original reports

Alliance A071401: Phase II Trial of Focal Adhesion Kinase Inhibition in Meningiomas With Somatic *NF2* Mutations

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abstract

PURPOSE Patients with progressive or recurrent meningiomas have limited systemic therapy options. Focal adhesion kinase (FAK) inhibition has a synthetic lethal relationship with *NF2* loss. Given the predominance of *NF2* mutations in meningiomas, we evaluated the efficacy of GSK2256098, a FAK inhibitor, as part of the first genomically driven phase II study in recurrent or progressive grade 1-3 meningiomas.

PATIENTS AND METHODS Eligible patients whose tumors screened positively for *NF2* mutations were treated with GSK2256098, 750 mg orally twice daily, until progressive disease. Efficacy was evaluated using two coprimary end points: progression-free survival at 6 months (PFS6) and response rate by Macdonald criteria, where PFS6 was evaluated separately within grade-based subgroups: grade 1 versus 2/3 meningiomas. Per study design, the FAK inhibitor would be considered promising in this patient population if either end point met the corresponding decision criteria for efficacy.

RESULTS Of 322 patients screened for all mutation cohorts of the study, 36 eligible and evaluable patients with *NF2* mutations were enrolled and treated: 12 grade 1 and 24 grade 2/3 patients. Across all grades, one patient had a partial response and 24 had stable disease as their best response to treatment. In grade 1 patients, the observed PFS6 rate was 83% (10/12 patients; 95% CI, 52 to 98). In grade 2/3 patients, the observed PFS6 rate was 33% (8/24 patients; 95% CI, 16 to 55). The study met the PFS6 efficacy end point both for the grade 1 and the grade 2/3 cohorts. Treatment was well tolerated; seven patients had a maximum grade 3 adverse event that was at least possibly related to treatment with no grade 4 or 5 events.

CONCLUSION GSK2256098 was well tolerated and resulted in an improved PFS6 rate in patients with recurrent or progressive *NF2*-mutated meningiomas, compared with historical controls. The criteria for promising activity were met, and FAK inhibition warrants further evaluation for this patient population.

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

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INTRODUCTION

Meningiomas are the most common primary brain tumor, representing 38% of all primary brain tumors.[1] Although most meningiomas can be managed primarily with surgery or radiation, a subset of meningiomas recur. Patients with progressive or recurrent meningiomas have limited treatment options after failure of surgery and radiation.[2] Furthermore, recurrent meningiomas are more aggressive with shorter progression-free survival (PFS) and higher likelihood of being refractory to treatment.[3-5] Historically, there have been multiple negative trials of systemic therapies in meningiomas.[2] Many prior trials were small and underpowered and based on a limited understanding of the molecular drivers of meningiomas.

In the 1990s, frequent inactivating mutations in *NF2* were discovered in sporadic meningiomas.[6-8] *NF2* is the most commonly mutated gene in meningioma, and progressive meningiomas are enriched for *NF2* mutations.[9-11] Recent advances in sequencing technologies have led to a number of seminal papers that further defined the genetic landscape of meningiomas.[9,12-16] Recurrent genetic alterations have now been described in a number of genes including *AKT1*, *PIK3CA*, and *SMO,* in addition to the well-established *NF2* gene.[9,13] The recurrent mutations in *AKT1*, *PIK3CA*, and

CONTEXT

Key Objective

Patients with recurrent or progressive meningiomas have limited therapeutic options once surgery and radiation fail. The objective of this study was to evaluate the efficacy of focal adhesion kinase (FAK) inhibition in meningiomas, as part of the national genomically driven phase II study in meningiomas.

Knowledge Generated

We demonstrated that FAK inhibition with GSK2256098 resulted in an improved 6-month progression-free survival compared with historical controls in patients with meningiomas harboring somatic alterations in *NF2*. Furthermore, treatment with GSK2256098 was well tolerated, with no grade 4 or 5 events.

Relevance

As this study met its overall trial end point, FAK inhibition is worthy of further exploration for patients with recurrent or progressive meningiomas.

SMO offer potential for therapeutic targets,[17,18] as they are hotspot mutations typical of oncogenic drivers[19] and are mutually exclusive from *NF2* alterations.

On the basis of these data, we initiated a national genomically guided National Cancer Institute–supported Cooperative Group Trial (Alliance A071401) in patients with progressive or recurrent meningioma harboring specific mutations. The arms of the study include an AKT inhibitor for *AKT*- or *PIK3CA*-mutated meningiomas, a SMO inhibitor for *SMO*-mutated meningiomas, a focal adhesion kinase (FAK) inhibitor for *NF2*-altered tumors, and a cyclin-dependent kinase (CDK) inhibitor for CDK pathway altered tumors. We now report the results from the *NF2*-altered cohort and the other study arms are ongoing.

FAK inhibition with GSK2256098 for *NF2*-mutant meningioma was evaluated because preclinical work in mesothelioma demonstrated a strong synthetic lethal relationship with loss of merlin, the protein product of *NF2*.[20] FAK is a protein tyrosine kinase that regulates cellular proliferation, invasion, and stem-cell renewal through integrating signals from growth factor receptors and integrins.[20] Preclinical studies have shown that low merlin expression is predictive of sensitivity to FAK inhibition, likely because of the disruption of the weak cell-extracellular matrix or cell-cell adhesions in merlin-negative cells.[20] The role of FAK inhibition in meningiomas has not previously been evaluated clinically. Herein, we present the results of the FAK inhibitor arm of Alliance for Clinical Trials in Oncology trial A071401, which has now completed accrual and met the primary end point.

PATIENTS AND METHODS

Study Oversight

The study was designed by the principal investigators and conducted in accordance with the provision of the Declaration of Helsinki and Good Clinical Practice guidelines. The Central Institutional Review Board approved the Protocol (online only). All patients provided signed informed consent.

Patients

Eligible patients had histologically proven intracranial meningioma as documented by central pathology review, and measurable disease as defined by bidimensionally measurable enhancing lesions with a minimum diameter of 10 mm in both dimensions. A tumor sample from each patient underwent central genetic testing for arm determination. Presence of an *NF2* alteration in the tumor tissue was required for the GSK2256098 treatment arm of the study. Patients must have had progressive or residual disease as defined by the following: residual measurable disease immediately after surgery for WHO grade 2 or 3 disease, progressive measurable disease as defined by an increase in the size of the measurable primary lesion on imaging by 25% or more in 12 months, or progressive disease after completion of radiation. For patients with residual measurable grade 1 disease immediately after surgery, progression preoperatively needed to be documented with an increase in size of the primary lesion on imaging by 25% or more in 12 months. Additional details regarding eligibility criteria are provided in the Data Supplement (online only).

Study Design, Treatment, and End Points

GSK2256098 was administered orally at 750 mg orally twice daily for a 28-day cycle until disease progression, excessive toxicity, symptomatic neurologic deterioration, or study consent withdrawal. Details regarding dose reductions are provided in the Data Supplement.

Contrast-enhanced brain magnetic response imaging was obtained every 8 weeks for restaging using a consensus magnetic response imaging protocol.[21] The coprimary end points were 6-month progression-free survival (PFS6) and response rate (RR) as determined using Macdonald criteria[22] by local investigator review. PFS6 was defined as the number of patients not having progressive disease or death within 6 months of the first day of treatment divided by the total number of evaluable patients. RR was defined as the number of responses divided by the total number of evaluable patients.

A patient was deemed to have a response if they had a confirmed partial response (PR) or complete response.

Statistical Analysis

This is a prospective, one-stage, multiarm phase II study evaluating the efficacy of targeted therapies in patients with specific mutations. Each of the mutation groups in this trial is evaluated in parallel with a separate phase II study design. Herein we are reporting the results of the FAK inhibitor treatment arm. Within each arm defined by tumor mutation and inhibitor, there are two different patient cohorts included on the basis of histology: grade 1 versus 2/3 meningiomas. Efficacy was evaluated using two coprimary end points: RR and PFS6. To accommodate these two coprimary end points and their simultaneous evaluation for a given treatment arm, a Bonferroni correction[23] was used to further constrain the one-sided type I error (bounded at 5% per arm). The RR end point was powered and evaluated across all patients regardless of grade for the given study arm ($\alpha = .012$). The PFS6 end point was calculated and powered as a proportion and evaluated within each grade cohort (nested within each arm; grade 1: $\alpha = .014$, grade 2/3: $\alpha = .020$). Power calculations were performed with EAST v6.3 and PASS 15.01. Per study design, the treatment would be considered promising in the mutation group for this patient population if the decision criteria for either end point were met.

For the GSK2256098 treatment arm reported here, a total of 36 evaluable patients were required to provide at least 94% power to detect a true RR of at least 20%, with a significance level of 0.013 against the null hypothesis of a true RR of 2.5%. For this end point, the agent would be considered worthy of further testing in this mutation-defined treatment arm if at least four responses (ie, $\geq 11.1\%$) were observed among the 36 evaluable patients. For the PFS end point within the grade 2/3 cohort of the GSK2256098 treatment arm, a total of 24 evaluable patients provided at least 85% power to detect a true PFS6 rate of at least 41.5%, with a significance level of 0.02 against the null hypothesis that the true PFS6 rate was 15%. If at least 8 of these 24 evaluable patients (at least 33.3%) were progression-free and alive at 6 months, the agent would be considered worthy of further testing in this mutation-defined grade 2/3 cohort. Within the grade 1 cohort, a total of 12 evaluable patients provided at least 79% power to detect a true PFS6 rate of at least 65%, with a significance level of 0.014 against the null hypothesis of 25% PFS6 rate. Here, if at least 7 of the 12 evaluable patients (at least 58%) demonstrated PFS6, the agent would be considered worthy of further testing in this mutation-defined grade 1 cohort. The null hypotheses for each of the grade-based subgroups described above were based on historical benchmark data obtained from a systematic review of prior published reports of medical therapies in meningiomas,[2] where PFS6 was 23%-29% in grade 1 meningioma and 0%-29% in trials of grade 2/3 meningiomas, with 14% as the median across most trials of grade 2/3 meningioma. The first 12 (grade 1 cohort) and 24 (grade 2/3 cohort) patients who met the eligibility criteria, signed the consent form, and began treatment were considered evaluable for the safety end points as well as secondary and exploratory end points. Patients also had to have had evaluable imaging data unless they died within the first 6 months of study entry to be included in the primary end point analysis.

The secondary end points, overall survival and progression free-survival, were summarized for each cohort within each treatment arm with Kaplan-Meier[24] curves and estimates. PFS is a time-to-event outcome defined as the time from initiation of treatment to the time of progression and/or death. Patients who were alive and progression-free at the time of their last evaluation were censored at that time point. No formal comparisons were made between the grade cohorts. An additional secondary end point was the rate of adverse events (AEs) in each cohort. AEs were graded by the site investigators according to CTCAE Version 4.0 and were summarized as the number and graded severity of each AE by type as well as aggregated and summarized by incidence of any AE, any AEs grade 3 or greater, and any AEs grade 4 or greater. Additional details regarding data collection, monitoring, and analysis are provided in the Data Supplement.

Targeted Molecular Profiling

Molecular profiling was carried out as described in the Data Supplement.[25-29]

RESULTS

Patients

A total of 322 patients were screened for all mutation cohorts of the study; 101 patients were preregistered to the study while the GSK2256098 treatment arm was open and 38 patients were enrolled to the GSK2256098 arm. Between August 28, 2015, and May 18, 2016, and between April 14, 2017 and July 19, 2017, 12 patients were enrolled to the WHO grade 1 cohort and 26 to the WHO grade 2/3 cohort (Fig 1). One grade 2/3 patient was deemed ineligible upon centralized review. Another patient received one cycle of therapy and went off study treatment because of grade 3 AST and grade 3 ALT (both deemed probably related to study treatment). Since no scans beyond baseline were available on this patient for the first year, they were not considered evaluable for the primary end points; this patient is still included in safety and baseline characteristic summaries. Thus, there were 12 grade 1 and 24 grade 2/3 patients evaluable for the coprimary end points (Table 1). Across all 37 eligible patients who received treatment on this study, the median age at study enrollment was 64 years (range, 22-76 years) and 18 were male (48.6%; Table 1). The majority of patients (33/37 = 89.2%) had an Eastern Cooperative Oncology Group performance status of 0 or 1 at study entry. All patients had received surgery related to their meningioma, 29 patients (78.4%) had received radiation therapy for their tumor, and 12

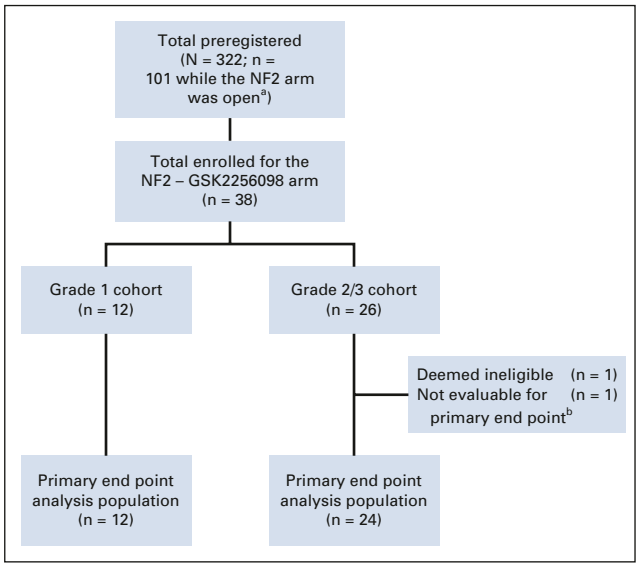

FIG 1. CONSORT diagram of patient population. [a]Eighty-nine patients were identified as having *NF2* mutation while the NF2 arm was opened to accrual and 12 were allowed to be registered while the NF2 arm was closed to accrual as they were already in preregistration. From May 8, 2016 to April 14, 2017 (when the *NF2* arm closed to accrual for grade 2/3 tumors), *NF2* mutation testing was performed if the patient had a grade 1 tumor. [b]Because of having resection after registration and tumor was multifocal. [c]One grade 2/3 cohort patient received only one cycle of treatment, then went off study treatment because of grade 3 AST and grade 3 ALT (both deemed probably related to study treatment). This patient had a baseline scan and no other scans until 1 year from study entry (because of patient follow-up visits cancellations) and was excluded from primary end point analysis. End of study treatment reasons (all enrolled patients): 1 grade 1 cohort patient and 3 grade 2/3 cohort patients withdrew/refused further treatment, 3 grade 1 cohort patients and 1 grade 2/3 cohort patient ended study treatment because of adverse events/side effects/complications, and 8 grade 1 cohort patients and 21 grade 2/3 cohort patients ended study treatment because of disease progression. One grade 2/3 cohort patient remains in study treatment 4 years from study initiation.

patients (32.4%) had received prior systemic therapy (Table 1). Twenty-eight patients (75.7%) received at least two prior treatment modalities.

Efficacy

In the grade 1 cohort, patients received a median of 11 treatment cycles and in the grade 2/3 cohort, four cycles (Data Supplement). At 6 months, 10 of 12 grade 1 patients (83%) and 8 of 24 (33%) grade 2/3 patients were progression-free and alive (Table 2). The best response was stable disease in 10 (83%) grade 1 and 14 (58%) grade 2/3 patients and PR in one grade 2/3 (4%) patient (Table 3). The decision rule was not met for RR, with only one PR observed in a grade 2/3 cohort patient with a 5.5-month duration of response. The PFS6 efficacy end point criteria were met for both grade-based cohorts and thus met the overall criteria for the FAK inhibitor to be considered promising in each of the cohorts. One patient still remains on treatment 4 years after starting on study. The median overall survival has not yet been reached for grade 1, and was 21.5 months (95% CI, 14.8 to 38.0) for grade 2/3 patients (Fig 2A). The median PFS was 12.8 months (95% CI, 9.2 to not reached) for grade 1 patients and 3.7 months (95% CI, 3.6 to 7.2) for grade 2/3 patients (Fig 2B). In a secondary analysis, the Alliance Imaging Central Lab centrally reviewed all images for 33 patients, where the remaining three patients did not have films available for central review (Data Supplement).

Toxicity

Five patients across both cohorts (13.9%) had dose modifications in at least once cycle (Data Supplement). Four patients were taken off study because of AEs, side effects, or complications (Data Supplement). Fifteen patients had grade 3 events regardless of attribution and seven patients had treatment-related grade 3 events (Data Supplement). Grade 3 AEs at least possibly related to treatment included proteinuria, pain, lymphopenia, rash, nervous system disorder, ALT/AST elevation, cholecystitis, and hypertriglyceridemia (Table 4).

Exploratory Analyses

In an exploratory analysis, when data were available (n = 10), we calculated pretreatment growth rates (Data Supplement). Those patients who were progression-free and alive at 6 months had an observable decline in their tumor growth rates in relation to the tumor growth rates observed in the 6 months before study entry. Changes in tumor size on treatment were also evaluated across all patients (Data Supplement). Seven patients with grade 1 tumors had observed reductions in tumor areas that did not meet criteria for PR, and nine with grade 2/3 tumors had observed reductions in tumor area, one of which met criteria for PR (Data Supplement). We did not detect a statistically significant difference in baseline tumor area measurements between those patients who were classified as progression-free and alive at 6 months and those who progressed at 6 months (Data Supplement).

Molecular profiling of all tumor samples using targeted next-generation sequencing was also carried out, which included genes implicated as being frequently altered and/or prognostic in meningioma including alterations in *CDKN2A, TERT* promoter, *SMARCB1, SMO, AKT, PIK3CA*, and *PTEN* (Fig 3 and Data Supplement). We evaluated whether specific genetic mutations correlated with clinical outcomes. Notably, we did not detect an association between PFS6 and mutational status of *CDKN2A* or *TERT* promoter (Data Supplement), both of which have been described to correlate with poor prognosis and progression in meningiomas.[5,30-33]

DISCUSSION

Approximately 33,000 meningiomas are diagnosed each year.[1] The management of recurrent and progressive meningioma represents an enormous unmet need in neuro-oncology. Recurrent meningiomas can have significant morbidity and mortality, and have no effective medical

TABLE 1. Patient Characteristics

Characteristic	Grade 1 (n = 12)	Grade 2/3 (n = 25)	Total (N = 37)
Age, years, No. (%)			
Mean (SD)	54.6 (16.1)	60.2 (14.5)	58.4 (15.1)
Median	50.5	64.0	64.0
Q1, Q3	45.0, 69.5	55.0, 70.0	46.0, 70.0
Range	22.0-75.0	23.0-76.0	22.0-76.0
Sex, No. (%)			
Female	8 (66.7)	11 (44.0)	19 (51.4)
Male	4 (33.3)	14 (56.0)	18 (48.6)
Race, No. (%)			
White	10 (83.3)	21 (84.0)	31 (83.8)
Black or African American	1 (8.3)	3 (12.0)	4 (10.8)
Asian	0 (0.0)	1 (4.0)	1 (2.7)
American Indian or Alaska Native	1 (8.3)	0 (0.0)	1 (2.7)
Ethnicity, No. (%)			
Hispanic	2 (16.7)	0 (0.0)	2 (5.4)
Non-Hispanic	9 (75.0)	24 (96.0)	33 (89.2)
Unknown	1 (8.3)	1 (4.0)	2 (5.4)
ECOG performance status, No. (%)			
0	3 (25.0)	8 (32.0)	11 (29.7)
1	9 (75.0)	13 (52.0)	22 (59.5)
2	0 (0.0)	4 (16.0)	4 (10.8)
Status of tumor at registration, No. (%)			
Progressive measurable disease	7 (58.3)	14 (56.0)	21 (56.8)
Residual measurable disease	4 (33.3)	6 (24.0)	10 (27.0)
Both	1 (8.3)	5 (20.0)	6 (16.2)
Multifocal disease, No. (%)			
Yes	4 (33.3)	10 (40.0)	14 (37.8)
No	8 (66.7)	15 (60.0)	23 (62.2)
Tumor grade, No. (%)			
1	12 (100.0)	0 (0.0)	12 (32.4)
2	0 (0.0)	19 (76.0)	19 (51.4)
3	0 (0.0)	6 (24.0)	6 (16.2)
Corticosteroid therapy at study entry, No. (%)			
No	11 (91.7)	20 (80.0)	31 (83.8)
Yes	1 (8.3)	5 (20.0)	6 (16.2)
Previous surgery related to this tumor (biopsies, resections, etc), No. (%)			
Yes	12 (100.0)	25 (100)	37 (100)
Prior radiation therapy for this tumor, No. (%)			
Yes	10 (83.3)	19 (76.0)	29 (78.4)
No	2 (16.7)	6 (24.0)	8 (21.6)

(continued on following page)

TABLE 1. Patient Characteristics (continued)

Characteristic	Grade 1 (n = 12)	Grade 2/3 (n = 25)	Total (N = 37)
Prior systemic (cancer) therapy for this tumor, No. (%)			
Yes	4 (33.3)	8 (32.0)	12 (32.4)
No	8 (66.7)	17 (68.0)	25 (67.6)
No. of prior systemic (cancer) therapy for this tumor, No. (%)			
1	3 (75.0)	5 (62.5)	8 (66.7)
2	1 (25.0)	1 (12.5)	2 (16.7)
3	0 (0.0)	2 (25.0)	2 (16.7)
Unknown	0	1	1
No. of prior systemic (cancer) therapies, No. (%)			
Mean (SD)	1.3 (0.5)	1.6 (0.9)	1.5 (0.8)
Median	1.0	1.0	1.0
Range	(1.0-2.0)	(1.0-3.0)	(1.0-3.0)
No. of prior therapy modalities, No. (%)			
1	2 (16.7)	7 (28.0)	9 (24.3)
2	6 (50.0)	10 (40.0)	16 (43.2)
3	4 (33.3)	8 (32.0)	12 (32.4)
No. of prior therapies (any modality), No. (%)			
Mean (SD)	5.2 (1.6)	5.6 (3.1)	5.5 (2.7)
Median	5.0	6.0	5.0
Range	2.0-8.0	1.0-12.0	1.0-12.0
Any prior cancer diagnosis, No. (%)			
Yes	5 (41.7)	5 (20.0)	10 (27.0)
Spine	1	1	2
Acute lymphoid leukemia	0	1	1
Anal	1	0	0
Pediatric cystic tumor	1	0	1
Prostate	0	1	1
Vestibular schwannoma	1	0	0
Leukemia	1	0	0
Petroclival meningioma	0	1	1
Skin, basal cell	0	1	1
No	7 (58.3)	20 (80.0)	27 (73.0)

NOTE. Excludes ineligible patient.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; Q1, quartile 1; Q3, quartile 3; SD, standard deviation.

therapy when surgery and radiation have failed. There has been a paucity of trials for meningiomas, which has further limited our ability to investigate the efficacy of therapeutic agents in this disease. The advent of improved sequencing technologies has led to an enhanced understanding of the molecular underpinnings driving meningiomas. We now know that meningiomas are characterized by distinct, mutually exclusive genetic subgroups.[9,12-16,30,34-36] To that end, to our knowledge, we conducted the first national genomically guided trial for this disease under the auspices of Alliance for Clinical Trials in Oncology. We demonstrated that this study design is feasible in a multicenter setting for this patient population. Importantly, FAK inhibition with GSK2256098 was well tolerated, with no grade 4 or 5 toxicities, and was associated with an improvement in PFS6 compared with historical controls.

Historically, targeting tumor suppressors, such as *NF2*, has been therapeutically challenging. Inhibition of FAK in *NF2*-mutated meningiomas clinically leveraged the concept of synthetic lethality, whereby loss of a tumor suppressor

TABLE 2. PFS at 6 Months

PFS at 6 Months	Grade 1 Cohort (N = 12), No. (%) (95% CI)	Grade 2/3 Cohort (N = 24), No. (%) (95% CI)	Total (N = 36), No. (%) (95%CI)
Progression-free and alive	10 (83) (52 to 98)	8 (33) (16 to 55)	18 (50) (33 to 67)
Progression or death	2 (17) (2 to 48)	16 (67) (45 to 84)	18 (50) (33 to 67)

Abbreviation: PFS, progression-free survival.

increases the efficacy of pharmacologically inhibiting another gene product.[20] This is analogous to poly(adenosine diphosphate-ribose) polymerase inhibition in tumors harboring mutations in *BRCA1* or *BRCA2*.[37,38] We demonstrate for the first time, to our knowledge, that this is a promising therapeutic approach in meningiomas. These data complement analogous results suggesting that GSK2256098 has clinical activity in patients with mesothelioma with merlin loss.[39]

We chose PFS6 and RR as coprimary end points because an improvement in either of these end points would be clinically meaningful for this patient population as there are no standard medical therapies. As such, the type I error for this study was tightly controlled to limit the likelihood of false-positive results and to further support our ability to evaluate the two clinical outcomes of interest for this patient population. One of the major challenges with designing trials in meningiomas is that previously conducted trials do not use consistent end points or uniform response criteria. A response assessment in neuro-oncology (RANO) systematic review of 47 prior studies of medical therapy in meningioma composed of 164 patients was conducted to carefully define the clinical course and benchmarks for overall survival, PFS, and PFS6; on the basis of recommendations from this systematic review, we chose PFS6 as one of the end points.[2] The null hypotheses for each of the grade-based subgroups were based on the historical data obtained from this previously published RANO review,[2] where PFS6 was reportedly 23%-29% in grade 1 meningioma and 0%-29% in trials of grade 2/3 meningiomas, with 14% as the median across most trials of grade 2/3 meningioma. Since the publication of this RANO review, recent clinical trials for patients with meningiomas have used PFS6 as a primary end point with similar null hypotheses as used in A071401.[40,41] The null hypothesis for RR was selected because RR has been close to 0% in the majority of studies of systemic therapies in recurrent or progressive meningiomas.[2] We demonstrated that the clinical benefit of GSK2256098 was primarily accomplished through stabilization of the meningioma and inhibition of growth: disease stability is clinically meaningful for this heavily pretreated patient population.

Toxicity of medical therapy is an important consideration for patients with meningioma who potentially could stay on therapy for prolonged periods of time. GSK2256098 was well tolerated with only seven patients experiencing grade 3 treatment-related AEs and none having grade 4 or 5 AEs. As the effect of long-term medical therapies on quality of life in meningiomas is an understudied area, future studies could benefit from more detailed neurocognitive evaluations and patient-reported outcomes to evaluate the impact of GSK2256098 on neurocognition and quality of life.

The study has some limitations. First, this was a small phase II study comparing to historical controls and not a randomized controlled trial. However, given the possible accrual challenges frequently encountered in trials for uncommon brain tumors, our goal was to limit the sample size, while powering the study to detect a promising signal. Before this study, there was no precedent for a national precision medicine trial in rare primary brain tumors using an umbrella approach where patients are assigned to treatment arms on the basis of molecular characteristics. In addition, the majority of prior meningioma trials of medical therapy have had very small patient numbers. Our objective was to design a trial that could be conducted within a reasonable time frame to demonstrate both that a genomically guided trial was feasible in this patient population and that this approach could swiftly guide the development of effective novel therapies for meningioma. To this end, we used the end point of PFS6 and historical control data as recommended by the recent RANO systematic review, which is becoming standard for the field of

TABLE 3. Best Response (Macdonald criteria)

	Grade 1 Cohort (n = 12)	Grade 2/3 Cohort (n = 24)	Total (N = 36)
Best Response	**No. (%) (95% CI)**	**No. (%) (95% CI)**	**No. (%) (95% CI)**
CR	0	0	0
PR	0	1 (4.2) (0.5 to 26.1)	1 (2.8) (0.4 to 18.7)
SD	10 (83.3) (55.2 to 95.3)	14 (58.3) (34.6 to 78.8)	24 (66.7) (46.3 to 82.3)
PD	2 (16.7) (4.7 to 44.8)	9 (37.5) (18.2 to 61.8)	11 (30.6) (15.7 to 50.9)

NOTE. Simultaneous CIs for multinomial proportions using the Quesenberry and Hurst (1964) method.
Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

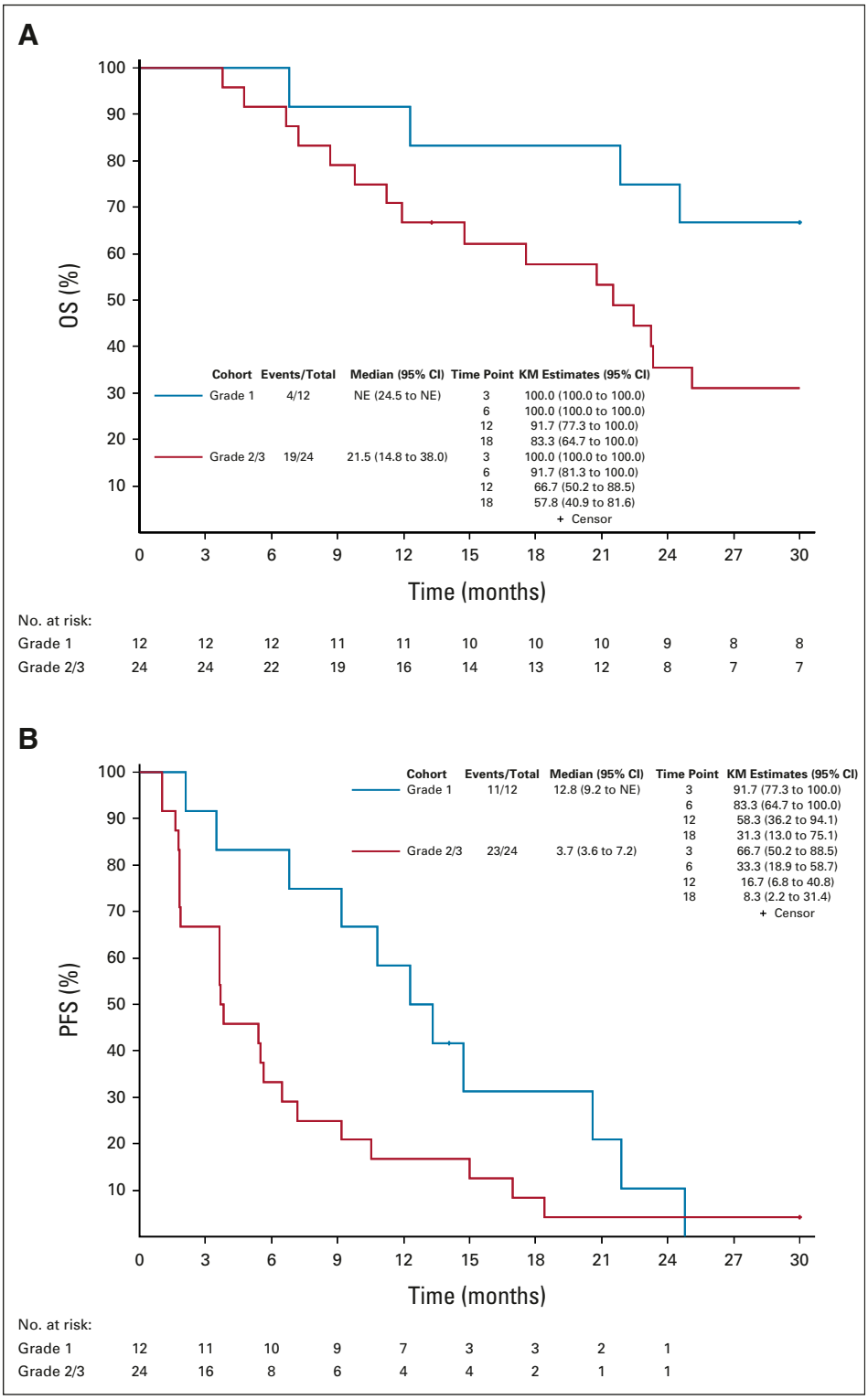

FIG 2. KM curves of OS and PFS for patients treated with GSK2256098. (A) KM curve of OS (note that a total of 13 censors were observed after month 30). The median OS for the grade 1 cohort was not yet reached and for the grade 2/3 cohort was 21.5 months. (B) KM curve of PFS. The median PFS was 12.8 months for the grade 1 cohort and 3.7 months for the grade 2/3 cohort. KM, Kaplan-Meier; NE, not evaluable; OS, overall survival; PFS, progression-free survival.

TABLE 4. Listing of Grade 3+ AEs Max Grade per Patient per Event at Least Possibly Related Number of Evaluable Patients: 37

AE	Grade of AE		
	3-Severe, No. (%)	4-Life-Threatening, No. (%)	5-Lethal, No. (%)
Hematologic AEs			
Blood/bone marrow			
Lymphopenia	1 (3)	0 (0)	0 (0)
Nonhematologic AEs			
Nervous system disorders	1 (3)	0 (0)	0 (0)
Rash maculopapular	1 (3)	0 (0)	0 (0)
Hepatic			
ALT, SGPT	1 (3)	0 (0)	0 (0)
AST, SGOT	1 (3)	0 (0)	0 (0)
Cholecystitis	1 (3)	0 (0)	0 (0)
Metabolic/laboratory			
Triglyceride, serum-high	1 (3)	0 (0)	0 (0)
Pain			
Pain	1 (3)	0 (0)	0 (0)
Renal/genitourinary			
Proteinuria	2 (5)	0 (0)	0 (0)

Abbreviation: AE, adverse event.

meningiomas.[2,40-42] Second, given the requirement for tissue, all patients needed a surgical intervention before this study. Future studies can benefit from the identification of noninvasive biomarkers such cell-free DNA for the detection of clinically actionable mutations,[43] as this would also enable a neoadjuvant approach in meningiomas as well as facilitate assessment of response to treatment.

In conclusion, we present the results of an umbrella, genomically driven clinical trial design for patients with meningioma focusing on the investigation of the efficacy of FAK inhibition in patients with *NF2*-mutated meningiomas. The trial met its overall trial end point, confirming that FAK inhibition is worthy of further exploration in patients with meningioma both in preclinical and clinical studies. Further investigation to evaluate FAK inhibition in combination with other compounds is also warranted. Trials evaluating the efficacy of agents such as dual mTOR inhibitors in *NF2*-driven meningioma are also being conducted and are preliminarily showing encouraging results.[42] Data from these trials may pave the way for promising combinatorial approaches for the management of patients with meningioma.

Additional arms of this novel genomically guided clinical trial are actively accruing. As more data emerge from this and other trials, precision medicine approaches are expected to be integrated into meningioma treatment paradigms.

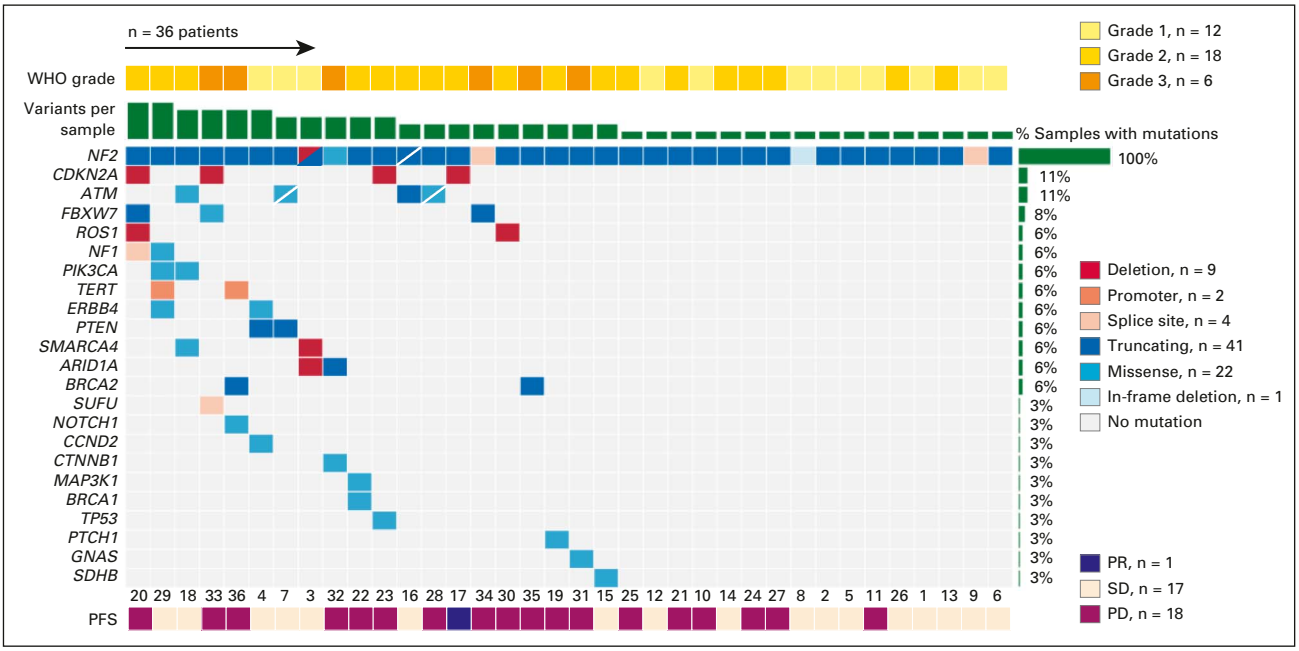

FIG 3. Mutational landscape in meningioma trial patients. CoMut plot displaying grade, genetic variants, and best response at 6 months. The top and side histograms (green) represent total number and fraction of reported variants per sample or gene, respectively. For a detailed list of variant annotations, see the Data Supplement. CoMut plot, Comutation plot; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

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DISCLAIMER

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REFERENCES

1. Ostrom QT, Patil N, Cioffi G, et al: CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2013-2017. Neuro Oncol 22:iv1-iv96, 2020
2. Kaley T, Barani I, Chamberlain M, et al: Historical benchmarks for medical therapy trials in surgery- and radiation-refractory meningioma: A RANO review. Neuro Oncol 16:829-840, 2014
3. Tian W, Liu J, Zhao K, et al: Analysis of prognostic factors of World Health Organization grade meningiomas. Front Oncol 10:593073, 2020
4. Wilson TA, Huang L, Ramanathan D, et al: Review of atypical and anaplastic meningiomas: Classification, molecular biology, and management. Front Oncol 10: 565582, 2020

5. Juratli TA, Thiede C, Koerner MVA, et al: Intratumoral heterogeneity and TERT promoter mutations in progressive/higher-grade meningiomas. Oncotarget 8: 109228-109237, 2017
6. Lekanne Deprez RH, Bianchi AB, Groen NA, et al: Frequent NF2 gene transcript mutations in sporadic meningiomas and vestibular schwannomas. Am J Hum Genet 54:1022-1029, 1994
7. Rouleau GA, Merel P, Lutchman M, et al: Alteration in a new gene encoding a putative membrane-organizing protein causes neuro-fibromatosis type 2. Nature 363:515-521, 1993
8. Ruttledge MH, Sarrazin J, Rangaratnam S, et al: Evidence for the complete inactivation of the NF2 gene in the majority of sporadic meningiomas. Nat Genet 6: 180-184, 1994
9. Brastianos PK, Horowitz PM, Santagata S, et al: Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. Nat Genet 45:285-289, 2013
10. Goutagny S, Yang HW, Zucman-Rossi J, et al: Genomic profiling reveals alternative genetic pathways of meningioma malignant progression dependent on the underlying NF2 status. Clin Cancer Res 16:4155-4164, 2010
11. Peyre M, Stemmer-Rachamimov A, Clermont-Taranchon E, et al: Meningioma progression in mice triggered by Nf2 and Cdkn2ab inactivation. Oncogene 32: 4264-4272, 2013
12. Abedalthagafi M, Bi WL, Aizer AA, et al: Oncogenic PI3K mutations are as common as AKT1 and SMO mutations in meningioma. Neuro Oncol 18:649-655, 2016
13. Clark VE, Erson-Omay EZ, Serin A, et al: Genomic analysis of non-NF2 meningiomas reveals mutations in TRAF7, KLF4, AKT1, and SMO. Science 339:1077-1080, 2013
14. Sahm F, Schrimpf D, Olar A, et al: TERT promoter mutations and risk of recurrence in meningioma. J Natl Cancer Inst 108:djv377, 2016
15. Sahm F, Schrimpf D, Stichel D, et al: DNA methylation-based classification and grading system for meningioma: A multicentre, retrospective analysis. Lancet Oncol 18:682-694, 2017
16. Shankar GM, Abedalthagafi M, Vaubel RA, et al: Germline and somatic BAP1 mutations in high-grade rhabdoid meningiomas. Neuro Oncol 19:535-545, 2017
17. Sekulic A, Migden MR, Oro AE, et al: Efficacy and safety of vismodegib in advanced basal-cell carcinoma. N Engl J Med 366:2171-2179, 2012
18. Yan Y, Serra V, Prudkin L, et al: Evaluation and clinical analyses of downstream targets of the Akt inhibitor GDC-0068. Clin Cancer Res 19:6976-6986, 2013
19. Vogelstein B, Papadopoulos N, Velculescu VE, et al: Cancer genome landscapes. Science 339:1546-1558, 2013
20. Shapiro IM, Kolev VN, Vidal CM, et al: Merlin deficiency predicts FAK inhibitor sensitivity: A synthetic lethal relationship. Sci Transl Med 6:237ra68, 2014
21. Ellingson BM, Bendszus M, Boxerman J, et al: Consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials. Neuro Oncol 17: 1188-1198, 2015
22. Macdonald DR, Cascino TL, Schold SC Jr, et al: Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 8:1277-1280, 1990
23. US Food and Drug Administration: Multiple Endpoints in Clinical Trials; Draft Guidance for Industry. Federal Register: The Daily Journal of the United States Government, Silver Spring, MD, Docket No. FDA-2016-D-4460:4353-4354, 2017
24. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Amer Statist Assoc 53:457-481, 1958
25. Zheng Z, Liebers M, Zhelyazkova B, et al: Anchored multiplex PCR for targeted next-generation sequencing. Nat Med 20:1479-1484, 2014
26. Cibulskis K, Lawrence MS, Carter SL, et al: Sensitive detection of somatic point mutations in impure and heterogeneous cancer samples. Nat Biotechnol 31:213-219, 2013
27. DePristo MA, Banks E, Poplin R, et al: A framework for variation discovery and genotyping using next-generation DNA sequencing data. Nat Genet 43:491-498, 2011
28. McKenna A, Hanna M, Banks E, et al: The Genome Analysis Toolkit: A MapReduce framework for analyzing next-generation DNA sequencing data. Genome Res 20:1297-1303, 2010
29. Van der Auwera GA, Carneiro MO, Hartl C, et al: From FastQ data to high confidence variant calls: The Genome Analysis Toolkit best practices pipeline. Curr Protoc Bioinformatics 43:11.10.1-11.10.33, 2013
30. Mirian C, Duun-Henriksen AK, Juratli T, et al: Poor prognosis associated with TERT gene alterations in meningioma is independent of the WHO classification: An individual patient data meta-analysis. J Neurol Neurosurg Psychiatry 91:378-387, 2020
31. Sievers P, Hielscher T, Schrimpf D, et al: CDKN2A/B homozygous deletion is associated with early recurrence in meningiomas. Acta Neuropathol 140:409-413, 2020
32. Williams EA, Santagata S, Wakimoto H, et al: Distinct genomic subclasses of high-grade/progressive meningiomas: NF2-associated, NF2-exclusive, and NF2-agnostic. Acta Neuropathol Commun 8:171, 2020
33. Bostrom J, Meyer-Puttlitz B, Wolter M, et al: Alterations of the tumor suppressor genes CDKN2A (p16(INK4a)), p14(ARF), CDKN2B (p15(INK4b)), and CDKN2C (p18(INK4c)) in atypical and anaplastic meningiomas. Am J Pathol 159:661-669, 2001
34. Sievers P, Stichel D, Hielscher T, et al: Chordoid meningiomas can be sub-stratified into prognostically distinct DNA methylation classes and are enriched for heterozygous deletions of chromosomal arm 2p. Acta Neuropathol 136:975-978, 2018
35. Clark VE, Harmanci AS, Bai H, et al: Recurrent somatic mutations in POLR2A define a distinct subset of meningiomas. Nat Genet 48:1253-1259, 2016
36. Juratli TA, McCabe D, Nayyar N, et al: DMD genomic deletions characterize a subset of progressive/higher-grade meningiomas with poor outcome. Acta Neuropathol 136:779-792, 2018
37. Iglehart JD, Silver DP: Synthetic lethality—A new direction in cancer-drug development. N Engl J Med 361:189-191, 2009
38. Kaelin WG Jr: The concept of synthetic lethality in the context of anticancer therapy. Nat Rev Cancer 5:689-698, 2005
39. Soria JC, Gan HK, Blagden SP, et al: A phase I, pharmacokinetic and pharmacodynamic study of GSK2256098, a focal adhesion kinase inhibitor, in patients with advanced solid tumors. Ann Oncol 27:2268-2274, 2016
40. Preusser M, Silvani A, Le Rhun E, et al: Trabectedin for recurrent WHO grade 2 or 3 meningioma: A randomized phase 2 study of the EORTC Brain Tumor Group (EORTC-1320-BTG). Neuro Oncol 24:755-767, 2022
41. Graillon T, Sanson M, Campello C, et al: Everolimus and octreotide for patients with recurrent meningioma: Results from the phase II CEVOREM trial. Clin Cancer Res 26:552-557, 2020
42. Plotkin S, Kumthekar P, Wen P, et al: Multi-center, single arm phase II study of the dual mTORC1/mTORC2 inhibitor vistusertib for patients with recurrent or progressive grade II-III meningiomas. J Clin Oncol 39, 2021 (suppl 15; abstr 2024)
43. Cheng J, Cao Y, MacLeay A, et al: Clinical validation of a cell-free DNA gene panel. J Mol Diagn 21:632-645, 2019

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Alliance A071401: Phase II Trial of Focal Adhesion Kinase Inhibition in Meningiomas With Somatic NF2 Mutations

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