Inaugural Results of the Individualized Screening Trial of Innovative Glioblastoma Therapy: A Phase II Platform Trial for Newly Diagnosed Glioblastoma Using Bayesian Adaptive Randomization

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ABSTRACT

PURPOSE The Individualized Screening Trial of Innovative Glioblastoma Therapy (INSIGhT) is a phase II platform trial that uses response adaptive randomization and genomic profiling to efficiently identify novel therapies for phase III testing. Three initial experimental arms (abemaciclib [a cyclin-dependent kinase [CDK]4/6 inhibitor], neratinib [an epidermal growth factor receptor [EGFR]/human epidermal growth factor receptor 2 inhibitor], and CC-115 [a deoxyribonucleic acid–dependent protein kinase/mammalian target of rapamycin inhibitor]) were simultaneously evaluated against a common control arm. We report the results for each arm and examine the feasibility and conduct of the adaptive platform design.

PATIENTS AND METHODS Patients with newly diagnosed O^6-methylguanine–DNA methyltransferase-unmethylated glioblastoma were eligible if they had tumor genotyping to identify prespecified biomarker subpopulations of dominant glioblastoma signaling pathways (EGFR, phosphatidylinositol 3-kinase, and CDK). Initial random assignment was 1:1:1:1 between control (radiation therapy and temozolomide) and the experimental arms. Subsequent Bayesian adaptive randomization was incorporated on the basis of biomarker-specific progression-free survival (PFS) data. The primary end point was overall survival (OS), and one-sided *P* values are reported. The trial is registered with ClinicalTrials.gov (identifier: NCT02977780).

RESULTS Two hundred thirty-seven patients were treated (71 control; 73 abemaciclib; 81 neratinib; 12 CC-115) in years 2017-2021. Abemaciclib and neratinib were well tolerated, but CC-115 was associated with ≥ grade 3 treatment-related toxicity in 58% of patients. PFS was significantly longer with abemaciclib (hazard ratio [HR], 0.72; 95% CI, 0.49 to 1.06; one-sided $P = .046$) and neratinib (HR, 0.72; 95% CI, 0.50 to 1.02; one-sided $P = .033$) relative to the control arm but there was no PFS benefit with CC-115 (one-sided $P = .523$). None of the experimental therapies demonstrated a significant OS benefit ($P > .05$).

CONCLUSION The INSIGhT design enabled efficient simultaneous testing of three experimental agents using a shared control arm and adaptive randomization. Two investigational arms had superior PFS compared with the control arm, but none demonstrated an OS benefit. The INSIGhT design may promote improved and more efficient therapeutic discovery in glioblastoma. New arms have been added to the trial.

ACCOMPANYING CONTENT

Editorial, p. 5497
Data Supplement
Protocol

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CONTEXT

Key Objective

Does the use of abemaciclib, neratinib, or CC-115 improve survival relative to the control arm in patients with newly diagnosed glioblastoma?

Knowledge Generated

Abemaciclib and neratinib were associated with an improvement in progression-free survival in newly diagnosed glioblastoma. Abemaciclib, neratinib, and CC-115 were, however, not associated with improvement in overall survival. The Individualized Screening Trial of Innovative Glioblastoma Therapy design allowed for simultaneous testing of three experimental arms using a shared control arm, and it promotes improved and efficient therapeutic discovery in glioblastoma.

Relevance *(J.P.S. Knisely)*

This clinical trial's innovative use of adaptive Bayesian randomization can permit more rapid and efficient testing of promising systemic agents in this notoriously refractory disease.*

*Relevance section written by *JCO* Associate Editor Jonathan P.S. Knisely, MD.

INTRODUCTION

Glioblastoma is the most common adult malignant primary brain tumor, and it continues to be associated with a dismal prognosis.[1] The development of therapeutics and predictive biomarkers in glioblastoma remains slow, expensive, and ineffective, and recent efforts have been associated with repeated failures at multiple stages in the regulatory approval process.[2,3] There have been repeated failures in drug development in glioblastoma,[4] including numerous resource-intensive phase III trials that have failed to improve outcomes.[5-8] Although there are many challenges in development of new therapeutic agents, more reliable and efficient trial design for early-phase testing is paramount to effective future drug development. Furthermore, increasing interest in targeted molecular and immunotherapies has further complicated therapeutic development, given the emphasis on identifying predictive biomarkers that can ascertain subgroups of patients who could benefit most from a particular therapy.[9]

To address these challenges of drug development in the era of precision medicine, adaptive platform trials (APTs) have been increasingly used.[10,11] The Individualized Screening Trial of Innovative Glioblastoma Therapy (INSIGhT) is a phase II randomized Bayesian APT in newly diagnosed O^6-methylguanine–DNA methyltransferase (MGMT) promoter unmethylated glioblastoma. The platform, which to our knowledge is the first multiarm platform trial in glioblastoma, was designed to test multiple investigational therapies simultaneously against a common control arm and generate data to support biomarker development.[12] Herein, we report results on the first three experimental therapies tested in INSIGhT: abemaciclib (a cyclin-dependent kinase [CDK]4/6 inhibitor), neratinib (an epidermal growth factor receptor [EGFR]/human epidermal growth factor receptor 2 [HER2] inhibitor), and CC-115 (a deoxyribonucleic acid–dependent protein kinase [DNA-PK]/mammalian target of rapamycin [mTOR] inhibitor). With overall survival (OS) as the primary end point, we examined whether adjuvant abemaciclib, adjuvant neratinib, or concurrent and adjuvant CC-115 had a survival benefit over standard-of-care temozolomide in participants.

PATIENTS AND METHODS

Study Design and Patient Eligibility

As previously described,[12] INSIGhT (ClinicalTrials.gov identifier: NCT02977780) is a randomized, multicenter, open-label phase II APT in newly diagnosed and untreated intracranial glioblastoma or gliosarcoma. Adult participants with Karnofsky performance status ≥60 were randomly assigned before initiation of radiation therapy either to control or one of three experimental arms (abemaciclib, neratinib, or CC-115) after surgery, provided that their tumors had unmethylated *MGMT* promoters. Additional exclusion criteria are provided in the Data Supplement (online only). INSIGhT was approved by the institutional review boards of each participating site before site activation. The study was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

The focus of the INSIGhT platform is to efficiently test therapeutic hypotheses, both evaluating the therapeutic efficacy and the predictive capability of the putative biomarkers (Fig 1). Participants eligible for treatment assignment required genotyping via whole-genome copy-number analysis and whole-exome sequencing process within the ALLELE-GBM biomarker consortium[13] or enrolling local site laboratories to identify biomarker signatures before treatment assignment. The biomarker signatures were formally scored

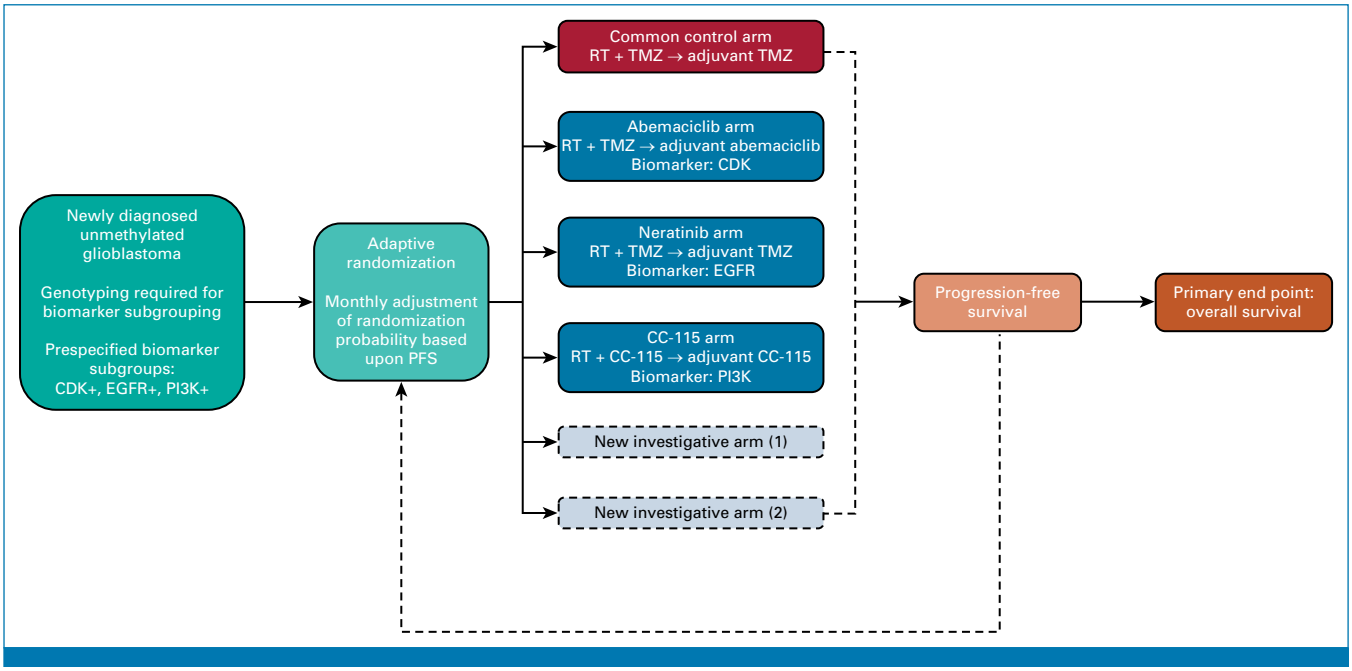

FIG 1. Overview of the INSIGhT clinical trial schema. CDK cyclin-dependent kinases; EGFR, epidermal growth factor receptor; INSIGhT, Individualized Screening Trial of Innovative Glioblastoma Therapy; PI3K, phosphatidylinositol 3-kinase; RT, radiation therapy; TMZ, temozolomide.

by central pathology reviewers (K.L.L., S.R., D.M., and S.S.) throughout the trial. The biomarkers were based on hypothesized determinants of response identified as the three most commonly altered pathways in glioblastoma and with direct relevance to the drugs evaluated.[14] Three biomarker status variables were defined as presence of one of the following aberrations: EGFR-positive (defined by investigators as EGFR amplification, rearrangement including EGFR variant III, or mutation); phosphatidylinositol 3-kinase (PI3K)–positive (defined by investigators as PI3K activation by PIK3CA or PIK3R1 mutation, PTEN loss through homozygous deletion or mutation plus deletion); and CDK-positive (defined by investigators as CDK4/6 amplification or CDKN2A nullisomy, and absence of RB1 mutation).

Adaptive Randomization

Adaptive randomization serves as a mechanism to improve efficiency of treatment development processes by increasing randomization probabilities to experimental arms that are more likely to confer an improved clinical outcome.[11,15,16] At the start of the INSIGhT trial, participants were randomly assigned equally to one of four treatment arms, regardless of biomarker signature, as there were no strong clinical data supporting the predictive capacity of a genomic biomarker for any of the experimental arms.[14] Throughout the course of the trial, hypotheses on efficacy and association with biomarkers were evaluated on a monthly basis. The accumulating clinical data influenced the randomization probabilities of the enrolled patients after the initial predetermined equal randomization period, as previously described.[12]

Abemaciclib Treatment Plan

Abemaciclib is an inhibitor of CDK4/6 that blocks Rb phosphorylation and thereby progression from G1 into S phase of the cell cycle, specifically in Rb-proficient tumors. In glioblastoma human xenograft models, abemaciclib generated tumor growth inhibition and a prolongation of survival.[17] Studies also demonstrated favorable blood-brain barrier penetration compared with palbociclib.[18,19]

Patients randomly assigned to the abemaciclib arm received radiation and concurrent temozolomide followed by adjuvant abemaciclib at 150 mg twice daily in 28-day cycles (with potential to increase to 200 mg twice daily after cycle 1 if tolerable) until progression or unacceptable toxicity. On the basis of its mechanism of action, CDK-positive tumors were hypothesized to be more likely to benefit from abemaciclib.

Neratinib Arm Treatment Plan

Neratinib is an orally available irreversible potent small-molecular inhibitor of EGFR, HER2, and HER4[20] that is FDA-approved in breast cancer and shown to have CNS activity for breast cancer brain metastases.[21] Preclinical work has shown antitumor activity in EGFR-activated glioblastoma cell lines with more activity than other EGFR inhibitors.[22,23] Patients randomly assigned to the neratinib arm received radiation and concurrent temozolomide followed by adjuvant neratinib at 240 mg once daily in 28-day cycles until progression or unacceptable toxicity. On the basis of its mechanism of action, EGFR-positive tumors were hypothesized to be more likely to benefit from neratinib.

CC-115 Arm Treatment Plan

CC-115 is a CNS-penetrant, oral inhibitor of mTOR kinase and DNA-PK.[24] CC-115 represented a promising therapy, given that the PI3K/AKT/MTOR pathway is hyperactive in most glioblastomas, and DNA-PK is integral for repair of DNA damage that is mediated by radiation therapy. Preclinical work demonstrated antitumor and radiosensitizing effects of CC-115 in glioblastoma models.[25] Patients randomly assigned to the CC-115 arm received 10 mg orally twice a day concurrently with RT and adjuvantly as monotherapy. CC-115 replaced temozolomide during RT based upon the potential for radiosensitization.[25,26] The starting dose was based on a previous phase I study in advanced malignancies including glioblastoma,[27] and preclinical data that supported CNS penetrance at this dose. Given that CC-115 had not previously been used in combination with RT in humans, a safety lead-in phase was incorporated with 10-week observation period for dose-limiting toxicities. Patients received CC-115 until progression or unacceptable toxicity. On the basis of its mechanism of action, tumors with aberrations in the PI3K pathway were hypothesized to be more likely to benefit from CC-115.

Control Arm Treatment Plan

Patients randomly assigned to the control arm received radiation to 60 Gy in 30 fractions and concurrent temozolomide 75 mg/m^2 once per day followed by six cycles of adjuvant temozolomide 150-200 mg/m^2 once per day for 5 days in 28-day cycles as per standard of care.[8] Patients were treated until completion of treatment, progression, or unacceptable toxicity.

Outcomes and Imaging Assessment

The primary end point was OS. Statistical analyses compared the experimental arms and the control arm using the proportional hazards model (PH-model) in (1) the full population and (2) in the biomarker-specific subpopulations. Statistical significance was set to control type I error (false positives) probabilities at 5% with one-sided testing. Three primary OS analyses were done with log-rank testing with three covariates: EGFR, CDK, and PI3K biomarker status compared with control arm patients receiving standard therapy. The adaptive algorithm used for INSIGhT has been previously described.[9,10] We report one-sided hypothesis testing for PFS and OS comparisons without multiplicity corrections.[28] Response assessment and additional details of statistical analysis are described in the Data Supplement.

Exploratory Analysis to Evaluate the Impact of Adaptive Randomization

We investigated if response-adaptive randomization, by reducing the enrollment rate of an unpromising arm, has an impact on the final number of patients assigned to a potentially unpromising or toxic arm. Further details of this analysis are available in the Data Supplement (Fig S1).

RESULTS

Patient characteristics for INSIGhT are presented in Table 1. Figure 2 presents the CONSORT diagram of the inclusion process. Every patient had tumor genomic characterization and biomarker subgroup classification (Fig 3). For each experimental arm, we report patient characteristics, efficacy, and biomarker-specific results. Efficacy and toxicity results are summarized in Tables 2 and 3, respectively.

Abemaciclib

During the period the abemaciclib arm was accruing (February 09, 2017-February 13, 2020), 73 patients were randomly assigned to the abemaciclib arm, and 51 patients were randomly assigned to the control arm. Abemaciclib was generally well tolerated with expected toxicities as previously described[6] (Data Supplement, Table S1).

PFS was significantly longer (hazard ratio [HR], 0.72; 95% CI, 0.49 to 1.06; one-sided P = .046, log-rank test; PH-model with three covariates: EGFR, CDK, and PI3K status; Fig 4A) with abemaciclib (median, 6.3 months) versus the control arm (median, 4.6 months). In the biomarker subgroup analysis, CDK-biomarker–positive patients did not have improved PFS in the abemaciclib arm (n = 58) compared with the control arm (n = 36; HR, 0.69; 95% CI, 0.45 to 1.08; one-sided P = .053; PH-model with two covariates: EGFR and PI3K status).

There was no significant improvement in OS (HR, 0.86; 95% CI, 0.58 to 1.28; one-sided P = .231; PH model with three covariates: EGFR, CDK, and PI3K status; Fig 4B) between abemaciclib (median, 15.3 months) and control arm (median, 14.7 months) in the overall population nor in the CDK+ biomarker subpopulation (HR, 0.76; 95% CI, 0.49 to 1.19; one-sided P = .12; PH model with two covariates: EGFR and PI3K status).

Neratinib

During the period of accrual to the neratinib arm (February 09, 2017-May 14, 2021), 81 patients were randomly assigned to the neratinib arm, whereas 71 patients were randomly assigned to the control arm concurrently. Neratinib was generally well tolerated with expected toxicities as previously described (Data Supplement, Table S2).

PFS was significantly longer (HR, 0.72; 95% CI, 0.50 to 1.02; one-sided P = .033, log-rank test; PH-model with three covariates: EGFR, CDK, and PI3K status; Fig 4C) with neratinib (median, 6.1 months) versus concurrent control arm (median, 4.7 months). In the biomarker subgroup analysis, EGFR-biomarker–positive patients had significantly longer PFS in the neratinib arm (n = 43) compared with the control arm (n = 31; HR, 0.42; 95% CI, 0.24 to 0.72; one-sided P < .001, log-rank test; PH-model with two covariates: PI3K and CDK status).

TABLE 1. Patient Characteristics

Characteristic	Experimental (N = 166)	Control (N = 71)	Abemaciclib (N = 73)	Neratinib (N = 81)	CC-115 (N = 12)
Age, years, median (range)	59 (24-78)	59 (24-75)	56 (29-77)	60 (24-78)	64 (33-74)
Sex, No. (%)					
Male	105 (63)	43 (61)	48 (66)	46 (57)	11 (92.5)
Female	61 (37)	28 (39)	25 (34)	35 (43)	1 (7.5)
Race, No. (%)					
White	150 (91)	65 (92)	66 (91)	74 (91)	10 (83)
Black	5 (3)	1 (1)	3 (4)	2 (3)	0 (0)
Asian	2 (1)	3 (4)	1 (1)	0 (0)	1 (7.5)
Other	9 (5)	2 (3)	3 (4)	5 (6)	1 (7.5)
Ethnicity, No. (%)					
Hispanic	3 (2)	2 (3)	1 (1)	2 (3)	0 (0)
Non-Hispanic	157 (95)	2 (3)	70 (96)	75 (92)	12 (100)
Unknown	6 (3)	67 (94)	2 (3)	4 (5)	0 (0)
KPS, No. (%)					
100	22 (13)	4 (6)	8 (11)	14 (17)	0 (0)
90	73 (45)	41 (57)	36 (49)	31 (38)	6 (50)
80	54 (33)	22 (31)	25 (34)	25 (31)	4 (33)
70	15 (9)	4 (6)	2 (3)	11 (14)	2 (17)
60	2 (1)	0 (0)	2 (3)	0 (0)	0 (0)
Steroid use,[a] No. (%)					
Yes	40 (24)	14 (20)	19 (26)	15 (19)	6 (50)
No	127 (76)	57 (80)	55 (74)	66 (81)	6 (50)
Antiepileptic use,[a] No. (%)	85 (51)	34 (48)	35 (47)	36 (44)	2 (17)
Extent of resection, No. (%)					
GTR	99 (59)	37 (52)	50 (68)	43 (53)	6 (50)
STR	60 (36)	28 (39)	21 (29)	33 (41)	6 (50)
Biopsy	7 (4)	6 (8)	2 (3)	5 (6)	0 (0)
Time of diagnosis to enrollment, days, median (range)	31 (10-51)	31 (19-56)	30 (20-41)	33 (20-51)	26.5 (10-40)
Time from diagnosis to RT start, days, median (range)	36 (14-57)	35 (23-63)	35 (21-46)	36 (25-57)	36 (14-42)
EGFR					
+	73 (44)	21 (30)	36 (49)	31 (38)	6 (50)
–	73 (44)	33 (46)	37 (51)	30 (37)	6 (50)
PI3K					
+	97 (58)	28 (39)	50 (69)	38 (47)	9 (75)
–	49 (30)	26 (37)	23 (31)	23 (28)	3 (25)
CDK					
+	117 (70)	38 (54)	58 (78)	49 (61)	10 (83)
–	29 (18)	16 (23)	15 (20)	12 (15)	2 (17)

Abbreviations: CDK, cyclin-dependent kinases; EGFR, epidermal growth factor receptor; GTR, gross total resection; INSIGhT, Individualized Screening Trial of Innovative Glioblastoma Therapy; KPS, Karnofsky performance status; PI3K, phosphatidylinositol 3-kinase; RT, radiation therapy; STR, subtotal resection.

[a]At the time of trial enrollment, all patients were required to have ≤2 mg daily dose of dexamethasone, stable or decreasing over 5 days, to be eligible to enroll onto INSIGhT.

There was no significant improvement in OS (HR, 1.00; 95% CI, 0.70 to 1.44; one-sided $P = .50$, PH-model with three covariates: EGFR, CDK, and PI3K status; Fig 4D) between neratinib (median, 14.3 months) and control arm (median, 14.9 months) in the overall population nor in the EGFR+ biomarker subpopulation (HR, 0.87; 95% CI, 0.52 to 1.46; one-sided $P = .30$; PH-model with two covariates: PI3K and CDK status).

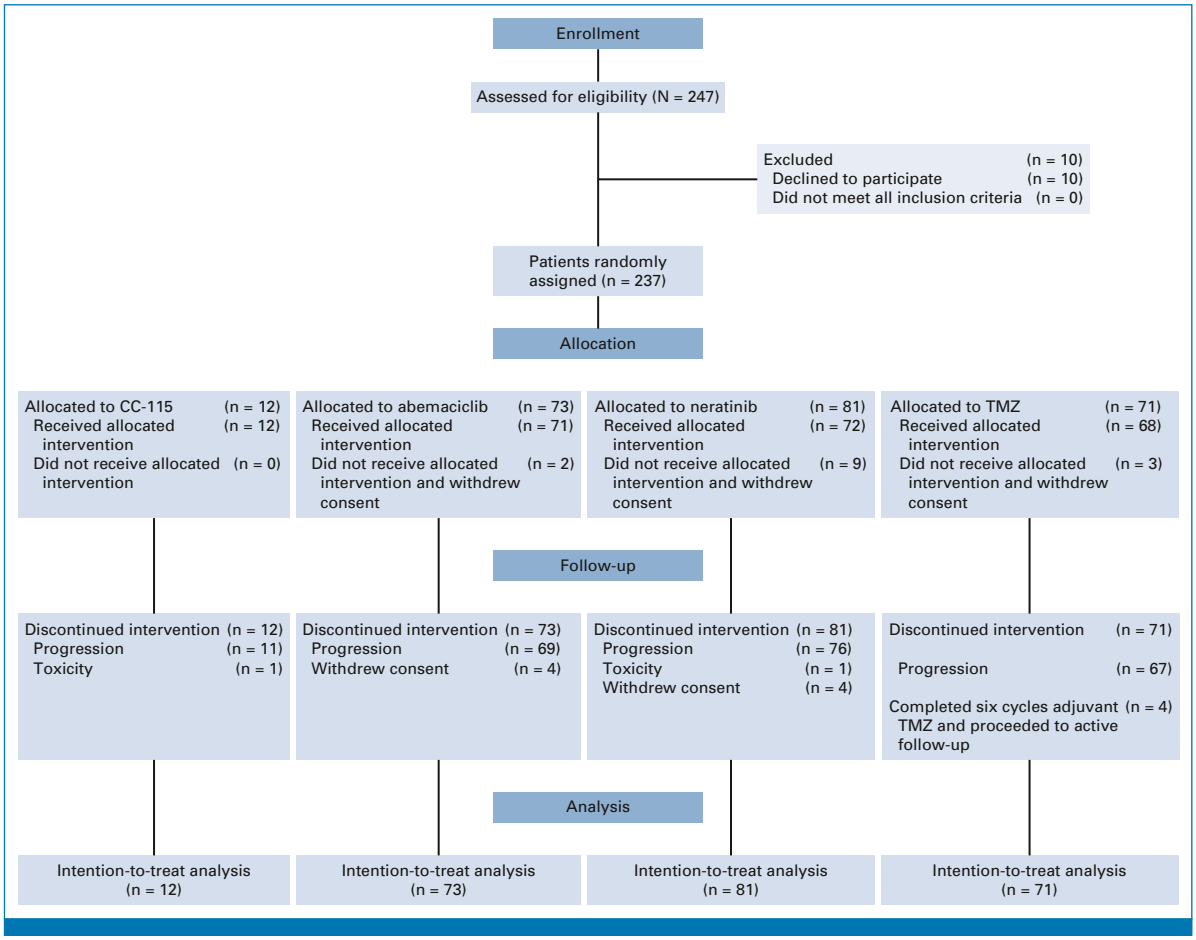

FIG 2. CONSORT diagram for INSIGhT. INSIGhT, Individualized Screening Trial of Innovative Glioblastoma Therapy; TMZ, temozolomide.

CC-115

During the period of accrual to the CC-115 arm (February 09, 2017-December 17, 2018), 12 patients were randomly assigned to the CC-115 arm, whereas 21 patients were randomly assigned to the control arm. Eight patients had CC-115 therapy held during administration, and seven patients had possible treatment-related CTCAE grade 3 or higher toxicity. This included four dose-limiting toxicities: transaminitis, hyperlipidemia, lipase elevation, and cerebral edema.

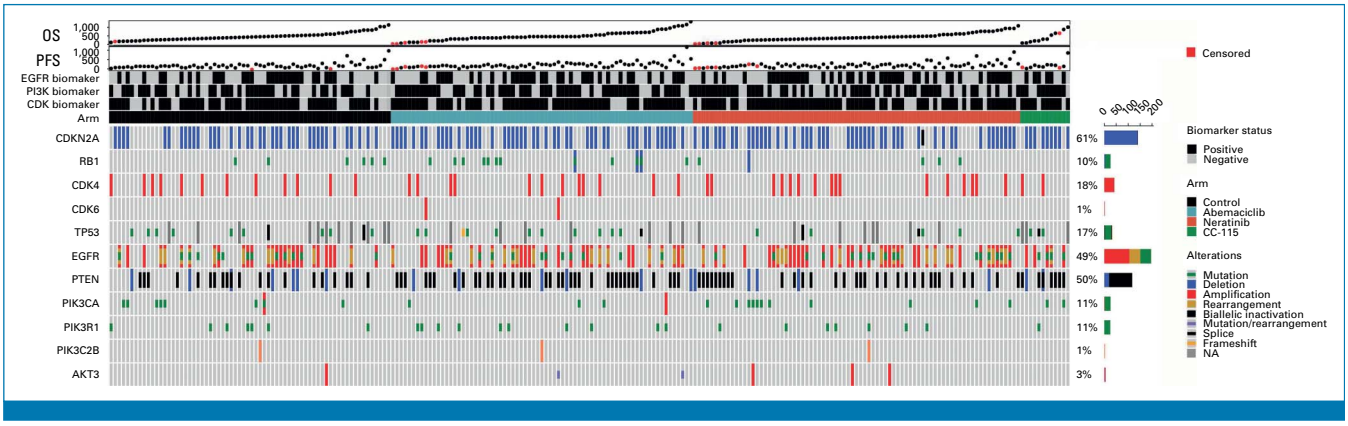

FIG 3. Overview of tumor genomic characterization, including specific type of alteration for specified genetic changes for INSIGhT patients with biomarker subgroup classification, treatment arm assignment, PFS, and OS for each participant. CDK cyclin-dependent kinases; EGFR, epidermal growth factor receptor; INSIGhT, Individualized Screening Trial of Innovative Glioblastoma Therapy; NA, not applicable; OS, overall survival; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase.

TABLE 2. Summary of Efficacy Results

Outcome	Control Arm	Abemaciclib	Neratinib	CC-115
PFS				
HR (95% CI), one-sided *P* value[a]		0.72 (0.49 to 1.06), *P* = .046	0.72 (0.50 to 1.02), *P* = .033	0.79 (0.34 to 1.81), *P* = .290
Median (95% CI), months	4.7 (4.4 to 6.2)	6.2 (5.1 to 7.9)	6.0 (4.8 to 7.8)	6.2 (3.4 to NA)
PFS-6 months, % (95% CI)	40 (30 to 54)	54 (43 to 67)	49 (39 to 62)	51 (28 to 94)
OS				
HR (95% CI), one-sided *P* value[a]		0.86 (0.58 to 1.28), *P* = .232	1.00 (0.70 to 1.44), *P* = .500	0.76 (0.34 to 1.71), *P* = .251
Median (95% CI), months	14.8 (13.1 to 16.8)	15.3 (14.0 to 17.2)	14.2 (12.2 to 15.5)	10.1 (6.6 to NA)
OS-12 months, % (95% CI)	65 (55 to 77)	78 (69 to 89)	61 (51 to 74)	42 (21 to 81)

Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
[a]HRs and 95% CI are based on experimental arm data and concurrent control data.

Initial dose was 10 mg orally twice a day, and one patient had dose reduction to 7.5 mg orally twice a day. As doses lower than 10 mg orally twice a day were unlikely to have sufficient CNS activity, the arm was closed in December 2018, given concerns of excess toxicity and absence of an efficacy signal.

There was no significant improvement in PFS (HR, 0.79; 95% CI, 0.34 to 1.81; one-sided $P = .29$, log-rank test; PH model with three covariates: EGFR, CDK, and PI3K status; Fig 4E) in the CC-115 arm versus the control arm. In the biomarker subgroup analysis, PI3K-biomarker–positive patients did not have a significantly improved PFS in the CC-115 arm (n = 9) compared with the control arm (n = 13; HR, 2.02; 95% CI, 0.65 to 6.25; one-sided $P = .11$; PH model with two covariates: EGFR and CDK status).

There was no significant improvement in OS (HR, 0.76; 95% CI, 0.34 to 1.71; one-sided $P = .25$; PH-model with three covariates: EGFR, CDK, and PI3K status; Fig 4F) between CC-115 versus control arm in the overall population nor in the PI3K+ biomarker subpopulation (HR, 0.71; 95% CI, 0.25 to 1.99; one-sided $P = .26$; PH model with two covariates: EGFR and CDK status).

For all three experimental arms, the results of the analysis were similar when the concomitant control (enrolled during the enrollment period of the experimental arm) or the full control arm population was used as a comparator. Time intervals from diagnosis to trial registration and administration of experimental therapy (Data Supplement, Table S5), as well as exploratory subgroup analyses based upon biomarker status (Data Supplement, Table S6) and best overall objective response (Data Supplement, Table S7) for each of the experimental therapies are available in the Data Supplement.

Impact of Adaptive Randomization

We performed an exploratory analysis evaluating the impact of adaptive randomization of the CC-115 arm. On the basis of early PFS results, randomization probability changed over time from 25% to 16% during the open enrollment periods of the CC-115 arm. Data Supplement (Fig S1A) illustrates the cumulative enrollment to CC-115 in 1,000 simulations (hypothetical enrollment with 1:1:1:1 randomization) compared with the actual enrollment of the CC-115 arm. Adaptive randomization slowed enrollment on the CC-115 arm during the trial. Standard 1:1:1:1 randomization would have enrolled an estimate of 18 patients on the CC-115 arm, compared with 12 patients enrolled in the actual trial.

DISCUSSION

To our knowledge, the INSIGhT trial is the first multicenter, multi-arm APT for glioblastoma, and it was specifically designed to address many of the shortcomings of the clinical trial landscape.[29] INSIGhT is designed to serve as an efficient testing platform by using a shared control arm, biomarker testing capabilities, Bayesian adaptive randomization, and the ability to add new experimental arms (ClinicalTrials.gov identifier: NCT02977780). Conducted across many institutions, the trial accrued rapidly, which demonstrates a feasibility of such master protocol trials for glioblastoma. The three initial experimental arms of INSIGhT demonstrated a lack of clinical benefit that would warrant late-phase testing, and the design obviated the need for three separate randomized phase II trials to evaluate these therapies.

Previous analyses have indicated that the use of single-arm trial designs is a key driver of false positives for experimental therapies that were ultimately found to be ineffective in glioblastoma.[2,30] Randomized designs with control arms have been shown to provide more accurate treatment effect less prone to the inflated type I error rates and biased treatment effect estimates,[31] Randomized designs for phase II studies remain uncommon, however, and enrollment can be challenging because of dropout rates for patients randomly assigned to the control arm.[2] With a shared control arm, INSIGhT increases the likelihood of patients receiving an experimental therapy (starting randomization probability to the control arm was 25%). In a relatively rare disease with a finite number of patients who can participate in clinical trials,[2] this increases the number of patients being evaluated

TABLE 3. Grade 3/4 Adverse Events Certain, Probable or Possibly Attributed to Experimental Therapy

	Abemaciclib		Neratinib		CC-115	
Category	G3	G4	G3	G4	G3	G4
Blood and lymphatic system disorders						
Febrile neutropenia	1	—	2	—	—	—
Gastrointestinal disorders						
Diarrhea	5	—	2	—	—	—
Nausea	1	—	1	—	—	—
Vomiting	—	—	1	—	—	—
General disorders and admin site conditions						
Fatigue	7	—	3	—	—	—
Gait disturbance	1	—	—	—	—	—
Investigations						
Lymphocyte count decrease	13	—	14	—	2	—
Neutrophil count decrease	8	2	—	3	—	—
Platelet count decrease	2	—	3	2	—	—
WBC count decrease	7	—	1	3	—	—
CD4 lymphocyte count decrease	—	—	1	—	—	—
Serum amylase increased	1	—	—	—	—	—
Lipase increased	1	—	—	—	1	—
Weight loss	—	—	1	—	—	—
Metabolism and nutrition disorders						
Anorexia	1	—	—	—	—	—
Dehydration	1	—	—	—	—	—
Hyperuricemia	1	—	—	—	—	—
Hyponatremia	1	—	—	—	—	—
Hyperglycemia	—	—	—	—	2	—
Hypertriglyceridemia	—	—	—	—	1	—
Nervous system disorders						
Headache	1	—	—	—	—	—
Cognitive disturbance	—	—	1	—	—	—
Brain edema	—	—	—	—	1	—
Psychiatric disorders						
Confusion	—	—	—	—	1	—
Skin and subcutaneous tissue disorders						
Rash, maculopapular	—	—	1	—	1	—
Vascular disorders						
Thromboembolic event	—	—	—	—	1	—

Abbreviations: G3, grade 3; G4, grade 4.

with promising experimental therapies without compromising the use of a control arm.

Precision medicine requires biomarker data and validation analyses, use of multiplexed screening procedures, and development of algorithms to optimize treatments.[32] Every patient on INSIGhT was required to undergo prespecified genomic analysis. Each of the three initial experimental therapies had a predetermined biomarker hypothesis that was tested during the trial (eg, EGFR positivity was a prespecified biomarker for neratinib). Furthermore, adaptive randomization probabilities were tailored to each biomarker configuration.[12]

Master protocol trials provide flexibility in trial conduct.[33] For example, a therapy may be more appropriate for testing concurrently with radiation therapy, adjuvantly after standard chemoradiation, or during both phases of therapy. For patients randomly assigned to abemaciclib and neratinib, patients received standard chemoradiation followed by the experimental therapy as adjuvant therapy. For CC-115, where its mechanism of action supported a possible benefit as both a radiosensitizer

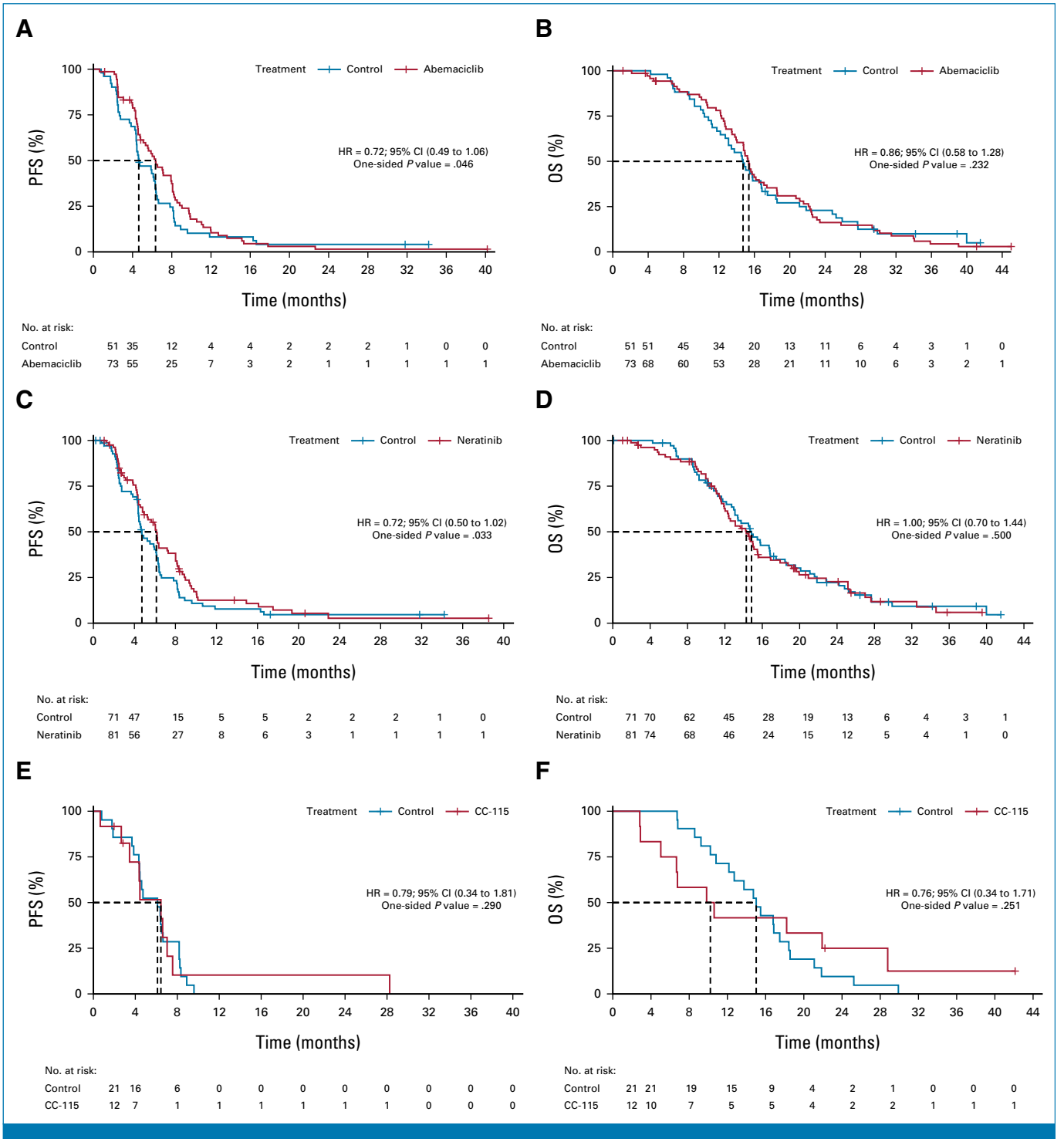

FIG 4. Kaplan-Meier survival curves for (A) PFS and (B) OS of abemaciclib, (C) PFS and (D) OS of neratinib, and (E) PFS and (F) OS of CC-115. HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

and adjuvant monotherapy, it replaced temozolomide during radiation and in the adjuvant phase. Another element of flexibility is the ability to add and drop treatment arms onto the testing platform, which can reduce costs and time by building on the existing INSIGhT infrastructure. Since the completion of the initial three arms, new arms have been added (ClinicalTrials.gov identifier: NCT02977780).

Bayesian adaptive randomization was used with the goal of accelerating accrual to arms that appeared promising based upon early PFS results. Although the attention on adaptive trial designs is often motivated by the potential of rapid identification of beneficial treatments,[11] an overlooked feature is the ability to slow accrual and discard ineffective therapies efficiently, reducing the number of patients

exposed to a therapy unlikely to be successful. With sufficiently mature data on time-to-event outcomes, the decision of discontinuing the evaluation of the experimental treatment can be based on a low number of patients with a sufficient follow-up. Our simulation-based comparison illustrated that the use of response-adaptive randomization reduced the number of patients randomly assigned to CC-115 relative to a conventional 1:1:1:1 randomized design (Data Supplement, Fig S1). Slowed accrual allowed for additional time for information on relevant end points to mature, including toxicity, PFS, and OS. In turn, mature data are crucial for early discontinuation decisions.

Since the initiation of the INSIGhT trial, GBM AGILE has launched as another multiarm platform trial. GBM AGILE shares many features with INSIGhT, including multiple arms, a shared control arm, and Bayesian adaptive randomization.[34] In contrast to INSIGhT, GBM AGILE was developed as a seamless phase II/III with a built-in registrational component for both patients with newly diagnosed and recurrent glioblastoma. The INSIGhT trial, GBM AGILE, other master platform trials such as the N2M2,[35] and the upcoming MAGMA trial[36] are poised to serve as efficient clinical testing platforms that accelerate efficient drug development for glioblastoma.

There were several challenges and limitations in the conduct of the INSIGhT trial that provide considerations for future trial design in glioblastoma. Bayesian adaptive randomization introduces statistical complexity that requires greater collaboration and dependence on biostatistical expertise. Adaptive randomization also requires more labor-intensive tracking of data (eg, to update randomization probabilities monthly per protocol). Of note, abemaciclib (median PFS 6.3 months *v* control median PFS 4.6 months) and neratinib (median PFS 6.1 months *v* control median 4.7 months) were associated with improved PFS, but this PFS improvement was small in magnitude and did not translate to a survival benefit. Although PFS was chosen as an end point to inform adaptive randomization and to identify early signals of efficacy, our results raise concern regarding the use of PFS as basis of adaptive randomization in this disease setting.[37] In reviewing patient imaging of trial patients across all arms, there were instances of misreported progression dates because of a lack of backdating to the initial scan of concern, as is required per RANO criteria[38]; this emphasizes the importance of central radiology review[39] for trials to minimize risk of this in the future. Since centralized MGMT pathology testing was not implemented, we cannot exclude the possibility of false negative testing results by locally determined MGMT assays.

In conclusion, the adaptive platform design of INSIGhT allows for efficient testing of experimental arms for glioblastoma. Although there was no evidence of survival benefit for abemaciclib, neratinib, or CC-115 compared with standard chemoradiation, additional experimental arms have been added and are now being evaluated through INSIGhT.

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CLINICAL TRIAL INFORMATION

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DATA SHARING STATEMENT

Although there is a plan for sharing of deidentified patient-level data, the INSIGhT trial is currently ongoing with new arms that use a shared control arm (per protocol). Data will be made available for sharing after the trial is completed.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Inaugural Results of the Individualized Screening Trial of Innovative Glioblastoma Therapy: A Phase II Platform Trial for Newly Diagnosed Glioblastoma Using Bayesian Adaptive Randomization

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