diagnosed *MGMT* unmethylated glioblastoma (NDU) or first/second recurrence of glioblastoma (RD), Karnofsky performance status ≥60% (ND) or 70 (RD), normal end-organ function, and no more than 4 mg of dexamethasone (or equivalent) per day within 5 days before random assignment. The full list of inclusion and exclusion criteria are included in Appendix Tables A1 and A2 (online only). The two stratification factors for random assignment in GBM AGILE are (1) clinical presentation as either ND or recurrent tumors, and (2) *MGMT* promoter methylation status for ND participants. Patients with *MGMT*-methylated glioblastoma were not eligible for the regorafenib arm because phase I data examining regorafenib in combination with temozolomide in this patient population were not available at the time the arm entered GBM AGILE.

The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines, and all participating clinical sites were approved for participation by their institutional review boards. Participants consented to study participation; details may be found in the Appendix 1. This trial is registered with ClinicalTrials.gov (identifier: NCT03970447), and is ongoing, as additional investigational arms are being evaluated.

Random Assignment and Treatment

Regorafenib entered GBM AGILE as the first investigational arm and was equally randomized against control to support the development of a robust control arm. Further description of randomization and screening procedures are described in the Appendix 1. Details regarding the intention-to-treat (ITT) and modified ITT (mITT) subsets are provided in the CONSORT diagram (Fig 1).

All NDU participants received concurrent temozolomide (75 mg/m^2) and radiation therapy (60 Gy/30 fractions). NDU participants randomly assigned to the control arm started maintenance temozolomide (150-200 mg/m^2) 2-6 weeks

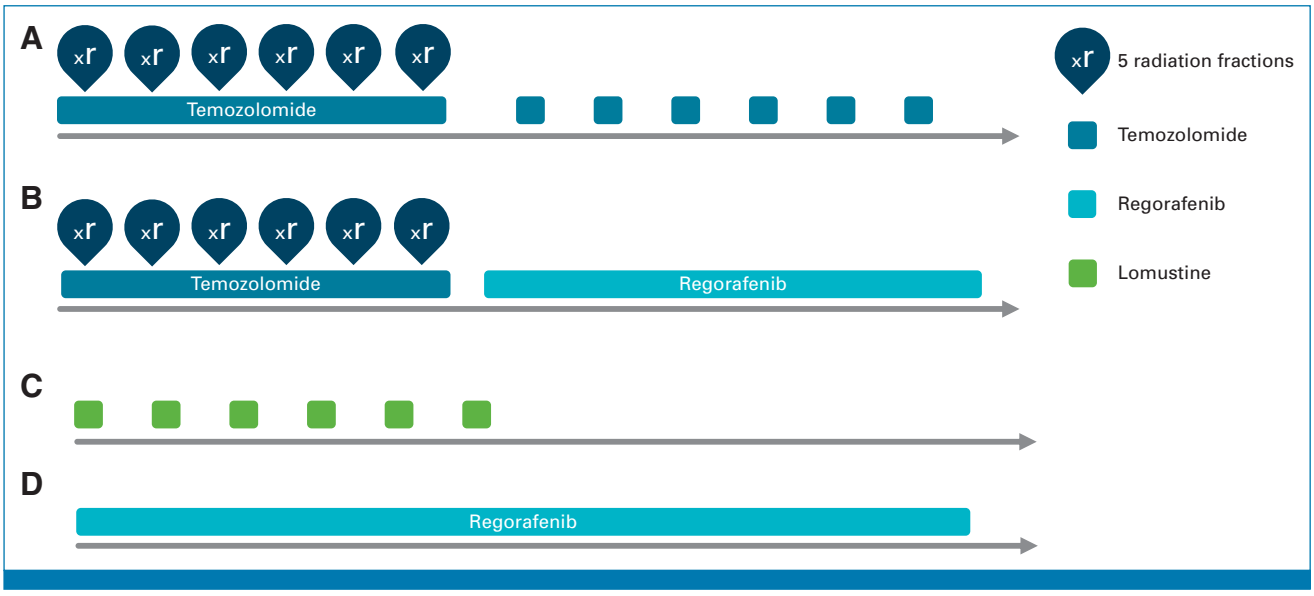


FIG 2. Regorafenib treatment schema. Random assignment of participants to either the control or regorafenib arm occurred before initiation of radiation therapy. All NDU participants received concurrent temozolomide (75 mg/m^2) and radiation therapy (60 Gy/30 fractions). (A) Control arm NDU participants started maintenance temozolomide (150-200 mg/m^2) 2-6 weeks after completing concurrent chemoradiation and continued for six cycles or until unacceptable toxicity or PD. (B) NDU participants randomly assigned to the regorafenib arm started regorafenib at 160 mg per day (1-21/28) starting 4-6 weeks after completing concurrent chemoradiotherapy. RD participants received either (C) lomustine at 110 mg/m^2 on day 1 of a planned 42-day cycle for up to six cycles (control arm) or (D) regorafenib at 160 mg per day (1-21/28). NDU, newly diagnosed unmethylated; PD, progressive disease; RD, recurrent.

after completing concurrent chemoradiation and continued for six cycles (28 days each) or until unacceptable toxicity or progressive disease (PD) based on modified Response Assessment in Neuro-Oncology (mRANO)[25] (Fig 2). NDU participants randomly assigned to regorafenib started regorafenib (Bayer Pharma AG, Leverkusen, Germany), at 160 mg per day (1-21/28) starting 4-6 weeks after completing concurrent chemoradiotherapy (Fig 2) until PD, unacceptable toxicity, or withdrawal. Participants in this arm did not receive adjuvant temozolomide.

RD participants received either lomustine at 110 mg/m^2, or as per institutional or country standard, on day one of a planned 42-day cycle for up to six cycles or regorafenib at 160 mg per day (1-21/28; Fig 2). Additional details regarding treatment and dose reductions are described in Appendix 1.

Outcomes

The primary end point in GBM AGILE is OS, defined as the time from random assignment until death from any cause, and the primary analysis of OS is ITT. Secondary end points include PFS, tumor response, and duration of response.

Statistical Analysis

The statistical considerations for the GBM AGILE master protocol are described in detail elsewhere.[21] The control arm in GBM AGILE is designed to have a randomization probability of 0.2 when there are two or more investigational arms in the trial enrolling in the same subtype, with the remainder of participants being randomly assigned to one of the available investigational arms. Investigational arms with low Bayesian predictive power and at least 50 participants enrolled to them can be stopped for limited efficacy, whereas investigational arms that have been assigned to at least 100 participants overall, and have a sufficiently high predictive power, seamlessly continue to stage 2.[21] Monthly evaluations are conducted by the Statistical Analysis and Monitoring Committee to monitor for stopping or continuation to stage 2. Efficacy in GBM AGILE is assessed by OS HR, arm/control. If the Bayesian predictive power for success in a future phase III trial is >80% for any predefined signature for an investigational arm, the arm continues to stage 2 for that signature. An arm in stage 1 will stop accruing patients if it reaches its maximal protocol-specified, predefined sample size, does not meet a predefined minimum threshold for continuing enrollment (a Bayesian PP <25% for all signatures, labeled limited efficacy), or evinces inadequate safety. In stage 2, randomization is fixed in only the signature that continues to this stage for an additional 50 participants on the investigational arm, to confirm the findings from stage 1 and the totality of data from stage 1 and stage 2 support drug approval.[21] Follow-up continues for 12 months after the last participant was randomly assigned to the investigational arm. Participants still alive or lost to follow-up are right-censored for OS.

An arm-specific appendix of the master protocol may include arm-specific customizations, which supersede the master protocol. Customization for the regorafenib arm is described in Appendix 1.

The primary analysis for the regorafenib arm includes all participants randomly assigned to either the regorafenib or control arm (ITT), with a secondary analysis performed on the mITT (excluding participants who did not receive any drug on study). The primary analysis was performed using R version 4.3.2.

A secondary analysis included PFS, which is described in Appendix 1.

RESULTS

Enrollment began July 31, 2019, and the last participant assigned to the regorafenib arm was randomly assigned on August 18, 2021. The final ITT sample sizes were 176 (49 NDU and 127 RD) participants randomly assigned to regorafenib and evaluable for the primary end point, and 179 (51 NDU and 128 RD) participants randomly assigned to the control arm (Fig 1). Baseline characteristics were generally well matched between the regorafenib arm and control arm for both NDU and RD participants (Table 1). An exception to this was the greater proportion of female participants in the regorafenib arm (53%) compared with control (27%; NDU only). The demographics of the participants in this study generally reflect glioblastoma patient demographics in national registries.

Regorafenib became eligible for stopping for limited efficacy or continuation to stage 2 at the June 2021 monthly interim evaluation. At the August 2021 evaluation, the predictive power for regorafenib in all three predefined signatures (NDU, RD, and all) was <0.25 (0.138 [NDU], 0.030 [RD], and 0.026 [all participants]). At this time, the algorithm stopped enrollment on the regorafenib arm for limited efficacy (Appendix Table A3 and Fig A1).

At the clinical cutoff date for final analysis (12 months after the last participant was randomly assigned to the regorafenib arm), similar levels of exposure (length of follow-up time) and number of deaths were observed between the regorafenib and control arms (Table 2). The final analysis did not show improvement in OS in the regorafenib arm compared with control with final probabilities of superiority (HR <1.00), which were all less than the prespecified significance threshold of 0.98 (Table 2). The Bayesian-modeled (smooth line in Appendix Figs A2 and A3) mOS was similar between the regorafenib and control arms for NDU (14.28 [95% credible internal (CI), 12.48 to 16.72] *v* 14.56 [95% CI, 12.69 to 17.14] months, HR, 1.05 [95% CI, 0.67 to 1.63]) and for the RD subtype (9.20 [95% CI, 7.91 to 10.92] *v* 9.69 [95% CI, 8.34 to 11.46] months, HR, 1.07 [95% CI, 0.81 to 1.42]; Fig 3 and Appendix Figs A2 and A3).The Bayesian posterior distributions, representing the range of likely HR by signature (NDU, RD, and all participants), demonstrate that the probability of superiority was <0.98 in all signatures (Appendix Fig A4).

A total of 25 participants randomly assigned to the control arm and seven participants randomly assigned to the regorafenib arm did not receive any treatment on study (Appendix Table A4). The mITT analysis was consistent with the intention-to-treat analysis and did not show an improvement in OS for participants on the regorafenib arm compared with control (Appendix Table A5). PFS was evaluated as a secondary end point in the mITT analysis set and is described in Appendix Table A6 and Fig A5.

The safety analysis included all randomly assigned patients who initiated study treatment. Patients were analyzed based on the actual treatment received. There were no new safety signals observed with regorafenib. The total frequency of treatment-related treatment emergent adverse events (TEAEs) by grade is shown in Table 3. The safety analysis subset for the regorafenib arm includes any participants who received at least one dose of regorafenib. Within the RD subtype, the total frequencies of grade 3/4 TEAEs in the regorafenib arm were 45%, compared with 32% in the control arm; whereas in the NDU subtype, the frequency was 74% in regorafenib compared with 30% in control (Table 3). The most common TEAEs (of any grade) on the regorafenib arm in NDU were fatigue, nausea, constipation, headache, and hypertension. Fatigue, headache, hypertension, increased ALT, and palmar-plantar erythrodysesthesia were the most common TEAEs in RD.

TEAEs leading to dose reduction occurred in 40% of regorafenib NDU participants, but only 4% of NDU participants on the control arm (Table 3). The frequency of TEAEs leading to dose reduction was <10% different between RD regorafenib participants (23%) and RD control participants (22%). The frequency of TEAEs leading to study drug discontinuation was numerically higher in NDU participants receiving regorafenib (26%) compared with control (8%), whereas frequencies were 18% in the regorafenib and 12% in control subsets of RD participants. There were two deaths attributed to TEAEs in the regorafenib NDU participants, three in the regorafenib RD participants, and one participant in the RD control subset (Table 3). None of the deaths were considered related to study treatment by the investigator.

DISCUSSION

In contrast to the REGOMA trial,[16] in which participants with recurrent glioblastoma exhibited a survival benefit with regorafenib, compared with controls, the regorafenib arm in GBM AGILE did not demonstrate an OS or PFS benefit in participants with RD glioblastoma. For participants with RD, adjusted mOS was 9.2 months with regorafenib, not significantly different than control (9.7 months). Notably, the adjusted mOS for RD control arm participants in GBM AGILE was similar to other trials in RD and markedly higher than

TABLE 1. Participant Demographics and Baseline Clinical Characteristics

Demographic and Clinical Characteristic	Newly Diagnosed Unmethylated		Recurrent Disease	
	Regorafenib (n = 49)	Control (n = 51)	Regorafenib (n = 127)	Control (n = 128)
Age, years				
Median	59	58	61	60
Min, max	22, 81	23, 74	32, 82	24, 93
Age, years, subgroups, No. (%)				
<65	31 (63)	37 (73)	81 (64)	83 (65)
≥65	18 (37)	14 (27)	46 (36)	45 (35)
Sex, No. (%)				
Male	23 (47)	37 (73)	80 (63)	79 (62)
Female	26 (53)	14 (27)	46 (37)	49 (38)
Race, No. (%)				
White	47 (96)	48 (94)	121 (95)	120 (94)
Black or African American	1 (2)	2 (4)	1 (1)	5 (4)
Native Hawaiian/Other Pacific Islander	0 (0)	0 (0)	0 (0)	0 (0)
Asian	0 (0)	0 (0)	1 (1)	2 (2)
American Indian/Alaskan Native	0 (0)	0 (0)	0 (0)	0 (0)
Other	0 (0)	0 (0)	1 (1)	0 (0)
Not reported	1 (2)	1 (2)	3 (2)	1 (1)
Ethnicity, No. (%)				
Hispanic or Latino	3 (6)	7 (14)	14 (11)	8 (6)
Not Hispanic or Latino	44 (90)	42 (82)	106 (83)	115 (90)
Not reported	2 (4)	2 (4)	7 (6)	5 (4)
Baseline Karnofsky status,[a] No. (%)				
100	9 (18)	8 (16)	9 (7)	10 (8)
90	16 (33)	23 (45)	50 (40)	37 (29)
80	14 (29)	12 (24)	35 (28)	40 (31)
70	9 (18)	2 (4)	25 (20)	21 (16)
60	0 (0)	1 (2)	0 (0)	0 (0)
Participants with any baseline glucocorticoid/steroid use,[b] No. (%)	15 (31)	21 (41)	55 (44)	56 (44)
Participants with any post-treatment glucocorticoid/steroid use,[c] No. (%)	36 (73)	30 (59)	74 (59)	72 (56)
Tumor location at screening, No. (%)				
Parietal lobe	7 (14)	12 (24)	28 (22)	33 (26)
Occipital lobe	3 (6)	6 (12)	5 (4)	3 (2)
Cerebellum	0 (0)	1 (2)	0 (0)	2 (2)
Temporal lobe	18 (37)	11 (22)	45 (35)	39 (30)
Frontal lobe	12 (24)	18 (35)	30 (24)	34 (27)
Brainstem	0 (0)	0 (0)	0 (0)	0 (0)
Other	9 (18)	3 (6)	19 (15)	17 (13)
Treatment at diagnosis, No. (%)				
RT alone	—	—	2 (2)	2 (2)
Induction chemotherapy followed by concurrent chemoradiotherapy	—	—	2 (2)	8 (6)
Concurrent chemoradiotherapy followed by maintenance chemotherapy	—	—	101 (80)	101 (79)
Concurrent chemotherapy/RT alone	—	—	12 (9)	7 (5)
Chemotherapy alone (induction/sequential chemotherapy)	—	—	1 (1)	0 (0)
Other	—	—	9 (7)	10 (8)
Baseline surgery, No. (%)				
Biopsy	8 (16)	2 (4)	—	—
Partial resection	7 (14)	5 (10)	—	—

(continued on following page)

TABLE 1. Participant Demographics and Baseline Clinical Characteristics (continued)

Demographic and Clinical Characteristic	Newly Diagnosed Unmethylated		Recurrent Disease	
	Regorafenib (n = 49)	Control (n = 51)	Regorafenib (n = 127)	Control (n = 128)
Total resection	28 (57)	33 (65)	–	–
Other	5 (10)	9 (18)	–	–
Missing data	1 (2)	2 (4)	–	–

Abbreviation: RT, radiotherapy.
[a]Baseline is defined as the last assessment collected prior to the first dose of study drug.
[b]Baseline glucocorticoid/steroid use is defined as any use within 5 days prior to random assignment. Eligibility criteria included that steroid dose had to be ≤4 mg dexamethasone once daily for this time period.
[c]Post-treatment glucocorticoid/steroid use is defined as any use after the first dose of study drug.

the OS for REGOMA control group participants (5.6 months), suggesting there may be inherent differences in the clinical characteristics of the participants in GBM AGILE compared with those in REGOMA.[16,26,27] One of these may be differences in restrictions around steroid use by participants in GBM AGILE compared with those in REGOMA, with REGOMA allowing for higher doses of steroids, suggesting the potential for a clinically worse population. Importantly, the two study arms in REGOMA showed imbalances of age, steroid use, *MGMT* status, and time to first progression, all favoring the regorafenib arm. An alternative interpretation is that the GBM AGILE control arm overperformed compared with the REGOMA control arm; however, the GBM AGILE control arm results were much more consistent with historical data[5] than REGOMA.[16]

In addition, GBM AGILE also evaluated regorafenib in NDU participants where it similarly did not show a benefit over control, either in OS or PFS. The adjusted mOS for NDU participants on the regorafenib arm was 14.3 months, consistent with historic controls and not significantly different than the internal control arm (14.6 months).

Although the results for the regorafenib arm in GBM AGILE did not confirm the therapeutic benefit reported in REGOMA, the arm affirmed the efficiencies of the adaptive platform design and the utility of Bayesian predictive quantities. The trial accurately predicted a low probability of success after 172 participants had been randomly assigned to the regorafenib arm, rather than the protocol maximum of 275, which triggered a stop to random assignment to regorafenib at a preplanned monthly evaluation. The low predictive probabilities at the interim analysis were confirmed at the final analysis, which did not show benefit of regorafenib after a significant increase in follow-up time.

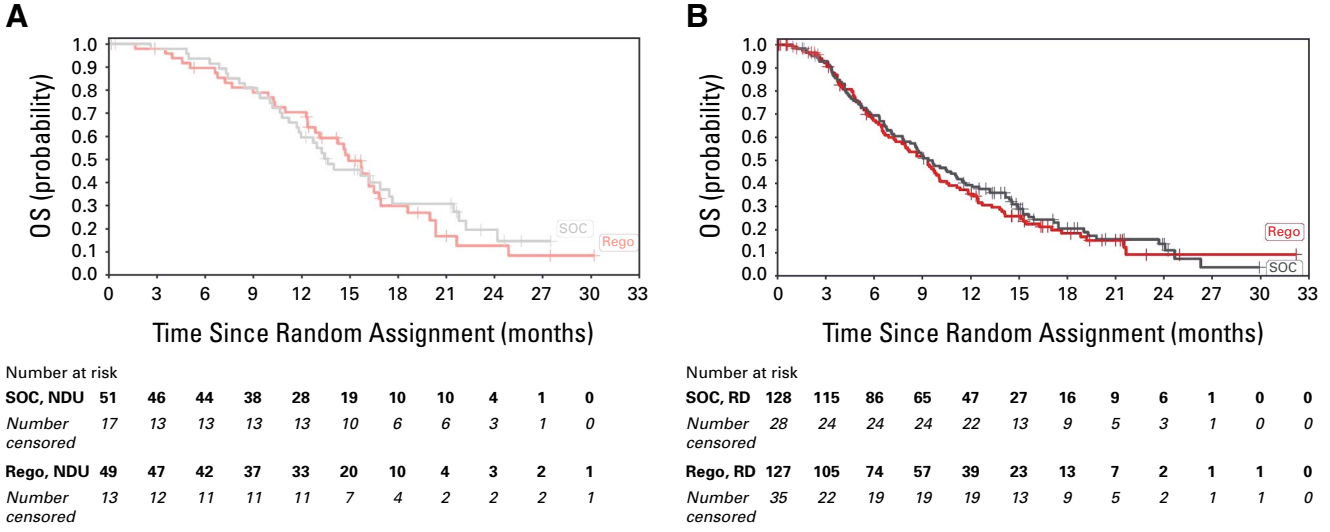
GBM AGILE evaluated the efficacy of regorafenib in both RD and NDU participants. The trial completed accrual (stopped for limited efficacy) on the regorafenib arm (n = 176 for RD and NDU participants combined) and accompanying control arm (n = 179 for RD and NDU combined) in approximately 25 months. A shared control arm further reduces the number of participants needed for evaluation of incoming arms and contributes to efficiency. In comparison two recent trials evaluating the efficacy of PD-1 blockade in glioblastoma, CheckMate 143 and CheckMate 498, enrolled 369 participants with RD only and 560 participants with NDU only, respectively.[28,29]

The safety profile of regorafenib was as expected, with no new safety signals observed. The total frequency of grade 3/4 TEAEs was greater in the regorafenib arm compared with the control arm for ND participants, although there was a smaller difference in frequency of events between regorafenib and control in the RD participants, likely because of the much shorter exposure to study drug in the RD arms. A larger number of participants on the regorafenib arm discontinued treatment or had a dose reduction due to a treatment-related TEAE compared with the control arm.

TABLE 2. Final Analysis

Signature	Sample Size (regorafenib/control), No.	Median HR[a] (95% CI)	Pr (HR <1)	PP	Exposure (months, regorafenib/control)	Deaths (regorafenib/control), No.
NDU	49/51	1.05 (0.67 to 1.63)	0.421	0.102	664.7/663.1	36/34
RD	127/128	1.07 (0.81 to 1.42)	0.312	0.038	1,134.2/1,301.7	92/100
All	176/179	1.07 (0.84 to 1.36)	0.296	0.031	–	–

Abbreviations: CI, credibility interval; HR, hazard ratio; NDU, newly diagnosed unmethylated; PP, predictive power; Pr (HR <1), probability of benefit; RD, recurrent.
[a]Median HR (95% CI) is calculated as the 50% (2.5% to 97.5%) of the Bayesian posterior distribution for the HR. Pr (HR <1) is the area of the posterior distribution of the HR that is <1—see Appendix Figure A4.



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Subtype	Arm	Median OS,[a] Months	Hazard Ratio (>1 favors control)
NDU	Rego	14.28	1.05
NDU	Control	14.56	
RD	Rego	9.20	1.07
RD	Control	9.69	

FIG 3. Final OS of participants with (A) NDU and (B) RD glioblastoma randomly assigned to regorafenib or control arms, shown according to subtype. (C) Kaplan-Meier OS results (in months), with median based on Bayesian modeling (protocol analysis of primary end point) given in the associated table. [a]Medians for OS are based on the Bayesian model, rather than the KM curves. NDU, newly diagnosed unmethylated; OS, overall survival; RD, recurrent; Rego, regorafenib; SOC, standard of care (control).

The lack of subset analyses defined by molecular biomarkers to examine potential benefit may be a limitation of GBM AGILE. Other glioblastoma studies[30,31] suggest potential for improved benefit in a biomarker-driven data set, such as *MGMT* methylation as a predictor of OS in RD participants. Methylation status in RD participants was not evaluated in

TABLE 3. Treatment-Related TEAEs

Treatment-Related TEAE	Regorafenib NDU (n = 42), No. (%)	Control NDU (n = 53), No. (%)	Regorafenib RD (n = 120), No. (%)	Control RD (n = 108), No. (%)
Participants with any TEAE (%)	40 (95)	46 (87)	104 (87)	78 (72)
Grade 1	1 (2)	16 (30)	13 (11)	12 (11)
Grade 2	8 (19)	14 (26)	37 (31)	32 (30)
Grade 3	26 (62)	14 (26)	48 (40)	28 (26)
Grade 4	5 (12)	2 (4)	6 (5)	6 (6)
Grade 5	0 (0)	0 (0)	0 (0)	0 (0)
Participants with any treatment-related serious TEAE (%)	7 (17)	6 (11)	15 (13)	5 (5)
TEAEs leading to any study drug discontinuation	11 (26)	4 (8)	22 (18)	13 (12)
TEAEs leading to dose interruption	29 (69)	17 (32)	59 (49)	18 (17)
TEAEs leading to dose reduction	17 (40)	2 (4)	27 (23)	24 (22)
TEAEs leading to death	2 (5)	0 (0)	3 (3)	1 (1)

Abbreviations: NDU, newly diagnosed unmethylated; RD, recurrent; TEAE, treatment-emergent adverse event.

GBM AGILE. Although imbalances in methylated *MGMT* in the RD participants in GBM AGILE could explain the benefit seen in the control arm, this seems unlikely, given the relatively large sample size. In GBM AGILE, most baseline characteristics were balanced between the regorafenib and control arms, in both NDU and RD participants. Sex of participants was also balanced in RD; however, in NDU, the control arm included a higher relative frequency of male participants (73%), compared with the regorafenib arm, in which male (47%)/female (53%) participants were more evenly distributed. Given the likelihood of longer OS and better outcomes in female participants,[32,33] the distribution would have been unlikely to weaken performance of the regorafenib arm. There may also be additional biomarkers associated with response to regorafenib, but these were not investigated in the current trial. Additional limitations may include the lack of central pathology/imaging review, a complex statistical design, and the use of a glioblastoma definition for inclusion that excluded glioblastoma patients defined based on the 2021 WHO update. Another potential limitation is that regorafenib was given as a single agent (throughout the treatment period for RD participants and in maintenance for ND participants) rather than in combination with the standard of care. However, it is unclear if this combination would be tolerable, and this evaluation was outside the scope of the current study. Finally, there is a potential limitation in the current study regarding the disparity in the number of participants who were randomly assigned to the control arm (ITT) and the number who received the assigned intervention (mITT). This difference is largely accounted for by a greater frequency of participants who withdrew from the trial after random assignment to the control arm. Additionally, results of the mITT subset analyses were consistent with the ITT analyses. These results suggest that the ITT analyses were representative of the participant population, despite these differences in the ITT and mITT participant numbers.

In conclusion, GBM AGILE did not show superiority of regorafenib over control in RD (lomustine) or NDU (temozolomide + radiotherapy) glioblastoma, yet caused increased toxicities. As a result of the failure to confirm the results of the smaller REGOMA trial, regorafenib has been removed from the NCCN guidelines[34] as a treatment option for recurrent disease. Efficiencies of the trial design included the use of a shared control arm with both concurrently randomized and time-adjusted controls, a fluid infrastructure for adding, evaluating, and concluding additional investigational arms, and the ability to use data as they accumulate. The regorafenib arm, although failing to demonstrate superior efficacy, demonstrated the utility of the adaptive platform structure of GBM AGILE. Stopping random assignment early based on the Bayesian predictive quantities reduced decision-making time and costs compared with a traditional large, fixed sample size clinical trial. The trial continues to assess other therapies efficiently, including using concurrent and previously accrued controls.

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REFERENCES

1. Ostrom QT, Price M, Neff C, et al: CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2016-2020. Neuro Oncol 25:iv1-iv99, 2023
2. Stupp R, Taillibert S, Kanner AA, et al: Maintenance therapy with tumor-treating fields plus temozolomide vs temozolomide alone for glioblastoma: A randomized clinical trial. JAMA 314: 2535-2543, 2015
3. Crompton DJ, Kern S, Bogan A, et al: Tumor treating fields utilization and efficacy for glioblastoma at a large multicenter academic practice. J Clin Neurosci 138:111395, 2025
4. Lassman AB, Polley MC, Iwamoto FM, et al: Dual immune check point blockade in MGMT-unmethylated newly diagnosed glioblastoma: NRG Oncology BN007, a randomized phase II/III clinical trial. J Clin Oncol 43:3032-3040, 2025
5. Wen PY, Weller M, Lee EQ, et al: Glioblastoma in adults: A Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions. Neuro Oncol 22:1073-1113, 2020
6. Lombardi G, Pambuku A, Bellu L, et al: Effectiveness of antiangiogenic drugs in glioblastoma patients: A systematic review and meta-analysis of randomized clinical trials. Crit Rev Oncol Hematol 111:94-102, 2017
7. Wick W, Gorlia T, Bendszus M, et al: Lomustine and bevacizumab in progressive glioblastoma. N Engl J Med 377:1954-1963, 2017
8. Wilhelm SM, Dumas J, Adnane L, et al: Regorafenib (BAY 73-4506): A new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int J Cancer 129:245-255, 2011
9. Zopf D, Fichtner I, Bhargava A, et al: Pharmacologic activity and pharmacokinetics of metabolites of regorafenib in preclinical models. Cancer Med 5:3176-3185, 2016
10. Mongiardi MP, Pallini R, D'Alessandris QG, et al: Regorafenib and glioblastoma: A literature review of preclinical studies, molecular mechanisms and clinical effectiveness. Expert Rev Mol Med 26: e5, 2024
11. Daudigeos-Dubus E, Le Dret L, Lanvers-Kaminsky C, et al: Regorafenib: Antitumor activity upon mono and combination therapy in preclinical pediatric malignancy models. PLoS One 10:e0142612, 2015
12. Van Looy T, Gebreyohannes YK, Wozniak A, et al: Characterization and assessment of the sensitivity and resistance of a newly established human gastrointestinal stromal tumour xenograft model to treatment with tyrosine kinase inhibitors. Clin Sarcoma Res 4:10, 2014
13. Schmieder R, Hoffmann J, Becker M, et al: Regorafenib (BAY 73-4506): Antitumor and antimetastatic activities in preclinical models of colorectal cancer. Int J Cancer 135:1487-1496, 2014
14. Huynh H, Ong R, Zopf D: Antitumor activity of the multikinase inhibitor regorafenib in patient-derived xenograft models of gastric cancer. J Exp Clin Cancer Res 34:132, 2015
15. Takigawa H, Kitadai Y, Shinagawa K, et al: Multikinase inhibitor regorafenib inhibits the growth and metastasis of colon cancer with abundant stroma. Cancer Sci 107:601-608, 2016
16. Lombardi G, De Salvo GL, Brandes AA, et al: Regorafenib compared with lomustine in patients with relapsed glioblastoma (REGOMA): A multicentre, open-label, randomised, controlled, phase 2 trial. Lancet Oncol 20:110-119, 2019

17. NCCN: Clinical Practice Guidelines in Oncology (NCCN Guidelines). 2024. https://www.nccn.org
18. Stupp R: Drug development for glioma: Are we repeating the same mistakes? Lancet Oncol 20:10-12, 2019
19. Wick W, Puduvalli VK, Chamberlain MC, et al: Phase III study of enzastaurin compared with lomustine in the treatment of recurrent intracranial glioblastoma. J Clin Oncol 28:1168-1174, 2010
20. Batchelor TT, Mulholland P, Neyns B, et al: Phase III randomized trial comparing the efficacy of cediranib as monotherapy, and in combination with lomustine, versus lomustine alone in patients with recurrent glioblastoma. J Clin Oncol 31:3212-3218, 2013
21. Alexander BM, Ba S, Berger MS, et al: Adaptive global innovative learning environment for glioblastoma: GBM AGILE. Clin Cancer Res 24:737-743, 2018
22. Berry DA: Adaptive clinical trials in oncology. Nat Rev Clin Oncol 9:199-207, 2011
23. Woodcock J, LaVange LM: Master protocols to study multiple therapies, multiple diseases, or both. N Engl J Med 377:62-70, 2017
24. Saville BR, Berry DA, Berry NS, et al: The Bayesian time machine: Accounting for temporal drift in multi-arm platform trials. Clin Trials 19:490-501, 2022
25. Ellingson BM, Wen PY, Cloughesy TF: Modified criteria for radiographic response assessment in glioblastoma clinical trials. Neurotherapeutics 14:307-320, 2017
26. 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
27. Chinot OL, Wick W, Mason W, et al: Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med 370:709-722, 2014
28. 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
29. 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
30. Caccese M, Desideri I, Villani V, et al: REGOMA-OSS: A large, Italian, multicenter, prospective, observational study evaluating the efficacy and safety of regorafenib in patients with recurrent glioblastoma. ESMO Open 9:102943, 2024
31. Taal W, Oosterkamp HM, Walenkamp AM, et al: Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): A randomised controlled phase 2 trial. Lancet Oncol 15:943-953, 2014
32. Carrano A, Juarez JJ, Incontri D, et al: Sex-specific differences in glioblastoma. Cells 10:1783, 2021
33. Massey SC, Whitmire P, Doyle TE, et al: Sex differences in health and disease: A review of biological sex differences relevant to cancer with a spotlight on glioma. Cancer Lett 498:178-187, 2021
34. NCCN: NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers. 2025. https://www.nccn.org

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Evaluation of Regorafenib in Newly Diagnosed and Recurrent Glioblastoma: GBM AGILE Phase II/III Bayesian Randomized Platform Trial

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No other potential conflicts of interest were reported.

APPENDIX 1. METHODS AND RESULTS

Consent and Approval of the Study

Participants underwent a two-step consenting process that included a screening consent first, describing the trial and all the required pretreatment tests and procedures that they would undergo up through random assignment to one of the available investigational arms or the control arm. Participants who completed screening and were randomly assigned were provided with the appropriate arm-specific treatment consent form based on their randomization assignment.

The protocol, protocol amendments, informed consent form, investigator brochure, and other relevant documents were submitted to an institutional review board (IRB)/independent ethics committee (IEC)/ethics committee (EC)/research ethics board (REB) by the sponsor and reviewed and approved by the IRB/IEC/EC/REB before the study was initiated. At both steps of the consenting process, participants were required to sign a statement of informed consent that met the requirements of the IRB/IEC/EC/REB. GBM AGILE's data safety monitoring board meets quarterly and reviews safety considerations regularly.

Randomization and Masking

As the first investigational arm in GBM AGILE, regorafenib was equally randomized to control. When additional investigational arms entered the trial, adaptive randomization was initiated, but the 1:1 random assignment (regorafenib: control) continued. GBM AGILE includes an intention-to-treat (ITT) analysis, and thus, all participants who are randomly assigned are included in the final analysis for the arm to which they were randomly assigned, regardless of whether they received the assigned treatment. The regorafenib arm was initially designed as a modified ITT (mITT, all participants who initiated treatment) analysis; however, this was updated in both the protocol and statistical analysis plan to ITT before conclusion of the enrollment of the investigational arm.

GBM AGILE participants are centrally assigned/randomly assigned to the investigational intervention using an interactive voice/web response system (IxRS). The participant randomization list is generated by Almac Clinical Technologies and is loaded into the IxRS for arm/treatment assignment. Randomization numbers are scrambled to mask the block sizes. The Statistical Analysis and Monitoring Committee (SAMC) regularly updates randomization probabilities after monthly interim analyses and uploads the new probability files to the ALMAC team; the files are then automatically pulled into the IxRS.

GBM AGILE is an open-label study. However, the status of an arm (eg, continuing to stage 2, limited efficacy, maximum enrollment) is confidential information and is not known to the study participants, treating investigators, or masked (blinded) sponsor personnel until a public announcement is made. This blinding in GBM AGILE is maintained, at minimum, until the clinical cutoff date (12 months after the last participant has been enrolled onto an arm) to allow data to mature before final analyses. Investigators and patients will only be informed if the DSMB feels that there is a safety concern. In that setting, it would be up to the treating investigator and patient if the patient continues with the investigational regimen. The communication plan for investigators and participants regarding the status of arms is designed to ensure optimal care, including safety, of participants in the trial and the integrity of the data.

Assessments and Additional Treatment Details

The following assessments were performed for both newly diagnosed (ND) and recurrent (RD) participants to assess baseline characteristics: neurologic examination, Karnofsky performance status assessment, vital signs, and laboratory blood tests. For newly diagnosed unmethylated (NDU) participants, the extent of resection was determined from the immediate postoperative magnetic resonance imaging (MRI) and the baseline for assessment of radiographic progression was the MRI scan performed after completing radiotherapy, before commencing maintenance temozolomide (control arm) or regorafenib (regorafenib arm), per mRANO guidelines.[26] For RD participants, the baseline MRI was the last scan performed before initiating treatment (ie, screening scan or scan performed before starting treatment on day one when applicable). Radiologic assessment was conducted every 8 weeks (±4 weeks) after completion of chemoradiotherapy and rest for ND participants, and every 6 weeks (±1 week) from day one of treatment (or screening as applicable, Appendix Table A2) in RD participants, until disease progression. With the mRANO criteria, confirmation of progression was required.

Radiographic response assessment was determined by mRANO[27] by the trial investigators using MRI scans acquired according to the standardized brain tumor imaging protocol.[28] Treatment of NDU participants with temozolomide beyond six cycles was permitted at the discretion of the treating investigator in consultation with the medical monitor. NDU participants randomly assigned to regorafenib started regorafenib (Bayer Pharma AG, Leverkusen, Germany), at 160 mg per day (1-21/28) starting 4-6 weeks after completing concurrent chemoradiotherapy (Fig 2) until progressive disease (PD), unacceptable toxicity, or withdrawal. Participants in this arm did not receive adjuvant temozolomide.

Regorafenib dose reductions to 120 mg and 80 mg per day were prescribed for specific grade 3-4 adverse events (AEs), with re-escalation permitted on improvement for grade 3 and disallowed for grade 4 AEs. RD participants on the regorafenib arm were treated until PD as per mRANO,[27] unacceptable side effects, or withdrawal of consent. Treatment beyond confirmed PD was allowed, after consultation with the medical monitor, if the investigator and the participant felt the participant was receiving benefit from continued treatment.

The use of TTF has not been included in GBM AGILE to date. At the time that this study was initiated, TTF was not used by most patients with glioblastoma. Phase I data for the combination of TTF and regorafenib were not available at the time of study initiation, and there were concerns about overlapping skin toxicities. Additionally, the trial is not equipped to collect usage data (eg, time with device worn, days worn, etc), and inconsistent TTF use could confound efficacy evaluations. Finally, other trials have stratified random assignment by intention to use; however, even among patients who declared intention to use if randomly assigned to control, <10% proceeded to use the device.[4] For these reasons, TTF have not been included in GBM AGILE.

Arm-Specific Customizations

The regorafenib investigational arm included such arm-specific customizations. Random assignment of participants was 1:1 regorafenib to control arm, and continued at this randomization ratio even when additional investigational arms entered the trial. Thus, for the duration of regorafenib enrollment, control allocation could be ≥20% even when there were two or more arms actively enrolling. In accordance with the master protocol, the efficacy threshold for the regorafenib arm's final analysis was set to a Bayesian probability of benefit (hazard ratio <1.00) ≥ 98% (roughly analogous *P* value: .02). The maximum sample size in stage 2 for the regorafenib arm was 200 participants (adjusted from 150 participants in the master protocol at that time), including NDU and RD participants, and a maximum stage 2 sample size of 75 participants (adjusted from 50 participants in the master protocol). The regorafenib arm required 150 randomly assigned participants to be eligible for monthly trial evaluations of limited efficacy (adjusted from 50 in the master protocol) and continuation to stage 2 (adjusted from 100 in the master protocol). Furthermore, although GBM AGILE is open to participants with any of the three subtypes of glioblastoma (ie, NDU, newly diagnosed methylated, or RD), random assignment to the regorafenib arm was limited to NDU and RD participants. Thus, there were three predefined signatures: NDU, RD, and All (NDU + RD). The primary statistical benefit attained from the regorafenib arm–specific customizations is to improve the arm's power by increasing the sample size. This customization was needed because regorafenib did not receive the statistical efficiency benefits of having other investigational arms included before its initiation in GBM AGILE. The regorafenib arm's maximum sample size was calculated by assessing the trial's characteristics across a wide range of simulated efficacy scenarios, which are described in the protocol appendix. The sample size was increased to 200 participants combined across NDU and RD, with the expectation that two thirds of participants will have recurrent disease and one third will be newly diagnosed. This results in a power of almost 90% if the HR of regorafenib is 0.65 in NDU and RD patients, and a power of almost 80% if the HR of regorafenib is 0.7 in NDU and RD patients.

Role of the Funding Source

The Global Coalition for Adaptive Research (GCAR), a 501c3 nonprofit corporation, is the study sponsor and contributed to the study design, data collection, interpretation, analysis, and writing of the manuscript. Bayer Pharma AG provided financial support and regorafenib supply and reviewed the clinical protocol, final analysis report, and manuscript before publication but had no role in data collection, interpretation, or analysis. The additional funders of the study (National Foundation for Cancer Research, National Brain Tumor Society, Asian Fund for Cancer Research Ltd, and Cure Brain Cancer Foundation) had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript.

Safety Reporting

For ND participants, safety reporting begins on the first day of the chemoradiotherapy treatment period (for both arms). For RD participants, safety reporting begins on the first day of the treatment period. After initiation of study treatment, all AEs, regardless

of relationship to study treatment, were to be reported until 28 days after the last dose of study treatment. After this period, any deaths, SAEs, or other AEs of concern that are believed to be related to study treatment were to be reported. Toxicity was evaluated according to the NCI CTCAE version 5 criteria and assessed by a qualified clinician.

Progression-Free Survival Analysis and Results

Progression-free survival (PFS) is defined as the time from random assignment to the date of first documentation of objective disease progression or until death from any cause, whichever occurs first. PFS estimates are calculated using the Kaplan-Meier curves. Progression is determined by mRANO assessment by the treating investigator and not through a central review, and specific criteria are applied to determine progression for inclusion in PFS analysis. If not reported, the disease progression date was identified as the first scan date with preliminary PD followed by a confirmed PD from the second scan, or the date of response assessment with PD due to symptomatic deterioration, whichever occurred first. For participants not known to have progressed or died, PFS was censored at the date of the last objective disease assessment. PFS analysis was performed using SAS Version 9.4 (SAS/STAT 15.1, SAS/IML 15.1).

PFS was evaluated as a secondary end point in the mITT analysis set. One month was considered equal to 30.44 days. A total of 35 (71%) NDU participants in the regorafenib arm and 35 (76%) NDU participants in the control arm experienced a progression event. For NDU participants, median PFS was similar between the regorafenib (6.60 months [95% CI, 5.55 to 7.59]) and control arms (5.72 [95% CI, 4.47 to 7.66] months). The 6-month survival probability was 63% in the regorafenib arm and 47% in the control arm (Appendix Table A6). A total of 95 (79%) RD participants in the regorafenib arm and 85 (79%) RD participants in the control arm experienced a progression event. In RD participants, median PFS was similar between the regorafenib (2.37 [95% CI, 1.64 to 2.66] months) and control arms (1.64 [95% CI, 1.54 to 2.46] months). The 6-month survival probability was 7% in the regorafenib arm and 19% in the control arm (Appendix Table A6, Fig A5).

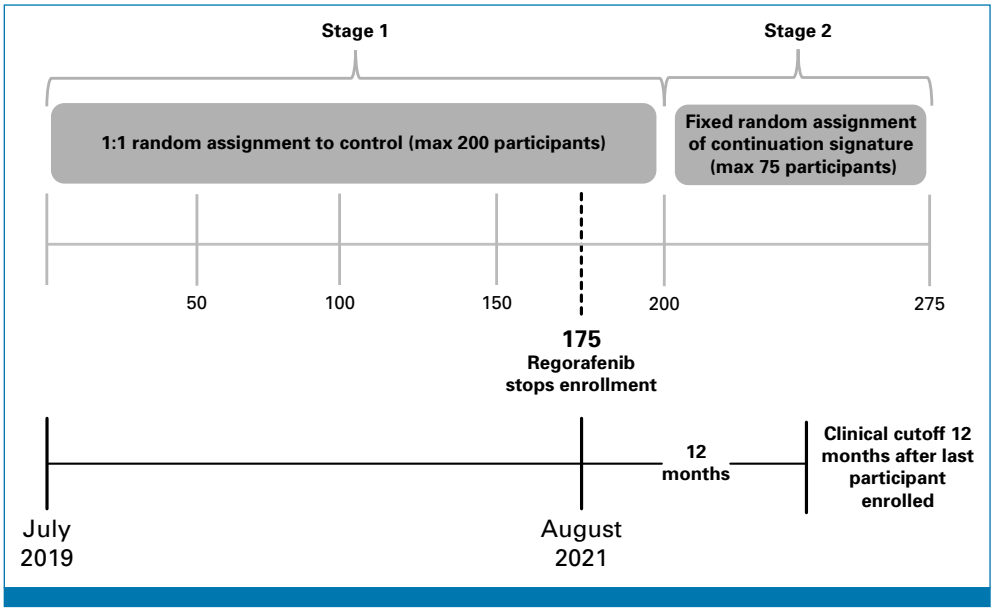

FIG A1. Regorafenib conclusion of enrollment. Participants were randomized 1:1 regorafenib to control arm. Interim analyses for limited efficacy and continuation to stage 2 began in June 2021 and continued monthly until the August 2021 interim analysis, when enrollment stopped because of limited efficacy. The clinical cutoff date for final analysis was 12 months after the last participant was randomly assigned to the regorafenib arm.

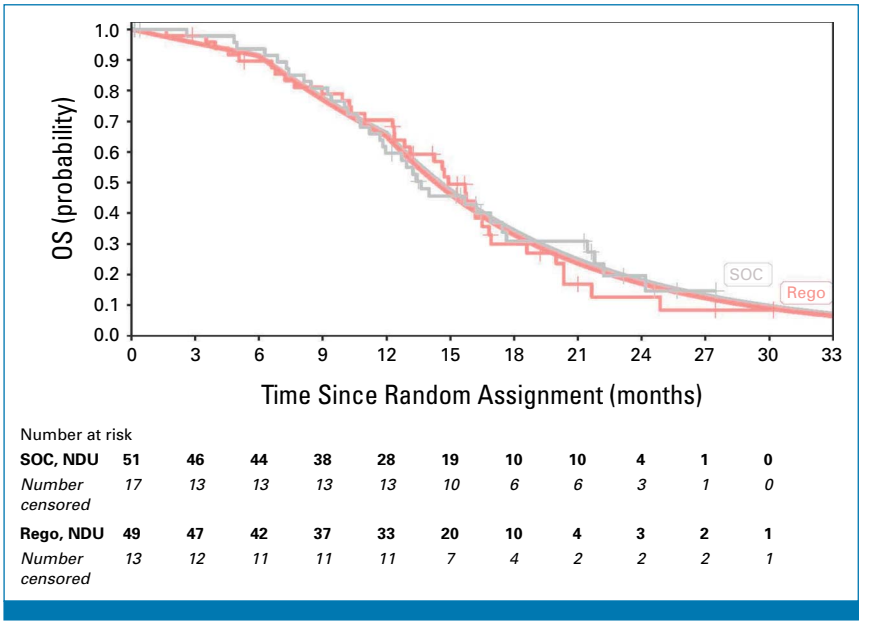

FIG A2. Regorafenib ITT population, NDU signature. The Kaplan-Meier curve (step function) shows the proportion of patients alive since random assignment for Rego versus standard of care. The symbol "|" along the curves represents censoring times. The smooth curve is the estimated probability of survival from the piecewise exponential model. ITT, intention-to-treat; NDU, newly diagnosed unmethylated; Rego, regorafenib; SOC, standard of care (control).

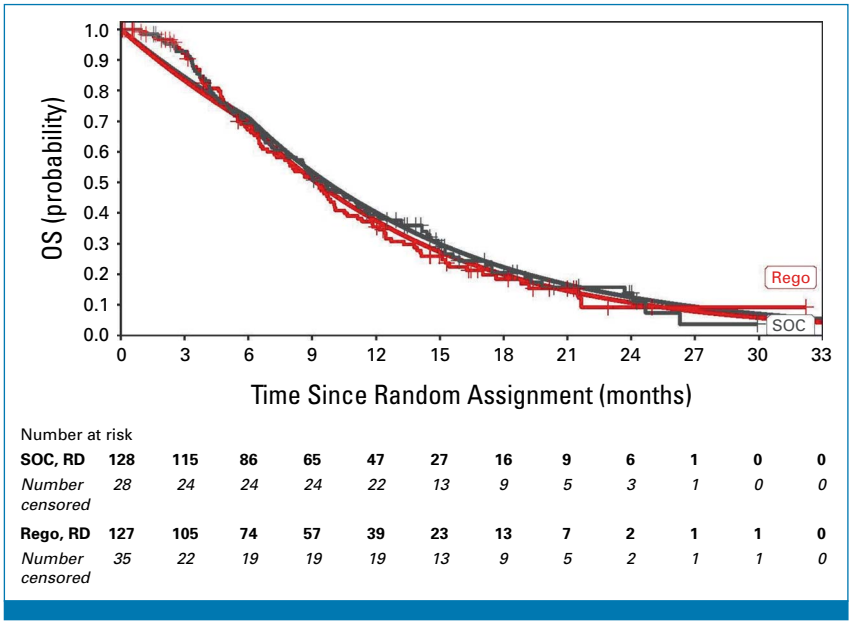

FIG A3. Regorafenib ITT population, RD signature. The Kaplan-Meier curve (step function) shows the proportion of patients alive since random assignment for Rego versus standard of care. The symbol "|" along the curves represents censoring times. The smooth curve is the estimated probability of survival from the piecewise exponential model. ITT, intention-to-treat; RD, recurrent; Rego, regorafenib; SOC, standard of care (control).

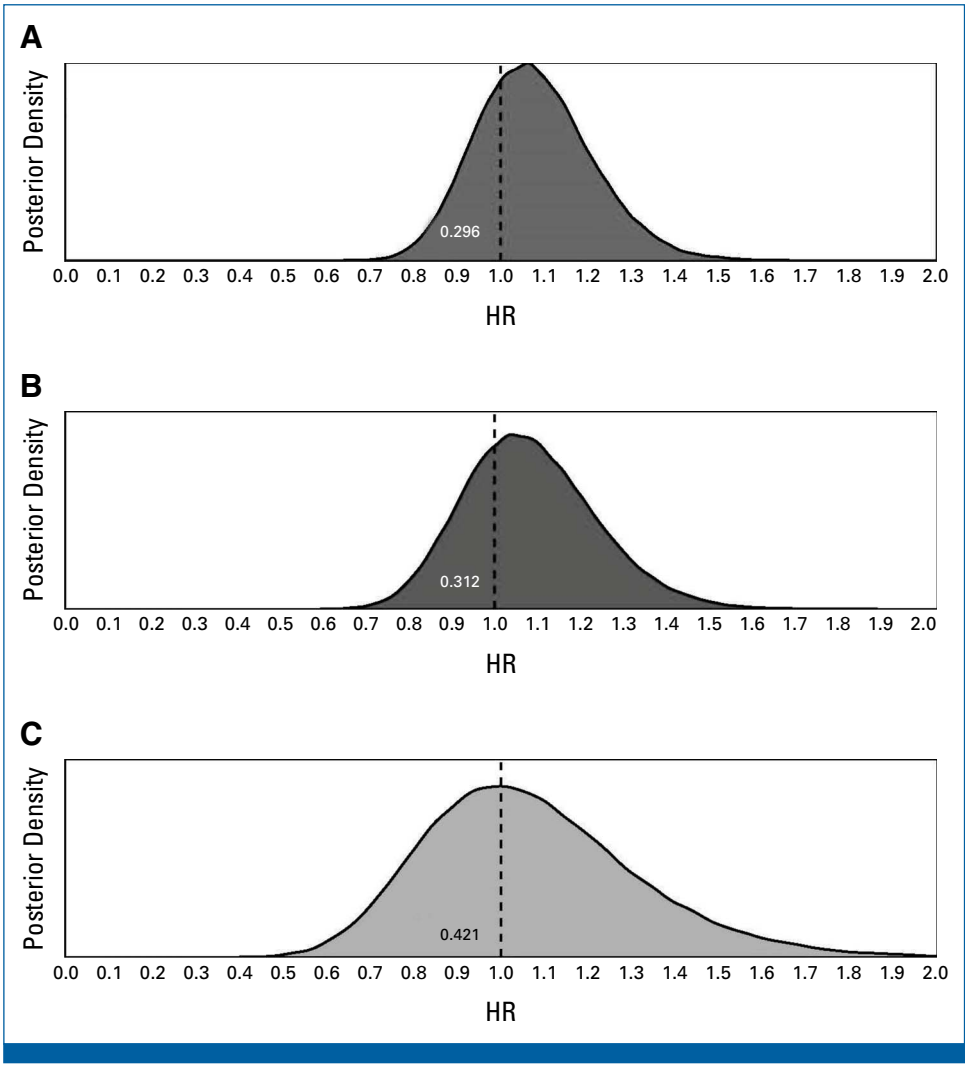

FIG A4. Bayesian posterior distribution of the hazard ratio by subtype/signature. (A) All participants; (B) RD; and (C) NDU. Each plot shows the final probability that HR is <1.0; the values for each are shown on the corresponding plot. HR, hazard ratio; NDU, newly diagnosed unmethylated; RD, recurrent.

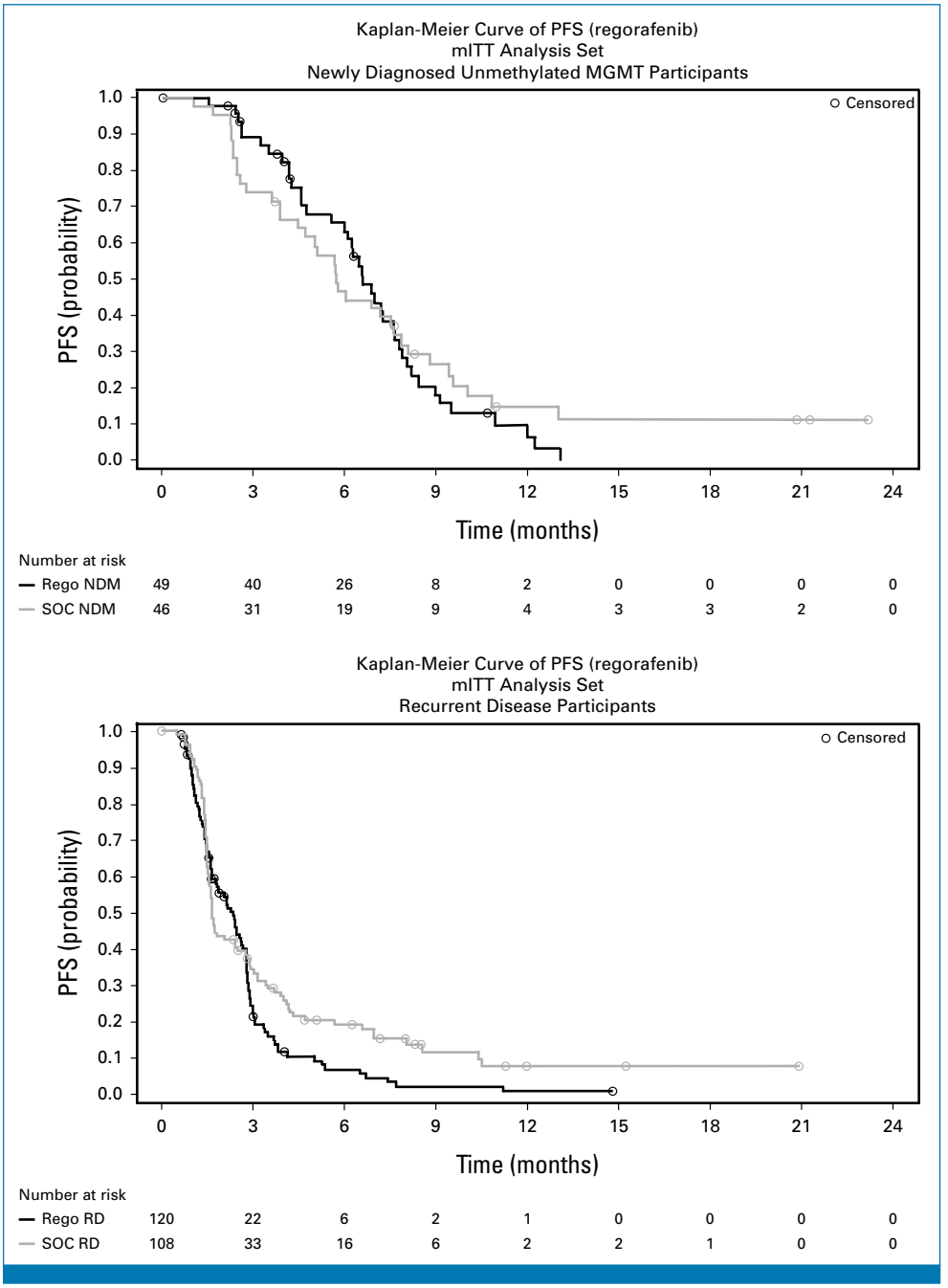

FIG A5. PFS (mITT analysis set). PFS is defined as the time from random assignment to first documentation of objective progression or death due to any cause, whichever occurs first. For the participant who is not known to have progressed or died, PFS is censored at the date of last disease assessment. One month is considered as 30.44 days. The Kaplan-Meier curve shows the proportion of patients alive and free of objective disease progression since random assignment for regorafenib versus control (standard of care) in (A) newly diagnosed and (B) recurrent disease participants. Participants at risk at each time point are given in the table below each plot. The derivation of PFS depends on the mRANO assessment, which is not centrally reviewed. mITT, modified intention-to-treat; NDM, newly diagnosed methylated; PFS, progression-free survival; RD, recurrent; Rego, regorafenib; SOC, standard of care (control).

TABLE A1. Inclusion and Exclusion Criteria for Participants With Newly Diagnosed Glioblastoma

Inclusion	Exclusion
Patients will be eligible to participate in the study if ALL the criteria below are met 1. Age ≥18 years 2. Histologically confirmed grade IV glioblastoma, inclusive of gliosarcoma (WHO criteria; IDH wild-type by IHC or sequencing for IDH) established after either a surgical resection or biopsy. This includes: a. Treatment-naïve (chemotherapy and RT) patients with a previous diagnosis of lower-grade astrocytoma. However, the previous low-grade glioma cannot have an IDH (IDH1 or 2) mutation 3. An MRI scan with the required imaging sequences performed within 21 days before random assignment preferably. The postoperative MRI scan performed within 96 hours of surgery, or the MRI scan performed for radiation therapy planning may serve as the MRI scan performed during screening if all required imaging sequences were obtained, and the scan is preferably performed within 21 days before random assignment 4. Postoperative MRI within 96 hours of surgery. This eligibility criterion is not applicable if the patient underwent a biopsy only and no postoperative MRI was required 5. Use of dexamethasone 4 mg or less per day within 5 days before random assignment 6. Karnofsky performance status ≥60% performed within a 14-day window before random assignment 7. Administration of any noncytotoxic potential antitumor agent (eg, interferon, tamoxifen, thalidomide, cis-retinoic acid) and/or herbal preparations/medications has been stopped at least 7 days before random assignment. The use of tetrahydrocannabinol/cannabidiol is strongly discouraged during study treatment. NOTE: No washout is necessary for alternating electrical fields 8. Have undergone recent surgery or biopsy provided that a. Craniotomy or intracranial biopsy site must be adequately healed and free of drainage or cellulitis, and the underlying cranioplasty must appear intact at the time of random assignment. b. Initiation of study treatment is at least 14 days from previous surgery/biopsy for glioblastoma 9. For women (any individual assigned female at birth) who are not postmenopausal (ie, <2 years after last menstruation) or surgically sterile (absence of ovaries and/or uterus) and who are sexually active: agreement to use a highly effective method of contraception (oral, intravaginal, transdermal combined [estrogen- and progesterone-containing] contraceptives, progesterone only oral, injectable or implantable contraceptives [eg, Depo Provera, Implanon, Nexplanon], intrauterine contraceptive device) or an adequate method (barrier method of contraception in conjunction with spermicidal jelly) in accordance with regulatory jurisdictions, during the treatment period and for at least 6 months after the last dose of study treatment. Sexual abstinence, defined as complete or true abstinence, is acceptable only when it is the usual and preferred lifestyle of the patient; periodic abstinence (eg, calendar, symptothermal, postovulation methods) is not acceptable 10. Male patients (any individual assigned male at birth) of reproductive potential must avoid pregnancy in partners who are women of childbearing potential, and such partners should not consider getting pregnant during the study and for at least 6 months after treatment is discontinued or longer if requested by local authorities. Male patients are considered to be of reproductive potential unless permanently sterile by bilateral orchidectomy or vasectomized with appropriate postvasectomy documentation of absence of sperm in ejaculate. Male patients of reproductive potential must agree to use a barrier method of contraception during the treatment period and for at least 6 months after the last dose of study treatment. Male patients must not donate semen for 6 months after the last dose of study treatment 11. Patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, isolated autoimmune skin disorders not requiring systemic treatment (eg, vitiligo, psoriasis, or alopecia), or conditions not expected to recur in the absence of an external trigger are eligible to participate	Patients who meet any of the following criteria will NOT be eligible to participate in the study 1. Received any previous treatment for glioma including: a. Previous polifeprosan 20 with carmustine wafer b. Previous intracerebral, intratumoral, or CSF agent c. Previous radiation treatment for glioblastoma or lower-grade glioma d. Previous chemotherapy or immunotherapy for glioblastoma or lower-grade glioma. NOTE: 5-aminolevulinic acid–mediated photodynamic therapy and fluorescein administered before surgery to aid in optimal surgical resection is not considered a chemotherapy agent. Additionally, fluorescein is allowed, as it is used to guide neurosurgical resection and is not considered a chemotherapy agent 2. Receiving additional, concurrent, active therapy (including experimental) for glioblastoma outside of the trial 3. Presence of extensive leptomeningeal disease 4. Candidate for urgent palliative intervention for primary disease (eg, impending herniation) as judged by the investigator 5. History of allergy or hypersensitivity to any of the study treatments or any of their excipients 6. Laboratory results must be obtained within 28 days before random assignment AND 7 days before the start of study treatment. NOTE: Laboratory blood tests should be repeated if initially performed >7 days before the start of study treatment. Laboratory results that meet the following parameters are exclusionary: a. ANC < 1.5×10^9/L (growth-factor support within 7 days [for filgrastim or other short-acting biosimilars] or 21 days [for pegfilgrastim or other long-acting biosimilars] to increase the ANC is not allowed) b. Platelet count <100×10^9/L (platelet transfusion within 7 days to increase the platelet count is not allowed, consult the medical monitor regarding romiplostim use) c. Hb <9.0 g/dL. NOTE: The use of transfusion or other intervention to achieve Hb ≥9 g/dL is acceptable d. Total bilirubin ≥1.5 × ULN; except in patients diagnosed with Gilbert's disease, for which bilirubin must be ≤2.0 × ULN e. AST/SGOT or ALT/serum glutamic-pyruvic transaminase ≥3 × ULN f. ALP ≥2.5 × ULN g. Persistent ≥grade 3 lipase (>2.0 to 5.0 × ULN with signs or symptoms; >5.0 × ULN and asymptomatic) h. Serum creatinine >1.5 × ULN or calculated CrCl <60 mL/min (using Cockcroft and Gault) i. Persistent ≥grade 3 proteinuria (dipstick ≥4+, urine protein ≥3.5 g/24 hours, or nephrotic syndrome) 7. INR, PT, or aPTT as follows: a. In the absence of therapeutic intent to anticoagulate the patient: i. INR >1.5 × ULN ii. PT >1.5 × ULN iii. aPTT >1.5 × ULN b. In the presence of therapeutic intent to anticoagulate the patient i. INR or PT and aPTT not within therapeutic limits (according to the medical standard in the institution) ii. Patient has not been on a stable dose of anticoagulants for at least 2 weeks before random assignment or a thromboembolic event >grade 2 at the time of random assignment c. Use of warfarin sodium (coumadin), or any other coumadin-derivative anticoagulant, is not permitted at any dose 8. QTc >450 ms if male and QTc >470 ms if female 9. Pregnant or lactating (or a positive serum β-HCG pregnancy test within 14 days before random assignment for women [any individual assigned female at birth]) 10. Unable or unwilling to undergo brain MRI scans with IV gadolinium

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TABLE A1. Inclusion and Exclusion Criteria for Participants With Newly Diagnosed Glioblastoma (continued)

Inclusion	Exclusion
12. Availability of tumor tissue representative of glioblastoma from definitive surgery or biopsy 13. Willingness and ability to provide written informed consent and to comply with the study protocol as judged by the investigator. Of note, if the patient has an impairment that prevents him/her from providing written consent, the site may follow local institutional procedures for obtaining consent	11. History of another malignancy in the previous 2 years, with a disease-free interval of <2 years. Patients with previous history of in situ cancer or basal or squamous cell skin cancer, any time before screening, are eligible 12. Serious, nonhealing wound, ulcer, bone fracture, or abscess 13. Any cerebrovascular accident (including transient ischemic attacks) within the last 6 months before initiation of study treatment 14. Any hemorrhage or bleeding event that is ≥grade 3 based on the NCI CTCAE or grade 2 intracranial hemorrhage within 4 weeks before the start of study treatment 15. Uncontrolled or severe cardiac disease (eg, history of unstable angina, myocardial infarction, coronary stenting, or bypass surgery within the last 6 months before initiation of study treatment), symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia (including atrial flutter/fibrillation), requirement for inotropic support or use of devices for cardiac conditions (eg, pacemakers/defibrillators), or hypertension (patients with systolic BP of >160 mm Hg or diastolic BP of >100 mm Hg despite optimal medical management are to be excluded) 16. History of interstitial lung disease, history of slowly progressive dyspnea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis, or symptomatic pleural effusion 17. Active, known, or suspected uncontrolled autoimmune disease, which required therapy in the past 2 years, including but not limited to systemic lupus erythematosus, Hashimoto's thyroiditis, scleroderma, polyarteritis nodosa, or autoimmune hepatitis 18. Known history of hepatitis B, HIV, or active hepatitis C infection requiring treatment with antiviral therapy. NOTE: HIV testing is not required in the absence of clinical suspicion 19. History of bleeding diathesis (irrespective of severity) in the absence of therapeutic anticoagulation 20. Uncontrolled intercurrent illness including (eg, symptomatic ascites), but not limited to ongoing or active infection 21. Any condition that could make the patient noncompliant with the study procedures and/or study requirements, as judged by the investigator (eg, cognitive impairment, psychiatric illness)

Abbreviations: ALP, alkaline phosphatase; ANC, absolute neutrophil count; aPTT, activated partial thromboplastin time; BP, blood pressure; CrCl, creatinine clearance; CSF, cerebral spinal fluid; CTCAE, Common Terminology Criteria for Adverse Event; Hb, hemoglobin; IDH, isocitrate dehydrogenase; IHC, immunohistochemistry; INR, international normalized ratio; IV, intravenous; MRI, magnetic resonance imaging; NCI, National Cancer Institute; PT, prothrombin time; RT, radiation therapy; ULN, upper limit of normal.

TABLE A2. Inclusion and Exclusion Criteria for Participants With Recurrent Glioblastoma

Inclusion	Exclusion
Patients will be eligible to participate in the study if ALL the criteria below are met 1. Age ≥18 years 2. Histologically confirmed grade IV glioblastoma inclusive of gliosarcoma (WHO criteria; IDH wild-type) at first or second recurrence after initial standard, control, or experimental therapy that includes at a minimum RT. NOTE: A local pathology report constitutes adequate documentation of histology for study inclusion. Surgery is not required at the time of relapse, provided archival tissue is available confirming diagnosis. Patients with an initial diagnosis of a lower-grade glioma are eligible if a subsequent tumor sample was determined to be glioblastoma and IDH wild-type by IHC or sequencing for IDH 3. Evidence of RD demonstrated by disease progression using slightly modified RANO criteria (using the postchemoradiation time point as baseline), defined by any of the following: a. ≥25% increase in sum of products of perpendicular diameters of measurable enhancing lesions, compared with the smallest tumor measurement obtained either at the postchemoradiation baseline (if no decrease) or best response (on stable or increasing steroid dose) b. Any new measurable (>1 × 1 cm) enhancing lesions after the postchemoradiation scan 4. Two scans to confirm progression are required: at least 1 scan at the time of progression and 1 scan before the time of progression. The progression scan should show a >25% increase in the contrast-enhancing tumor size or show at least 1 new measurable (>1 × 1 cm) contrast-enhancing lesion. In addition, the total daily steroid dose taken on the day of each MRI scan (±5 days) should be documented to ensure that the radiographic changes were not due solely to tapering of steroids. NOTE: Ideally, MRI scans that conform to the standardized Brain Tumor Imaging Protocol 1 (see GBM AGILE Imaging Guidelines in the Reference Binder) should be used for all documented scans at the time of Screening for random assignment into the GBM AGILE study for recurrent patients 5. Baseline MRI performed within 14 days before random assignment. NOTE: If the MRI is performed within 14 days before random assignment AND cycle 1 day 1 (C1D1), then the patient does not require the additional MRI at C1D1 6. Use of dexamethasone 4 mg per day or less within 5 days before random assignment 7. Karnofsky performance status ≥70% performed within a 14-day window before random assignment 8. Administration of the following previous therapy, with a minimum time of: a. 28 days or 5 half-lives, whichever is shorter, elapsed from the administration of any experimental agent before initiation of study treatment. b. 28 days elapsed from the administration of any previous cytotoxic agents except 14 days from vincristine and ≥21 days from procarbazine and TMZ before initiation of study treatment 9. Administration of any noncytotoxic potential antitumor agent (eg, interferon, tamoxifen, thalidomide, cis-retinoic acid) and/or herbal medicine has been stopped at least 7 days before random assignment. NOTE: No washout is necessary for alternating electrical fields 10. Have undergone recent surgery for recurrent or progressive brain tumor are eligible provided that: a. Before surgery there was imaging evidence of measurable PD as described above. b. Craniotomy or intracranial biopsy site must be adequately healed and free of drainage or cellulitis, and the underlying cranioplasty must appear intact at the time of random assignment c. Initiation of study treatment is at least 14 days from previous surgery/biopsy 11. Patients are on a stable or decreasing dose of corticosteroids within 5 days before random assignment 12. Previous therapy with gamma knife or other focal high-dose radiotherapy is allowed, but the patient must have subsequent histologic documentation of recurrence, unless the recurrence is a new lesion outside the irradiated field	Patients who meet any of the following criteria will NOT be eligible to participate in the study 1. Early disease progression before 3 months (12 weeks) from the completion of RT 2. Had more than two previous lines for chemotherapy administration. NOTE: In the first-line adjuvant setting, combination of TMZ with an experimental agent, is considered one line of chemotherapy 3. Any previous treatment with lomustine, agents part of any of the experimental arms, and bevacizumab or other VEGF- or VEGF receptor–mediated targeted agent 4. Any previous treatment with polifeprosan 20 with carmustine wafer 5. Any previous treatment with an intracerebral agent 6. Receiving additional, concurrent, active therapy (including experimental) for glioblastoma outside of the trial 7. Presence of extensive leptomeningeal disease 8. Candidate for urgent palliative intervention for primary disease (eg, impending herniation) as judged by the investigator 9. History of allergy or hypersensitivity to any of the study treatments or any of their excipients 10. Laboratory results must be obtained within 28 days before random assignment AND 7 days before the start of study treatment. NOTE: Laboratory blood tests should be repeated if initially performed >7 days before the start of study treatment. Laboratory results that meet the following parameters are exclusionary: a. ANC <1.5 × 10^9/L (growth-factor support within 7 days [for filgrastim or other short-acting biosimilars] or 21 days [for pegfilgrastim or other long-acting biosimilars] to increase the ANC is not allowed b. Platelet count <100 × 10^9/L (platelet transfusion within 7 days to increase the platelet count is not allowed, consult the medical monitor regarding romiplostim use) c. Hb <9.0 g/dL within 7 days before enrollment. NOTE: The use of transfusion or other intervention to achieve Hb ≥9 g/dL is acceptable d. Total bilirubin ≥1.5 × ULN (except in patients diagnosed with Gilbert's disease) e. AST/SGOT or ALT/SGPT ≥3 × ULN f. ALP ≥2.5 × ULN g. Persistent ≥ grade 3 lipase (>2.0 to 5.0 × ULN with signs or symptoms; >5.0 × ULN and asymptomatic) h. Serum creatinine >1.5 × ULN or calculated CrCl <60 mL/min (using Cockcroft and Gault) i. Persistent ≥grade 3 proteinuria (dipstick ≥4+, urine protein ≥3.5 g/24 hours, or nephrotic syndrome) 11. INR, PT, or aPTT as follows: a. In the absence of therapeutic intent to anticoagulate the patient: i. INR >1.5 ii. PT > 1.5 × ULN iii. aPTT >1.5 × ULN b. In the presence of therapeutic intent to anticoagulate the patient i. INR or PT and aPTT not within therapeutic limits (according to the medical standard in the institution) ii. Patient has not been on a stable dose of anticoagulants for at least 2 weeks before random assignment or a thromboembolic event >grade 2 at the time of random assignment c. Use of warfarin sodium (coumadin), or any other coumadin-derivative anticoagulant, is not permitted at any dose 12. QTc >450 ms if male and QTc >470 ms if female 13. Pregnant or lactating (or a positive serum β-HCG pregnancy test within 14 days before random assignment for women [any individual assigned female at birth]) 14. Unable or unwilling to undergo brain MRI scans with IV gadolinium 15. History of another malignancy in the previous 2 years, with a disease-free interval of <2 years. Patients with previous history of in situ cancer or basal or squamous cell skin cancer, any time before screening, are eligible 16. Serious nonhealing wound, ulcer, bone fracture, or abscess 17. Any cerebrovascular accident (including transient ischemic attacks) within the last 6 months before initiation of study treatment

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TABLE A2. Inclusion and Exclusion Criteria for Participants With Recurrent Glioblastoma (continued)

Inclusion	Exclusion
13. For women (any individual assigned female at birth) who are not postmenopausal (ie, <2 years after last menstruation) or surgically sterile (absence of ovaries and/or uterus) and who are sexually active: agreement to use a highly effective method of contraception (oral, intravaginal, transdermal combined [estrogen- and progesterone-containing] contraceptives, progesterone only oral, injectable, or implantable contraceptives [eg, Depo Provera, Implanon, Nexplanon], intrauterine contraceptive device) or an acceptable method (barrier method of contraception in conjunction with spermicidal jelly) in accordance with regulatory jurisdictions, during the treatment period and for at least 6 months after the last dose of study treatment. Sexual abstinence, defined as complete or true abstinence, is acceptable only when it is the usual and preferred lifestyle of the patient; periodic abstinence (eg, calendar, symptothermal, postovulation methods) is not acceptable 14. Male patients (any individual assigned male at birth) of reproductive potential must avoid pregnancy in partners who are women of childbearing potential, and such partners should not consider getting pregnant during the study and for at least 6 months after treatment is discontinued or longer if requested by local authorities. Male patients are considered to be of reproductive potential unless permanently sterile by bilateral orchidectomy or vasectomized with appropriate postvasectomy documentation of absence of sperm in ejaculate. Male patients of reproductive potential must agree to use a barrier method of contraception during the Treatment period and for at least 6 months after the last dose of study treatment. Male patients must not make semen donations for 6 months after the last dose of study treatment 15. Availability of tumor tissue representative of GBM from initial definitive surgery and/or, recurrent surgery, if performed 16. Willingness and ability to provide written informed consent and to comply with the study protocol as judged by the investigator. Of note, if the patient has an impairment that prevents him/her from providing written consent, the site may follow local institutional procedures for obtaining consent	18. Any hemorrhage or bleeding event that is ≥grade 3 based on NCI CTCAE or grade 2 intracranial hemorrhage within 4 weeks before the start of study treatment 19. Uncontrolled or severe cardiac disease (history of unstable angina, myocardial infarction, coronary stenting, or bypass surgery within the previous 6 months), symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia (including atrial flutter/fibrillation), requirement for inotropic support or use of devices for cardiac conditions (pacemakers/defibrillators), or hypertension (systolic BP of >160 mm Hg or diastolic BP of >100 mm Hg despite optimal medical management) 20. History of interstitial lung disease, history of slowly progressive dyspnea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis, or symptomatic pleural effusion 21. Active, known, or suspected uncontrolled autoimmune disease, which required therapy in the past 2 years, including but not limited to systemic lupus erythematosus, Hashimoto's thyroiditis, scleroderma, polyarteritis nodosa, or autoimmune hepatitis 22. Patients with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, isolated autoimmune skin disorders not requiring systemic treatment, (eg, vitiligo, psoriasis, or alopecia), or conditions not expected to recur in the absence of an external trigger are eligible to participate 23. Known history of hepatitis B, HIV, or active hepatitis C infection requiring treatment with antiviral therapy. NOTE: HIV testing is not required in the absence of clinical suspicion 24. History of bleeding diathesis (irrespective of severity) in the absence of therapeutic anticoagulation 25. Uncontrolled intercurrent illness including (eg, symptomatic ascites), but not limited to ongoing or active infection 26. Any condition that could make the patient noncompliant with the study procedures and/or study requirements, as judged by the investigator (eg, cognitive impairment, psychiatric illness)

Abbreviations: ANC, absolute neutrophil count; aPTT, activated partial thromboplastin time; CTCAE, Common Terminology Criteria for Adverse Event; Hb, hemoglobin; IDH, isocitrate dehydrogenase; INR, international normalized ratio; MRI, magnetic resonance imaging; NCI, National Cancer Institute; PD, progressive disease; PT, prothrombin time; RD, recurrent; RT, radiation therapy; TMZ, temozolomide; ULN, upper limit of normal; VEGF, vascular endothelial growth factor.

TABLE A3. August 2021 Interim Analysis Concluded to Stop for Limited Efficacy

Signature	Sample Size (Rego/control)	Median HR[a] (95% CI)	Pr (HR <1)	PP
NDU	48/47	1.16 (0.54 to 2.55)	0.35	0.138
RD	124/126	1.22 (0.80 to 1.87)	0.18	0.030
All	172/173	1.20 (0.82 to 1.78)	0.17	0.026

Abbreviations: CI, credibility interval; HR, hazard ratio; Pr (HR < 1.0), probability of benefit; PP, predictive power; RD, recurrent; NDU, newly diagnosed unmethylated; Rego, regorafenib.
[a]Median HR (95% CI) are calculated as the 50% (2.5%, 97.5%) of the Bayesian posterior distribution for the HR. Pr(HR < 1) is the area of the posterior distribution of the HR that is < 1—see Appendix Figure A4.

TABLE A4. Summary of Data Availability for Patients Who are Not in the Modified Intention-to-Treat Analysis Set

Arm	Randomly Assigned, No.	NDU, No.	RD, No.	No. of Deaths, %
Control	25	5	20	17
Regorafenib	7	0	7	1
Total	32	5	27	18

Abbreviations: NDU, newly diagnosed unmethylated; RD, recurrent.

TABLE A5. Modified Intention-to-Treat Final Analysis

Signature	Rego/Control, No.	Median HR (95% credible interval)	Pr[a] (HR <1)	Median OS[b] Rego/Control, Months
NDU	49/46	1.08 (0.69 to 1.7)	0.364	14.34/14.83
RD	120/108	1.12 (0.84 to 1.5)	0.221	9.27/10.10
All	169/154	1.11 (0.87 to 1.43)	0.198	

Abbreviations: HR, hazard ratio; NDU, newly diagnosed unmethylated; OS, overall survival; RD, recurrent; Rego, regorafenib.
[a]Posterior probability.
[b]Model estimates of median overall survival.

TABLE A6. PFS (modified intention-to-treat analysis set)

	NDU		RD	
PFS	Regorafenib (n = 49)	Control (n = 46)	Regorafenib (n = 120)	Control (n = 108)
PFS events, No. (%)				
Progression	35 (71)	35 (76)	95 (79)	85 (79)
Death without progression	5 (10)	0 (0)	3 (3)	3 (3)
PFS censored, No. (%)	9 (18)	11 (24)	22 (18)	20 (19)
PFS, months				
25th percentile (95% CI)	4.57 (3.25 to 6.08)	2.76 (2.27 to 4.70)	1.31 (1.08 to 1.51)	1.45 (1.31 to 1.48)
Median (95% CI)	6.60 (5.55 to 7.59)	5.72 (4.47 to 7.66)	2.37 (1.64 to 2.66)	1.64 (1.54 to 2.46)
75th percentile (95% CI)	8.21 (7.23 to 9.53)	9.46 (7.13 to 13.01)	2.92 (2.79 to 3.48)	4.11 (3.02 to 6.97)
Survival probability				
6 months (95% CI)	0.63 (0.47 to 0.76)	0.47 (0.31 to 0.61)	0.07 (0.03 to 0.14)	0.19 (0.12 to 0.28)
12 months (95% CI)	0.06 (0.01 to 0.18)	0.15 (0.05 to 0.28)	0.01 (0.00 to 0.06)	0.08 (0.03 to 0.16)
HR (95% CI)		1.09 (0.69 to 1.73)		1.31 (0.98 to 1.76)
P value from the log-rank test		.7046		.0666

Abbreviations: HR, hazard ratio; NDU, newly diagnosed unmethylated; PFS, progression-free survival; RD, recurrent.

TABLE A7. GBM AGILE Regorafenib Study Group (in alphabetical order)

Name	Affiliation	Contributions
Brian Alexander	Valo Health, Global Coalition for Adaptive Research	Study design, review and final approval of the manuscript
Mark D. Anderson	University of Mississippi Medical Center	Data collection; review and final approval of the manuscript
Lars Anker	Providence St Joseph Hospital, Orange, CA	Data collection; review and final approval of the manuscript
Donald A. Berry	Berry Consultants, LLC	Study design; data analysis; data interpretation; drafting, editing, and final approval of the manuscript
Nicholas S Berry	Berry Consultants, LLC	Data analysis; data interpretation; review, editing, and final approval of the manuscript
Nicholas A. Blondin	Yale University	Data collection; data interpretation; review and final approval of the manuscript
Omar H. Butt	Washington University in Saint Louis	Data collection; review and final approval of the manuscript
Meredith B. Buxton	Global Coalition for Adaptive Research	Study design; data interpretation; drafting, editing, and final approval of the manuscript
Webster K. Cavenee	University of California San Diego, Global Coalition for Adaptive Research	Study design; review and final approval of the manuscript
Tim Cloughesy	University of California Los Angeles, Global Coalition for Adaptive Research	Study design; data analysis; data interpretation; drafting, editing, review and final approval of the manuscript
Howard Colman	Huntsman Cancer Institute, University of Utah	Study design, data collection; review, editing, and final approval of the manuscript
Jennifer Connelly	Medical College of Wisconsin	Data collection; review and final approval of the manuscript
Denise M. Damek	University of Colorado School of Medicine Anschutz Medical Campus	Data collection; review, editing, and final approval of the manuscript
John de Groot	University of California San Francisco	Study design; data collection; review and final approval of the manuscript
Macarena I. de la Fuente	Sylvester Comprehensive Cancer Center, University of Miami	Data collection; review and final approval of the manuscript
Michelle A. Detry	Berry Consultants, LLC	Data analysis; data interpretation; review and final approval of the manuscript
Jan Drappatz	University of Pittsburgh Medical Center	Data collection; review, editing, and final approval of the manuscript
Erin Dunbar	Piedmont Brain Tumor Center	Data collection; review and final approval of the manuscript
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Mark Fitzgerald	Berry Consultants, LLC	Data analysis; data interpretation; review, editing, and final approval of the manuscript
Evanthia Galanis	Mayo Clinic	Data collection; review and approval of manuscript
Elizebeth Gerstner	Massachusetts General Hospital	Data Collection; review and final approval of the manuscript
Pierre Giglio	The Ohio State University Wexner Medical Center	Data collection; review and approval of manuscript
Gary Gordon	Global Coalition for Adaptive Research	Study design; data interpretation; review, editing, and final approval of the manuscript
Jerome J. Graber	University of Washington	Data collection; review and approval of manuscript
Todd L. Graves	Berry Consultants LLC	Study design; data analysis; data interpretation; review, editing, and final approval of the manuscript
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Kurt A. Jaeckle	Mayo Clinic Florida	Data collection; review, editing, and approval of manuscript
Adam Johnson	Global Coalition for Adaptive Research	Data analysis; data interpretation; review, editing, and approval of manuscript
Marija Kalabic	Global Coalition for Adaptive Research	Data analysis; review and approval of manuscript
Mustafa Khasraw	Duke University	Study design; review, editing, and approval of the manuscript
Lyndon Kim	Icahn School of Medicine at Mount Sinai	Data collection; review and approval of manuscript
Andrew B. Lassman	Columbia University Irving Medical Center	Study design; data collection; data interpretation; drafting, review, editing, and approval of the manuscript
Eudocia Q. Lee	Dana-Farber Cancer Institute, Harvard University	Data collection; review and approval of the manuscript

(continued on following page)

TABLE A7. GBM AGILE Regorafenib Study Group (in alphabetical order) (continued)

Name	Affiliation	Contributions
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Michael Lim	Stanford University School of Medicine	Study design; review and approval of manuscript
Megan Mantica	University of Pittsburgh Medical Center	Data collection; review, editing, and approval of manuscript
Joe Marion	Berry Consultants, LLC	Data analysis; data interpretation; review and approval of manuscript
Anna McGlothlin	Berry Consultants, LLC	Study design; data analysis; data interpretation; review, editing, and approval of manuscript
Ingo Mellinghoff	Memorial Sloan Kettering Cancer Center	Study design; data collection; review and approval of manuscript
Tom Mikkelsen	Henry Ford Health	Data collection; review and approval of manuscript
Burt Nabors	University of Alabama at Birmingham	Data collection; review and approval of manuscript
Herbert B. Newton	University Hospitals Cleveland Medical Center and Seidman Cancer Center	Data collection; review, editing, and approval of manuscript
Jeffrey J. Olson	Emory University School of Medicine	Data collection; review and approval of manuscript
Scott Owen	McGill University Health Center	Data collection; review and approval of manuscript
James R Perry	Sunnybrook Health Sciences Centre, University of Toronto	Study design; data collection; review and approval of manuscript
Katherine B. Peters	Duke University Medical Center	Data collection; review and approval of manuscript
Ashley Powell	Global Coalition for Adaptive Research	Study design; review and approval of manuscript
Christina T. Saunders	Berry Consultants, LLC	Data analysis; review and approval of manuscript
David Schiff	University of Virginia	Data collection; review, editing, and approval of manuscript
Erik P. Sulman	New York University Grossman School of Medicine	Study design; review and approval of manuscript
Kirk Tanner	Autem Therapeutics	Study design; review and approval of manuscript
Sarah Untch	Global Coalition for Adaptive Research	Data interpretation; review, editing, and approval of manuscript
Tobias Walbert	Henry Ford Health, Michigan State and Wayne State University	Data collection; review, editing, and approval of manuscript
Shiao-Pei Weathers	University of Texas MD Anderson Cancer Center	Data collection; review and approval of manuscript
Michael Weller	University Hospital and University of Zurich	Study design; data interpretation; review, editing, and approval of the manuscript
Patrick Y. Wen	Dana-Farber Cancer Institute, Mass General Brigham Cancer Institute and Harvard Medical School	Study design; data collection; data interpretation; drafting, review, editing, and final approval of the manuscript
Emma Wilcox	Global Coalition for Adaptive Research	Data analysis; data interpretation; review, editing, and approval of the manuscript
W. K. Alfred Yung	University of Texas MD Anderson Cancer Center, Global Coalition for Adaptive Research	Study design; review and approval of the manuscript