Stipulation(s):
A response to the following is required:

Protocol:

1. On page 82, Table #3T, "Slice Thickness" row, add the reference to footnote (i) in the "3DT1 Post" Column.

   PI Response: This has been corrected in Appendix II in the 3T Protocol table.

Recommendation(s):
A response to the following is not required because these recommendations do not impact the protection of study participants or the regulatory criteria for IRB approval.

Protocol
Summary of Change Table:

1. Fix the typo in the change that references section 3.3; "…the word "no" has been **adding**…". Change to added.

   PI Response: This has been corrected in the summary of changes.

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE A071401

PHASE II TRIAL OF SMO/AKT/NF2 INHIBITORS IN PROGRESSIVE MENINGIOMAS WITH SMO/AKT/NF2 MUTATIONS

Industry-supplied agent(s): Vismodegib (IND #126926) and GSK2256098 (IND #126926); IND holder: Alliance

X	**Update:**		**Status Change:**
	Eligibility changes		Activation
	Therapy / Dose Modifications / Study Calendar changes		Closure
X	Informed Consent changes		Suspension / temporary closure
X	Scientific / Statistical Considerations changes		Reactivation
	Data Submission / Forms changes		
X	Editorial / Administrative changes		
X	Other: Added requirement for all scans to be submitted for retrospective central radiology review		

Expedited review is allowed. IRB approval (or disapproval) is required within 90 days. Please follow your IRB of record guidelines.

UPDATES TO THE PROTOCOL

Cover Page
Meagan Wilts has replaced Carla Hilton as the data manager. Contact information has been updated accordingly.

Section 1.2 (Genetic Analysis of Meningioma)
In the first paragraph, a new second from last sentence has been added for clarity ("Additionally, 7% of NF2-wildtype meningiomas harbor oncogenic alterations in PIK3CA").

Section 1.11 (Central Radiology Review)
With this update, the protocol will be modified to require all scans to be submitted for retrospective central radiology review. This section has been added to provide background regarding this change.

Section 2.2 (Secondary Objectives)
Objective 2.2.3 has been added to include the new objective to determine activity of SMO and FAK inhibitor as measured by response rate by central radiology review.

Section 3.3 (Registration Eligibility Criteria)
In Section 3.3.7 (Patient History), the word "No" has been added to the beginning of bullets 4-9 for clarity.

Section 5.0 (Study Calendar)
- Footnote 3 has been revised to state that all MRIs must be submitted to the Imaging Core Laboratory, not just DCE MRI.
- A new final sentence has been added to Footnote A: "All MRIs should follow the consensus MRI protocol outlined in Appendix II even if the site is not acquiring the DCE sequence."

Section 6.5 (CT and MRI Imaging Data Submission)
- A new first paragraph has been added (starting with "Acquisition of MR imaging…") in order to state the defined MR imaging parameters.
- The second paragraph of Section 6.5 has been modified to state that all MR images should be submitted to IROC. A sentence has also been added to state that any MRI performed prior to approval of Update #05 should be transmitted to IROC.
- In the third paragraph, a new final sentence has been added for clarity: "The DCE MRI acquisition protocol is outlined in Appendix III."
- In the fourth paragraph, the phrase, "For all patients," has been added to the first sentence.

Section 9.3 (Expedited Adverse Event Reporting [CTEP-AERS])
At the bottom of the table in Section 9.3.1, the following statement has been removed "NOTE: Deaths clearly due to progressive disease should NOT be reported via CTEP-AERS but rather should be reported via routine reporting methods (e.g., CDUS and/or CTMS)." Below the table, this statement also appeared as the seventh bullet under the heading "Additional Instructions or Exclusions to CTEP-AERS Expedited Reporting Requirements for Phase 1 and Early Phase 2 Trials Utilizing an Agent Under a non-CTEP IND:" Therefore, the seventh bullet has been removed as this exclusion is not correct. All deaths, even those clearly due to progressive disease are required to be submitted as an adverse event via CTEP-AERS.

Section 11.0 (Measurement of Effect)
The following sentence has been added to the end of the section: "Primary endpoint will be based on local radiology review. Central radiology review will be carried out for measurement of secondary endpoint."

Section 12.1 (Duration of Treatment)
In Section 12.1.1 (CR, PR or SD), the following underlined text has been added for clarity: ": Patients who are in CR, PR or SD , as assed by local radiology review, will continue on therapy…."

Section 13.4 (Supplementary Analysis Plans)
- The following underlined text has been added to the first sentence: "Overall survival and progression free survival will be summarized…."
- A third paragraph has been added to outline how response rate will be determined by central review.

Appendix II (Required Consensus MRI Acquisition Parameters)
- Appendix II has been added in order to provide a clear distinction between the required consensus MRI acquisition parameters (formerly referred to as "Standard MRI Protocols") and the advanced

DCE imaging protocols that are to be used for patients who elect to participate in the advanced imaging study.

- Above the tables, a second paragraph describing the MRI acquisition parameter requirements has been added. A third paragraph has also been added that states: "For any patients enrolled prior to Update #05 (or with images acquired prior to Update #05), MRI parameters should remain consistent with baseline or prior image acquisition protocols."
- In the 1.5T table, the following changes have been made:
    - Footnote j has been added below the table, which reads: "FOV and matrix size should be chosen to keep resolution *less than* 1.5mm isotropic voxel size. Note that all voxel measurements should be equal in x, y, and z dimensions."
    - In the "FOV" row, the following has been added in the "3D T1 Pre" and "3D T1 Post" columns: "(for ≤ 1.5mm isotropic)[j]"
    - In the "Slice Thickness" row, references to footnote j have been added in the "3D T1 Pre" and "3D T1 Post" columns.
    - In the "Parallel Imaging" row, the text has been changed from "Yes-If available" to "Up to 2x.
- In the 3T Protocol table, the following changes have been made:
    - Footnote i has been added below the table, which reads: "FOV and matrix size should be chosen to keep resolution at 1mm isotropic voxel size. Note that all voxel measurements should be equal in x, y, and z dimensions."
    - In the "FOV" row, references to footnote i have been added in the "3D T1 Pre" and "3D T1 Post" columns.
    - In the "Slice Thickness" row, references to footnote i have been added in the "3D T1 Pre" and "3D T1 Post" columns.

Appendix III 1.5T & 3T ADVANCED MRI PROTOCOL

- The 1.5T and 3T advanced MRI protocols have been separated out into two separate tables.
- The parameters for 1.5T and 3T MRI have been completely revised for clarity and to allow for whole brain coverage given that meningiomas can be larger and occasionally there can be multiple.

CHANGES TO THE MODEL CONSENT

What extra tests and procedures will I have if I take part in this study?

At the end of the section, a paragraph has been added to describe that image submission to a central image library is now required as part of the patient's study participation. This was also added to clarify that only the advanced imaging is optional, not image submission.

A replacement protocol document and model consent form have been issued

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ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A071401

PHASE II TRIAL OF SMO/AKT/NF2 INHIBITORS IN PROGRESSIVE MENINGIOMAS WITH SMO/AKT/NF2 MUTATIONS

Industry-supplied agent(s): Vismodegib (IND #126926), GSK2256098 (IND #126926); IND holder: Alliance

ClinicalTrials.gov Identifier: NCT 02523014

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Study Resources:

Expedited Adverse Event Reporting **http://eapps-ctep.nci.nih.gov/ctepaers/**	**Medidata Rave iMedidata portal** https://login.imedidata.com
OPEN (Oncology Patient Enrollment Network) https://open.ctsu.org	**Biospecimen Management System** http://bioms.allianceforclinicaltrialsinoncology.org

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Protocol-related questions may be directed as follows:

Questions	Contact (via email)
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox regulatory@allianceNCTN.org
Questions regarding CTEP-AERS reporting:	Regulatory Affairs Manager regulatory@allianceNCTN.org (773) 702-9814
Questions regarding initial specimens/specimen submissions:	Sandro Santagata, MD, PhD

Document History	Effective Date:		
Activation	08/28/2015	Update #05	XX/XX/XXXX
Update #01	11/01/2015		
Update #02	12/01/2015		
Update #03	06/15/2016		
Update #04	06/15/2016		

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead National Clinical Trial Network (NCTN) Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only)	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Do <u>not</u> submit study data or forms to CTSU Data Operations. Do <u>not</u> copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member website located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
<u>For clinical questions (i.e., patient eligibility or treatment-related)</u> see the Protocol Contacts, Page 2.		
<u>For non-clinical questions (i.e., or questions unrelated to patient eligibility, treatment, or clinical data submission</u> contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU website is located at https://www.ctsu.org.		

Phase II Trial Of SMO/AKT/NF2 Inhibitors In Progressive Meningiomas With SMO/AKT/ NF2 Mutations

Pre-Registration Eligibility Criteria (see Section 3.2)
Local diagnosis of meningioma and have tissue available for central path review and SMO and NF2 testing.

Registration Eligibility Criteria (See Section 3.3)
Presence of SMO or NF2 mutation (see section 3.3.1)
Progressive or residual disease as defined in section 3.3.1
Measurable disease as defined by a bi-dimensionally measurable main lesion on MRI or CT images (MRI preferred)
(See Section 3.3.2)
No chemotherapy, other investigational agents within 28 days of study treatment.
No other concurrent investigational agents or other meningioma-directed therapy (chemotherapy, radiation)
> 24 weeks must have elapsed from completion of XRT to registration
Steroid dosing stable for at least 4 days
Recovered to CTCAE grade 1 or less toxicity
Not pregnant and not nursing
Age ≥ 18 years
ECOG Performance Status ≤ 2
Stable for lesions for 6 months for patients with history of NF. See 3.3.7.
No metastatic meningiomas (as defined by extracranial meningiomas).
No history of allergic reactions attributed to compounds of similar biologic composition to assigned study drug
No known active hepatitis B or C
Current Child Pugh Class B or C liver disease
No uncontrolled gastric ulcer disease (See Section 3.3.7)
No uncontrolled diabetes. See Section 3.3.7.
No abdominal fistula, GI perforation, or intra-abdominal abscess within 28 days prior to registration
No CYP3A4 inhibitors for 14 days prior to registration. See Section 7.2

Required Initial Laboratory Values

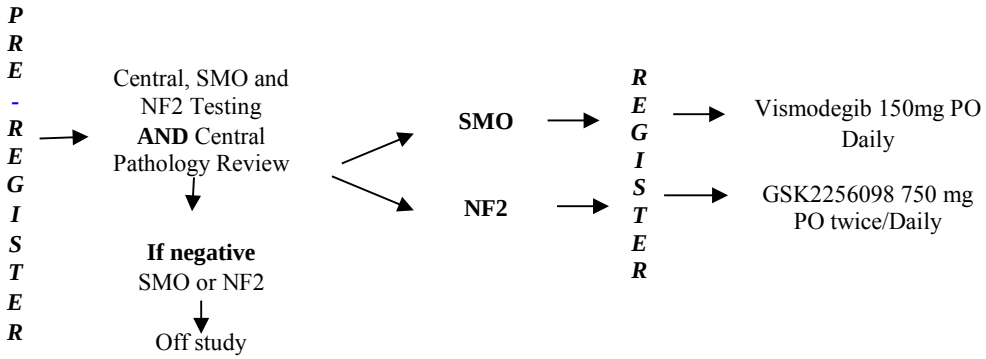
Absolute neutrophil count (ANC)	≥ 1500/mm^3
Platelet Count	≥ 100,000/mm3
Creatinine OR	≤ 1.5 mg/dl x upper limit of normal (ULN) OR
Calc. Creatinine Clearance	> 45 mL/min
UPC	≥ 45mg/mmol*
Total Bilirubin	≤ 1.5 x ULN**
AST / ALT	≤ 2.5 x ULN
Fasting triglyceride	≤ 200mg/dL*
Fasting cholesterol	≤ 240mg/dL*
QTcF***	≤ 500 msec*

* ONLY APPLICABLE for patients with NF2 mutation
** Except in cases of Gilbert's disease
*** QT calculated using Fridericia formula: QTc = QT/(RR^0.33), where RR = 60/HR

Schema

1 Cycle = 28 Days

Note: Pregnancy prevention must start 4 weeks prior to study drug.



Treatment is to continue until disease progression or unacceptable adverse event. Patients discontinuing treatment for reasons other than progressive disease, will continue following the Study Calendar for disease assessments until progressive disease is documented, for a maximum of 2 years. Patients will be followed for survival up to a maximum of 5 years from registration.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

Table of Contents

1.0 BACKGROUND

1.1 The Natural History of Meningioma

Meningiomas are the most common primary brain tumor, with a prevalence of 170,000 cases in the US and an annual incidence of 18,000 new cases. Most meningiomas are of the typical (Grade I) variety. However, depending on their location within the nervous system, grade I meningiomas can cause significant morbidity or mortality. Even after surgical resection, recurrence rates can be as high as 20%[1-3], and patients with Grade I tumors have reduced long-term survival.

Approximately 20% of meningiomas are atypical (Grade II) and anaplastic (Grade III), defined by increased mitoses, necrosis, higher nuclear to cytoplasmic ratios, or histologic appearance resembling carcinoma, sarcoma, or melanoma[4]. Recurrence rates for Grade II and III meningiomas are 40% and 80%, respectively[3]. The prognosis of atypical and anaplastic meningiomas is poor, with 5-year overall survival rates between 47-65%[5,6].

Treatment options, particularly for the atypical or anaplastic meningiomas, are limited[5]. Radiation is frequently used as an adjunct to surgery; however, there are no effective chemotherapeutic options when surgery and radiation fail to offer durable long-term disease control[7]. Traditional cytotoxic agents have minimal activity in this setting[8,9], and targeted agents in unselected patients[10] have demonstrated modest benefit at best. Response rate has been 0% in nearly all studies of systemic therapy in recurrent tumors of all grades[9,11-13]. A poor understanding of what drives meningioma development has hampered the development of therapeutic agents to supplement surgery and radiation. Therefore these patients have limited therapeutic options and effective treatments are greatly needed.

Agent	Result
Irinotecan[8]	0% response rate, 5 month TTP
Hydroxyurea[9]	0% response rate, 2 month median PFS
Imatinib + Hydroxyurea[10]	0% response rate, 7month median PFS
Interferon[12]	0% response, 7month TTP
Gefitinib[13]	0% response, 16 week median PFS
Erlotinib[13]	0% response, 9 week median PFS

1.2 Genetic Analysis of Meningioma

The tumor suppressor *NF2* is disrupted in approximately half of meningiomas. A subset of meningiomas lacking *NF2* alterations harbor recurrent oncogenic mutations in *AKT1,* a member of the PI3K/AKT/mTOR pathway, and *SMO,* a key component of the hedgehog pathway[14,15]. Specifically, 8-13% of meningiomas have recurrent oncogenic mutations in *AKT1* (E17K)[14,15] and 15% exhibit immunohistochemical evidence of PI3K/AKT/mTOR pathway activation[14]. Five percent of meningiomas harbor mutations in *SMO* (W535L and L412F)[14,15] and 10% exhibit evidence of Hedgehog pathway activation (Figure 1)[14]. Additionally, 7% of NF2-wildtype meningiomas harbor oncogenic alterations in PIK3CA{Abedalthagafi, 2016 #92}. Notably, many of these mutations occur in meningiomas of the skull base, which are historically the most difficult to treat surgically[15,16].

Based on this data, there are several potential biomarkers that have now been identified in meningioma. As this is a disease which lacks effective therapies, the potential for biomarker driven therapy is of great interest.

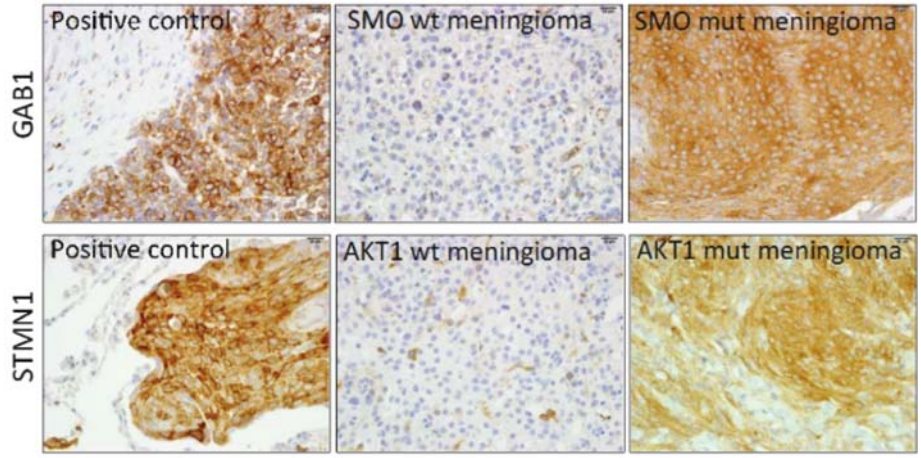


Figure 1: Immunohistochemistry indicates activation of the Hedgehog (GAB1) and AKT-mTOR (STMN1) pathways in meningiomas harboring *SMO* and *AKT1* mutations, respectively. (Brastianos et al. Nature Genetics 2013)

1.3 Available Agents that act on SMO, AKT and NF-2 mutated tumors.

NOTE: Afuresertib, the agent identified for patients with *AKT1* mutation is not currently available. Testing for the *AKT1* mutation will commence once afuresertib becomes available and sites are notified via a protocol amendment. Tumor samples will only be tested for *SMO* and *NF2* mutations until further notice.

Therapies that target these mutations are currently in clinical use in other cancers. SMO mutations lead to aberrant activation of the Hedgehog (Hh) pathway. Evidence suggests that antagonism of excessive Hh signaling may provide a route to unique mechanism-based anticancer therapies[17]. Vismodegib, a small-molecule inhibitor of SMO, is associated with tumor responses in patients with basal-cell carcinoma, the majority of which have genetic alterations in the hedgehog signaling pathway. In a Phase II trial of vismodegib in locally advanced or metastatic basal cell carcinoma, response rates ranged from 30-43%[18]. Vismodegib is well-tolerated. Common adverse events of any grade of vismodegib included muscle spasms (68%), alopecia (63%), dysgeusia (51%), weight loss (46%), fatigue (36%), nausea (29%), decrease in appetite (23%) and diarrhea (22%). Serious adverse events were reported in 25% of patients.

AKT is a serine/threonine protein kinase with 3 isoforms (AKT1, AKT2, and AKT3) that participate in multiple pathways regulating several cellular processes, including survival, proliferation, tissue invasion, and metabolism. The importance of AKT-mediated pathways in tumor proliferation, survival, and resistance to chemotherapy and targeted agents, make AKT kinases promising targets for therapeutic intervention. Afuresertib is an investigational oral, low nanomolar pan-AKT kinase inhibitor that is being developed for the treatment of hematologic and solid tumor malignancies.[19,20] As of 29-Jun-2014, 302 subjects have been exposed to afuresertib. In a Phase I study of 73 patients with advanced hematologic malignances, afuresertib had a favorable safety profile with the most frequent adverse events being nausea (35.6%), diarrhea (32.9%), and dyspepsia (24.7%). In the limited clinical data available from current studies, responses have been reported in multiple myeloma, Non-Hodgkin's lymphoma and Landerhans cell histiocytosis (GlaxoSmithKline Investigator's Brochure).

FAK is a nonreceptor protein tyrosine kinase that integrates signals from integrins and growth factor receptors; it regulates proliferation, survival, migration, invasion, and cancer stem cell renewal[21]. It is overexpressed in many cancers, including anaplastic meningiomas[22]. Low merlin product (the protein product of NF2) predicts sensitivity to FAK inhibition, likely because of the disrupted balance between cell-extracellular matrix and cell-cell interactions[23, 24]. Given the predominance of NF2 inactivating events in meningiomas[14], we chose to evaluate FAK inhibition as a potential therapy for patients with *NF2*-mutated tumors.

GSK2256098 is a potent small molecule inhibitor of focal adhesion kinase (FAK) that is in clinical development for the treatment of cancer. As of August 2014, there was 1 completed Phase I study in healthy volunteers and two ongoing Phase I studies in subjects with solid tumors. In a Phase I single arm study in subjects with advanced, refractory solid tumors, subjects received continuous daily oral doses of GSK2256098 at doses ranging from 80 mg to 1500 mg BID. Overall, in 62 patients, the most frequently reported AEs associated with continuous oral BID dosing of GSK2256098 were nausea (76%), diarrhea (65%), vomiting (58%), decreased appetite (47%), proteinuria (26%), fatigue (24%), asthenia (23%), hyperbilirubinaemia (23%), constipation (21%) and hypercholesterolemia (21%). In the 55 patients that underwent at least one post-dose imaging assessment, stable disease (SD) was achieved by 28 subjects 14 mesothelioma subjects, 4 subjects with ovarian cancer and, 2 subjects with colorectal cancer and 1 subject with each of the following cancers: bile duct, kidney, melanoma, nasopharynx, non-small cell lung cancer, pancreas, renal cell, and thyroid. (GSK Investigator's Brochure).

1.4 Vismodegib (GDC-0449)

The hedgehog (Hh) signaling pathway is a crucial mediator of embryogenesis[25]. Signaling is initiated by the binding of the secreted morphogen, Hh, to its receptor, patched 1 (Ptch1). In the unbound state, Ptch1 inhibits Smoothened (SMO), a G-protein coupled phosphoprotein receptor, by preventing its localization to the cell surface; however, in the presence of the Hh ligand, the Hh-Ptch1 complex is internalized and the repression of Ptch1 on SMO is relieved. Surface localization of SMO is thought to initiate a signaling cascade, leading to the activation of the glioma-associated (*Gli*) family of zinc finger transcription factors, many of which are involved in proliferation, survival, and angiogenesis.

Aberrant activation of the Hh pathway in cancers is caused by mutations in the pathway or through Hh overexpression, termed either ligand-independent or ligand-dependent, respectively[26,27]. Past studies have identified mutations in the Hh receptor components, Ptch1 or SMO in basal cell carcinoma (BCC), medulloblastoma, and meningiomas resulting in pathway activation[14,28,29]. Excessive or inappropriate expression of the Hh ligand has been found in a significant proportion of patients with sporadic cancers of the gastrointestinal tract, pancreas, lung and prostate, suggesting that disruption of Hh signal transduction could potentially be beneficial in a broad array of tumor types[30,31]. Evidence suggests that antagonism of excessive Hh signaling may provide a route to unique mechanism-based anticancer therapies, blocking tumor growth and stimulating tumor regression without toxic effects on normal adjacent tissue[17].

Vismodegib is a small-molecule antagonist of the Hh signal pathway. Specifically, vismodegib binds to and inhibits SMO, blocking Hh signal transduction. *In vitro* and *in vivo* preclinical studies have demonstrated inhibition of Hh signaling following vismodegib administration. Vismodegib has demonstrated efficacy against a variety of primary human tumor xenografts, including colorectal cancer (CRC) and pancreatic adenocarcinoma, and tumor cell-line

xenograft models. Inhibition of Hh signaling in xenograft models has been correlated with a decrease in tumor growth.

Vismodegib has been studied in several clinical trials including a phase 1 clinical trial in patients with advanced solid malignancies[32], which demonstrated that vismodegib is well-tolerated with no dose-limiting toxicities (DLTs) observed at any of the doses tested (150, 270, and 540 mg of vismodegib). A Phase II study in basal cell carcinoma demonstrated response rates of 30-43% in locally advanced and metastatic basal cell carcinoma, with a well-tolerated toxicity profile[18].

1.5 Clinical Experience with Vismodegib

SHH3925g

A Phase I, company-sponsored clinical trial (SHH3925g) assessed the safety and pharmacokinetics (PK) of vismodegib and responses of 68 patients with solid tumors[33]. Thirty-three of the 68 patients had metastatic or locally advanced BCC. They received oral vismodegib at one of three doses: 17 patients received 150 mg per day, 15 patients received 270 mg per day, and 1 patient received 540 mg per day (median duration of treatment was 9.8 months).

Pharmacokinetic and pharmacodynamics studies with concentration-time profiles at 150 mg, 270 mg, or 540 mg showed that patients achieved Cmax by Day 2, with little decline in concentrations over the ensuing 6-day washout period. Also there was similar steady-state levels of vismodegib across all dosing cohorts, indicating non-linearity in PK with regard to dose. The PK study demonstrated high-affinity, reversible binding to AAG and binding to albumin, in addition to solubility-limited absorption and slow metabolic elimination properties.

EKG studies were performed and showed no apparent relationship between plasma vismodegib concentrations and prolongation of the QT interval.

The rate of grade 4 events for the trial was 9%. Of the 33 patients with basal cell carcinoma, 18 had an objective response to vismodegib, 2 had complete responses (CRs) and 16 had partial responses (PRs). The other 15 patients had either stable disease (11 patients) or progressive disease (4 patients). A patient with medulloblastoma also responded.

SHH4318g

Study SHH4318g was an open-label study planned for a single refractory medulloblastoma pediatric patient. The cerebrospinal fluid (CSF) concentration of vismodegib reached a maximum concentration on Day 14 with a value of 14.9 ng/mL. The estimated unbound concentration of vismodegib in CSF was similar to the unbound concentration measured in plasma, suggesting that effective levels of drug reached the CNS.

SHH4476g

A multicenter, international, two-cohort, nonrandomized, pivotal, Phase II, company-sponsored study (SHH4476g) enrolled patients with metastatic BCC and those with locally advanced BCC who had inoperable disease or for whom surgery was inappropriate (because of multiple recurrences and a low likelihood of surgical cure, or substantial anticipated disfigurement)[18]. In 33 patients with metastatic BCC, the independently assessed response rate was 30% (95% confidence interval [CI], 16 to 48; p=0.001). In 63 patients with locally advanced BCC, the independently assessed response rate was 43% (95% CI, 31 to 56; p<0.001), with complete responses in 13 patients (21%). The median duration of response was 7.6 months in both cohorts at the time of data cutoff.

Muscle spasms, alopecia, dysgeusia, weight loss, and fatigue occurred in more than 30% of patients, whereas serious adverse events (SAEs) were reported in 25% of patients. Seven deaths due to AEs were reported and none of the deaths were related to vismodegib. Based on the results of this pivotal trial, vismodegib was approved on January 30, 2012 by the United States Food and Drug Administration (US FDA) for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation[34].

Most Frequent Treatment Emergent Adverse Events (>10% of patients) at the 18-Month Update

Adverse Event, n (%)	NCI CTCAE Grade, (N = 104)					
	Total	**1**	**2**	**3**	**4**	**5**
Any adverse events	**104 (100.0)**	**11 (10.6)**	**38 (36.5)**	**34 (32.7)**	**13 (12.5)**	**7 (6.7)**
Muscle spasms	74 (71.2)	49 (47.1)	19 (18.3)	6 (5.8)	0	0
Alopecia	68 (65.4)	48 (46.2)	20 (19.2)	n/a	n/a	n/a
Dysgeusia	57 (54.8)	31 (29.8)	26 (25.0)	n/a	n/a	n/a
Weight decreased	53 (51.0)	29 (27.9)	17 (16.3)	7 (6.7)	n/a	n/a
Fatigue	44 (42.3)	32 (30.8)	7 (6.7)	4 (3.8)	1 (1.0)	0
Nausea	34 (32.7)	25 (24.0)	9 (8.7)	0	0	0
Decreased appetite	28 (26.9)	18 (17.3)	7 (6.7)	3 (2.9)	0	0
Diarrhea	28 (26.9)	20 (19.2)	5 (4.8)	3 (2.9)	0	0
Constipation	20 (19.2)	14 (13.5)	6 (5.8)	0	0	0
Cough	20 (19.2)	16 (15.4)	4 (3.8)	0	0	0
Vomiting	18 (17.3)	15 (14.4)	3 (2.9)	0	0	0
Arthralgia	17 (16.3)	12 (11.5)	4 (3.8)	1 (1.0)	0	0
Headache	15 (14.4)	12 (11.5)	3 (2.9)	0	0	0
Nasopharyngitis	13 (12.5)	11 (10.6)	2 (1.9)	0	0	0
Squamous cell carcinoma	12 (11.5)	3 (2.9)	5 (4.8)	3 (2.9)	0	0
Ageusia	12 (11.5)	8 (7.7)	4 (3.8)	n/a	n/a	n/a
Hypogeusia	11 (10.6)	10 (9.6)	1 (1.0)	n/a	n/a	n/a

Expanded Access Study (SHH4811g) in Advanced BCC

An open-label, single-arm, multicenter, expanded access study (SHH4811g) of an oral repeating dose of vismodegib was conducted in patients with locally advanced or metastatic BCC, who are otherwise without satisfactory treatment options. Safety of vismodegib and objective response in patients with measurable disease (RECIST v1.0) were assessed[35]. The observed objective response rates were 46.4% (95% CI, 33.0%, 60.3%) for patients with laBCC (n = 56) and 30.8% (95% CI, 17.0%, 47.6%) for patients with mBCC (n = 39). Complete response, partial response and stable disease were observed in 10.7%, 35.7%, and 48.2%, respectively, of patients with laBCC; no patients in this cohort exhibited PD as best response. For patients with mBCC, complete response, partial response and stable disease rates observed were 5.1%, 25.6%, and 51.3%, respectively. 7.7% of patients in this cohort exhibited PD as best response. Among patients with laBCC who responded the median and mean times to response were 2.6 months and 3.5 months, respectively; and among patients with mBCC who responded the median and mean times to response were 2.6 months and 3.8 months, respectively.

As of the final analysis data cutoff date of 23 April 2012, 116 of 119 safety evaluable patients (97.5%) experienced at least one adverse event (22 SAEs total). Adverse events that had the highest reported occurrences (≥ 20%) in 119 safety evaluable patients were: muscle spasms (84 patients; 70.6%), dysgeusia (84 patients; 70.6%), alopecia (69 patients; 58.0%), and diarrhea (30 patients; 25.2%). Only one of 22 SAEs (4.5%) was assessed as being related to treatment with vismodegib: a Grade 3 muscle spasm, reported in 1 patient. There have been three deaths among 119 safety-evaluable patients (2.5%); 2 assessed as unrelated to study drug, and 1 patient with PD.

SHH4811g Vismodegib Expanded Access Study Common Treatment-Emergent Adverse Events

TEAEs (n=120)	Median Time to AE Onset, Days (95% CI)*	All AEs, n (%)	Gr 1, n (%)	Gr 2, n (%)	Gr 3, n (%)	Gr 4, n (%)	Gr 5, n (%)
Muscle spasms	37 (28-44)	84 (70.0)	63 (52.5)	19 (15.8)	2 (1.7)	–	–
Dysgeusia	41 (30-51)	84 (70.0)	68 (56.7)	16 (13.3)	n/a	n/a	n/a
Alopecia	87 (74-104)	69 (57.5)	57 (47.5)	12 (10.0)	n/a	n/a	n/a
Diarrhea	38 (22-116)	30 (25.0)	23 (19.2)	5 (4.2)	1 (0.8)	1 (0.8)	–
Nausea	30 (11-130)	23 (19.2)	19 (15.8)	4 (3.3)	–	–	–
Fatigue	42 (16-120)	23 (19.2)	14 (11.7)	8 (6.7)	1 (0.8)	–	–
Weight decreased	175 (114-293)	19 (15.8)	12 (10.0)	7 (5.8)	–	–	–

*For those patients experiencing the TEAE

MO25616

Study MO25616 ("STEVIE") is an ongoing Phase II open-label, single-arm, multicenter (ex-United States) study of vismodegib in patients with locally advanced or metastatic BCC who are otherwise without satisfactory treatment options. As of 19 Oct 2012, data were available for 300 patients (278 patients with laBCC and 22 patients with mBCC) with follow-up information for at least 3 months after treatment. The median age of the 300 patients was 72.5 years.

As of 19 Oct 2012, 278 of 300 safety-evaluable patients (92.7%) experienced Grade 3 to 5 treatment-emergent adverse events. The most frequently reported adverse events (≥ safety-evaluable patients), regardless of relationship to study drug, in descending order of frequency, were: muscle spasms (178 patients; 59.3%); alopecia (148 patient; 49.3%); dysgeusia (123 patients; 41.0%); ageusia (77 patients; 25.7%); and asthenia (70 patients; 23.3%).

As of 19 Oct 2012, 53 of 300 patients (17.7%) experienced 74 SAEs. There were 13 deaths reported in the study; 2 were due to disease progression (1 patient each for laBCC and mBCC), 9 were due to AEs assessed by the investigator as unrelated to study drug, 1 was due to an AE assessed by the investigator as related to treatment (cardiopulmonary failure) and 1 was due to "other reason" (multi-organ failure).

A total of 251 of 300 patients had RECIST-measurable disease at baseline and at least one post-baseline assessment. Preliminary efficacy data analysis showed an investigator assessed best overall response (complete response + partial response) of 144/251 (57%). The median time to first best response was 57 days (range, 13 to 363 days).

STEVIE MO25616 Treatment-Emergent Adverse Events (>10% of patients)

Most common TEAEs[a]	All (n=300)	Grade 3	Grade 4
Muscle spasms	178 (59.3%)	15 (5.0%)	0
Alopecia	148 (49.3%)	3 (1.0%)*	n/a
Dysgeusia	123 (41.0%)	6 (2.0%)	0
Ageusia	77 (25.7%)	9 (3.0%)	2 (0.7%)*
Asthenia	70 (23.3%)	5 (1.7%)	0
Weight decreased	48 (16.0%)	3 (1.0%)	0
Decreased appetite	47 (15.7%)	4 (1.3%)	0
Nausea	43 (14.3%)	0	0
Fatigue	38 (12.7%)	5 (1.7%)	0

*Adverse events shown here are as reported by the investigator.

Pharmacokinetics of vismodegib

Briefly, vismodegib's pharmacokinetic profile is a result of high affinity, reversible binding to Alpha-1 acid Glycoprotein (AAG) and binding to albumin, in addition to solubility limited

absorption and slow metabolic elimination properties[36]. Initiation of less frequent administration schedules than the approved dose and schedule of vismodegib of 150 mg orally once daily,(i.e. 150 mg three times weekly or 150 mg once weekly dosing), was associated with marked decrease in the pharmacologically active unbound fraction. Unbound steady-state vismodegib concentrations were 60% and 85% lower for the TIW and QW dose groups, respectively, relative to the QD dose group[32]. Such decreases may be associated with loss of vismodegib activity based on findings from nonclinical models. Integrated PK/PD modeling of vismodegib in xenograft models has revealed a steep relationship between pathway modulation (GLI1 inhibition) and anti-tumor effect, suggesting that even small reductions in exposure could lead to dramatic loss in vismodegib activity. Dose reduction of vismodegib is not permitted as there is only a 150-mg capsule strength available.

1.6 Afuresertib

NOTE: Afuresertib, the agent identified for patients with *AKT1* mutation is not currently available. Testing for the *AKT1* mutation will commence once afuresertib becomes available and sites are notified via a protocol amendment. Tumor samples will only be tested for SMO and NF2 mutations until further notice.

Afuresertib (GSK2110183) is a novel member of the N-alkyl pyrazole class of orally available kinase inhibitors and has been shown to be a potent, pan-AKT inhibitor, with potency (Ki*) values for AKT 1, 2, and 3 kinases being 0.084, 2.0, and 2.6 nM, respectively. In vitro, afuresertib causes a concentration- and time-dependent reduction in phosphorylation of multiple proteins downstream of AKT such as glycogen synthase kinase 3 (GSK3), proline-rich AKT1 substrate 1 (PRAS40), Forkhead (FOXO1/3a), and Caspase 9. Treatment of tumor cells with afuresertib resulted in a concentration- dependent increase in the nuclear translocation of the FOXO-3a transcription factor as a functional consequence of reduced phosphorylation of FOXO-3a. Afuresertib has been shown to inhibit the proliferation of a range of tumor cell lines from multiple histologies including breast, hematological, colon, ovarian, and prostate (EC50 <1 μM). AKT signaling is inhibited in cell lines both sensitive and less sensitive to afuresertib, suggesting that resistance to afuresertib is not due to a lack of AKT kinase inhibition. Afuresertib has been shown to induce cell cycle arrest at G1 phase or apoptosis in a concentration-dependent manner depending on the cellular context.

As of Jun-2014, afuresertib has been evaluated in 8 GSK-sponsored clinical studies: 4 completed and 4 ongoing. In addition, 1 GSK-supported, investigator sponsored clinical study is ongoing. In the 8 GSK-sponsored studies, afuresertib has been administered to 302 subjects with hematologic malignancies or solid tumors, for periods up to 27 months. Doses being evaluated in these studies range from 25 mg to 175 mg. Additionally, 54 healthy volunteers have received low dose (25 mg) afuresertib. The recommended Phase 2 dose identified in the First Time in Human (FTIH) trial for continuous once daily dosing of afuresertib administered as a monotherapy was 125 mg. Review of the dose limiting toxicities reported in that study led to the exploration of higher doses (150 mg and 175 mg) in the Phase 1 dose escalation evaluation of afuresertib in combination with bortezomib and dexamethasone. The MTD for afuresertib in this combination has been established at 150 mg daily.

1.7 Clinical Experience with Afuresertib as Monotherapy

PKB112835

PKB112835 was an open-label, 2-stage, FTIH study designed to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of afuresertib in subjects with advanced hematologic malignancies. This study is complete.

PKB112835 consisted of a dose escalation phase (Part 1) to determine the MTD of afuresertib, in which the drug was administered orally once daily at doses of 25 mg, 75 mg, 100 mg, 125 mg, or 150 mg to 26 subjects. This was followed by a cohort-expansion phase (Part 2), in which 47 subjects received 125 mg of afuresertib administered once daily. PKB112835 is complete and all 8 subjects who were still receiving afuresertib at study completion transitioned to the treatment continuation study (PKB115131). The most frequent type of malignancy in the trial was MM (34 subjects; 47%), followed by NHL (13 subjects, 18%), Hodgkin's lymphoma (8 subjects, 11%), AML (9 subjects, 12%), CLL (7 subjects, 10%), ALL (1 subject, 1%), and LCH (1 subject, 1%). The most common Grade 3/4 AEs were hematologic abnormalities. The majority of the hematologic abnormalities were not considered related to study treatment. The Grade 3 gastrointestinal AEs were diarrhea (3%) and nausea (1%); there were no grade 4 gastrointestinal events. In addition, Grade 3 liver function test abnormalities were reported by 3% of subjects (ALT and AST increased) and Grade 3 rash was reported in 4% of subjects; there were no Grade 4 events of rash.

In total, 37 (50.7%) subjects reported Grade 3 or Grade 4 AEs. The following Grade 3 AEs were reported: neutropenia (9.6%), anemia (5.5%), febrile neutropenia (4.1%), odynophagia (4.1%), rash (4.1%), sepsis (4.1%), thrombocytopenia (4.1%), asthenia (2.7%), diarrhea (2.7%), fatigue (2.7%), liver function test abnormal (2.7%), pneumonia (2.7%), abdominal pain, ALT increased, amnesia, arthralgia, AST increased, atrial fibrillation, back pain, bone pain, dysphagia, dyspnea, dysuria, eating disorder, gastroesophageal reflux disease, herpes zoster, lethargy, lipase increased, nausea, squamous cell carcinoma, and urinary tract infection (1 occurrence each). In addition, the following Grade 4 AEs were reported: anaemia (4.1%) and thrombocytopenia (2.7%). Overall, 11 subjects discontinued treatment with study drug because of AEs: 8 subjects who were receiving 125 mg afuresertib and 3 subjects who were receiving 150 mg afuresertib. The AEs leading to discontinuation were as follows: liver function test abnormal (2 subjects), odynophagia (2 subjects), rash (2 subjects), and nausea, sepsis, septic shock, asthenia, and amnesia (1 subject each). Three subjects died while on study. Two subjects, 1 with MM and 1 with AML, died from disease progression and 1 subject with AML died from septic shock, which was considered by the investigator as not related to study drug. Twenty-eight serious AEs (SAEs) have been reported in 20 subjects. Of these, 3 subjects each had an SAE that was considered to be related to afuresertib, in the opinion of the investigator: 1 subject in the 125 mg/day group had an SAE of nausea (onset: 24 days; resolved) and 2 subjects in the 150 mg/day groups each had an SAE of abnormal liver function test (onset: 18 days; resolved and onset: 4 days; unresolved). The events were reported as related to drug by the investigator. In 1 subject, the event of abnormal liver function test was reversible upon drug discontinuation. The second subject had lymphoma with hepatic involvement and had persistent liver enzyme elevations despite drug discontinuation. Two of 6 subjects in the 150 mg/day cohort in Part 1 experienced a DLT, both of which were related to elevations in liver function tests (LFTs). No DLT was reported in any subject enrolled in Part 1 at a lower dose.

LCH115397

LCH115397 was an open label, repeat-dose study designed to investigate the efficacy and safety of afuresertib in subjects with LCH. This study is complete. In total, 17 subjects were enrolled in the study at doses up to 125 mg administered continuously, once daily. Of these, 16 of the 17 subjects completed the study. One subject, receiving 125 mg/day, discontinued treatment

because of an AE (Grade 2 impaired gastric emptying), which was considered to be not related to afuresertib, in the opinion of the investigator. No hyperglycaemia was reported in this study. Five (29%) subjects had AEs of Grade 3 or higher. These AEs were: ALT increased, diarrhea, fatigue, hyponatraemia, impaired gastric emptying, lung infection, esophageal ulcer, pain, perineal pain, pseudomonas infection, soft tissue necrosis, macula-papular rash, and vulvovaginal pain. None of these occurred in more than 1 subject.

Two subjects in LCH115397 (afuresertib monotherapy 125 mg daily in LCH subjects) developed abnormal liver enzyme elevations. One subject developed Grade 3 increased ALT, Grade 2 increased AST and Grade 2 increased gamma-glutamyl transpeptidase (GGT) in the setting of a normal bilirubin and a hypotensive event. The second subject developed Grade 1 increased AST after 18 weeks on monotherapy; this value remained increased at the final study visit. A Grade 1 increased ALT was also noted at the final study visit. The bilirubin values were normal.

No subject died during the study. Five SAEs have been reported in 3 subjects, only 1 of which (soft tissue necrosis) was considered possibly related to afuresertib

Pharmacokinetics of Afuresertib

Briefly, following single doses of afuresertib in subjects with relapsed or refractory hematologic malignancies, plasma concentrations were measured for all subjects over the 72 hour sample collection period. Afuresertib accumulated 1.4- to 5.1-fold with repeat daily dosing. Single-dose and repeat-dose mean AUC (0-24) and Cmax values increased with increasing doses; however, given the intersubject variability, there was substantial overlap in the AUC (0-24) and Cmax values between successive dose groups. The 100 mg and 125 mg multiple-dose exposure data were similar. Median tmax across doses was 2 hours. Based on available data from all cohorts, the mean accumulation half-life (t1/2) is approximately 1.7 days and the median tmax on Day 8 is 2 hours.

1.8 GSK2256098

Focal adhesion kinase (FAK) is a non-receptor tyrosine kinase that integrates signals from integrins and growth factor receptors. FAK has been reported to have a role in the regulation of cell survival, signalling, growth, adhesion, migration, and invasion[37]. Overexpression of FAK mRNA and/or protein has been documented in many solid human tumors[37]. FAK is key in suppressing suspension-induced cell death (anoikis) with both phosphorylation of FAK and FAK kinase activity being important[38]. Suppressing FAK activity by antisense oligonucleotides or antibody injection leads to induction of apoptosis[39,40].

Because of the role of FAK in cancer progression, invasion, and metastasis, several small molecule inhibitors of FAK are in clinical development. GSK2256098 is a potent, reversible inhibitor of FAK enzymatic activity with an apparent Ki = 0.4 nM against the purified enzyme. GSK2256098 is very selective with no significant inhibitory activity from screening approximately 300 kinases. GSK2256098 inhibits phospho-FAK (pFAK, (Y397)) in a concentration-dependent manner in human tumor cells. The IC50 value determined in the human ovarian OVCAR8 cell line is 15 nM. FAK remains inhibited in the continued presence of compound for up to 24 hours, the longest time point evaluated. Evaluations of GSK2256098 in other cell lines that are derived from different tissues of origin (lung and brain) have very similar IC50 values. GSK2256098 does not inhibit the growth of human tumor cell lines tested in a standard two dimensional cell culture growth assay. Importantly, growth inhibitory activity for

GSK2256098 is observed in a concentration and a tumor cell line dependent manner when evaluated in anchorage independent cell growth assays.

Oral administration of GSK2256098 induces a PD response (pFAK, (Y397) inhibition) in tumor tissue from mice bearing human tumors. Dose and time dependent inhibition of pFAK was observed in subcutaneous xenograft models with mice bearing OVCAR8 (ovarian) or U87MG (glioma) human tumors. The amount of pFAK inhibition correlates well with the concentrations of GSK2256098 in blood. (GSK Investigator's Brochure).

1.9 Clinical Experience with GSK2256098

FAK113581

FAK113581 was a single ascending dose, placebo-controlled study in healthy subjects at doses ranging from 20 – 240 mg. Safety evaluations included AE reporting, clinical laboratory tests (hematology, chemistry, urinalysis), vital signs (blood pressure and heart rate), 12-lead ECGs, clinical monitoring and observations. AEs were reported in 18 of 28 subjects (64%) who received GSK2256098 and in 4 of 10 subjects (40%) who received placebo. The most frequently reported AEs were headache (5 subjects, 13%; 3 subjects in active dose groups) and lethargy (3 subjects, 8%; all active dose groups). Adverse events were distributed across all dose groups, with no obvious dose-related trends, and resolved prior to completion of the study. Except for six Grade 2 (moderate severity) AEs in three subjects, all adverse events were Grade 1 (mild) severity. The Grade 2 AE were: 1 subject with headache and presyncope in the placebo group, 1 subject with post procedural discomfort and soft tissue injury in the 80 mg Group, 1 subject with urinary casts and proteinuria in the 140 mg with food group. Clinically significant changes in clinical laboratory values, vital signs, and ECGs were not observed, with the exception of a single post-dose, reversible increase in proteinuria after a single oral dose of GSK2256098 of 140 mg. No deaths, SAEs, or premature withdrawals due to AEs were reported.

FAK113517

Sixty-two subjects were enrolled in Study FAK113517, Parts 1, 2, and 3, a multiple ascending dose, single arm study in subjects with advanced, refractory solid tumors. Subjects received continuous daily oral doses of GSK2256098 at doses ranging from 80 mg to 1500 mg BID. Overall in Parts 1, 2 and 3 of FAK113517, the most frequently reported AEs associated with continuous oral BID dosing of GSK2256098 were nausea (76%), diarrhea (65%), vomiting (58%), decreased appetite (47%), proteinuria (26%), fatigue (24%), asthenia (23%), hyperbilirubinaemia (23%), constipation (21%) and hypercholesterolemia (21%).

All AEs at the 80 mg BID, 160 mg BID, and 600 mg BID dose levels were Grade 1 or 2. Twenty-six subjects had AEs Grade 3. There were two Grade 4 AEs: reversible, exercise-induced increase in blood creatinine phosphokinase level and cerebral vascular accident. There were no Grade 5 AEs. There were two AEs with unknown toxicity Grade (blister in one subject and Dupuytren's Contracture in another). AEs related to changes in clinical laboratory tests occurred at the 300 mg, 750 mg, 1000 mg, 1250 mg and 1500 mg BID dose levels. The most common (occurring in >10% of subjects) were proteinuria (26% of subjects), hyperbilirubinaemia (23%), hypercholesterolemia (21%), hematuria (16%), hypertriglyceridaemia (15%), anemia (13%), hypoalbuminaemia (10%) and hypomagnesaemia (10%). All AEs related to clinical laboratory tests were Grade 1, Grade 2 or Grade 3, except for a single Grade 4, reversible, exercise-induced AE of increase in blood creatinine phosphokinase level. The MTD of GSK2256098 was

established at 1000 mg BID based upon an overall assessment of safety and tolerability. During the dose escalation phase of the study, dose-limiting toxicities (DLTs) were reported by 4 subjects. One subject enrolled in the 1000 mg BID dosing cohort, experienced intermittent, Grade 2 urine protein/creatinine ratio increased. One subject enrolled in the 1250 mg BID dosing cohort experienced intermittent, Grade 2 nausea, vomiting and fatigue (even though only one DLT was experienced at the 1250 mg dose, the overall tolerability was poor, eliminating this as the recommended dose). Two subjects enrolled in the 1500 mg BID dosing cohort experienced dose-limiting AEs; one subject experienced Grade 2 fatigue and one subject experienced intermittent, Grade 3 asthenia. Five subjects had events that led to permanent discontinuation of study medication. One subject enrolled in the 1000mg BID dosing level experienced intermittent, Grade 2 decreased appetite. One subject enrolled in the 1250 mg BID dosing level experienced intermittent, Grade 2 asthenia. One subject enrolled in the 1500 mg BID dosing level, experienced intermittent, Grade 3 loss of consciousness. Two subjects enrolled in the 1000 mg BID Dose Expansion dosing cohort experienced AEs that lead to permanent discontinuation of study medication. One subject experienced a single episode of Grade 3 bile duct obstruction and a single episode of Grade 1 cholangitis, and one subject experienced a single episode of Grade 3 interstitial lung disease. Fourteen SAEs were reported (12 subjects), all at the MTD or higher. Pleural effusion (n=2) was the only event reported for more than one subject. There were no fatal AEs or SAEs. Four subjects (6%) died on study, all attributable to disease progression.

Pharmacokinetics of GSK2256098

In subjects with solid tumors, GSK2256098 is rapidly absorbed with a time to maximal concentration of about 1 to 3 hours. At the 1000 mg dose level, the geometric mean half-life was 4.4 h (25% CV). (GSK Investigator's Brochure).

1.10 Registration Quality of Life (QOL) Measurements

QOL measurements of fatigue and overall perception of QOL are routinely included in Alliance studies and will be assessed upon registration in this study. Evidence has arisen indicating that baseline single-item assessments of fatigue and overall QOL are strong prognostic indicators for survival in cancer patients, independent of performance status. This evidence was derived from two separate meta-analyses recently presented at ASCO, the first involving 23 NCCTG and Mayo Clinic Cancer Center oncology clinical trials, the second involving 43 clinical trials. Routine inclusion of these measures should be considered similar to that of including performance status, either as stratification or prognostic covariates. It will take approximately one minute to complete this measure.[41, 42]

1.11 Central Radiology Review

Scans will be collected, stored and centrally reviewed as a secondary endpoint. As this is the first trial to evaluate the role of these inhibitors in meningiomas, central review and storage of images will allow us to collect additional information on the effect of these agents radiographically, in particular, to look tumor volumetric changes which may be more informative than area measurements. Furthermore, as the radiographic response to these agents is not known, central review of the meningiomas will allow us to more uniformly assess the response of therapy.

1.12 Impact of the Trial

Based on the biomarker work, we have designed a phase 2 study of vismodegib or GSK2256098 (a FAK inhibitor) in patients with recurrent or progressive meningiomas harboring SMO or NF2

mutations, respectively. This study represents a novel therapeutic approach in meningioma, a disease with a critical need for effective therapy.

2.0 OBJECTIVES

2.1 Primary objectives

2.1.1 To determine the activity of a SMO inhibitor in patients with meningiomas harboring *SMO* mutations as measured by 6-month PFS and response rate.

2.1.2 To determine the activity of a FAK inhibitor in patients with meningiomas harboring NF2 mutations as measured by 6-month PFS and response rate.

2.2 Secondary objectives

2.2.1 To determine overall survival and progression-free survival of SMO and FAK inhibitors in patients with meningioma.

2.2.2 To determine adverse event rates of SMO and FAK inhibitors in patients with meningioma.

2.2.3 To determine the activity of SMO and FAK inhibitor as measured by response rate by central radiology review.

2.3 Correlative science objectives

2.3.1 To evaluate genetic biomarkers in meningioma.

2.3.2 To evaluate dynamic contrast enhanced MRI during treatment with SMO and FAK inhibitors for meningioma.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

Prior to discussing protocol entry with prospective patients, site staff must go to the A071401 study page on the CTSU web site to check cohort status and accrual. If patient is eligible (from local pathology review) for pre-registration, and 20 or more patients have accrued to any cohort, contact the Alliance Registration Office at random01@mayo.edu or 507-284-4130 (during regular business hours 8:00-4:30 CT) to be sure that there is an available spot for the patient. If the Registration Office has confirmed that a spot is available, site staff may then proceed to consent and pre-register the patient.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

The following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.

- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years.
- Patients who cannot swallow oral formulations of the agent(s).

In addition:

Reproductive considerations, vismodegib:

Serious or Life-threatening Birth Defect Effects of Vismodegib

Studies have demonstrated that inhibition of the Hh pathway in embryos results in brain, facial, and other midline defects, including holoprosencephaly or microencephaly, cyclopia, absent nose, cleft palate, tooth abnormalities, and bone development abnormalities (Bale, 2002). While the effects of vismodegib on the developing human fetus at the recommended therapeutic dose are unknown, women of childbearing potential and men must agree to use two methods of contraception (i.e., barrier contraception and another method of contraception) prior to study entry, for the duration of study participation, and for 12 months following treatment.

Vismodegib may impair fertility. Amenorrhea has been observed in clinical trials in women of childbearing potential. Based on animal studies, reversibility of fertility impairment is unknown. Fertility preservation strategies should be discussed with women of childbearing potential prior to starting treatment with vismodegib. Effects on testes and epididymides characterized by mild to moderate germ cell degeneration in seminiferous tubules, relative paucity of spermatozoa, and increased cellular debris in epididymides were observed in male dogs at all dose levels tested and were consistent with the pharmacologic activity of the drug. There were no changes in Leydig or Sertoli cells in any animal. Evidence of partial recovery was noted after a 4-week recovery period.

Germ cell degeneration in male patients is likely to occur at pharmacologically active doses. There is no specific mitigation strategy for this Vismodegib toxicity; however, male patients should be made aware of it during the consent process. Although this effect is expected to be reversible with discontinuation of dosing, long-term effects on male fertility cannot be excluded at this time.

Women of child-bearing potential must use two forms of contraception (including 1 form of barrier contraception) starting at least 4 weeks prior to study entry, for the duration of study participation, and for at least 7 months post-treatment. Appropriate methods of birth control include abstinence, combination hormonal contraceptives, subcutaneous hormonal implant, hormonal patch, hormonal contraceptives (levonorgestre-releasing intrauterine system, medroxyprogesterone acetate depot), tubal sterilization, intrauterine device, vasectomy or barrier method. Acceptable forms of barrier contraception include the following: Any male condom (with spermicide) or diaphragm (with spermicide). Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

Vismodegib is present in semen. It is not known if the amount of vismodegib in semen can cause embryo-fetal harm. Advise male patients to use condoms, even after a vasectomy, to avoid drug exposure to pregnant partners and female partners of reproductive potential initiated prior to registration, for the duration of study participation, for 3 months after the final dose of Vismodegib. Advise males of the potential risk to an embryo or fetus if a female partner of reproductive potential is exposed to Vismodegib. Advise males not to donate semen during therapy with and for 3 months after the final dose of Vismodegib.

See section 9.3.1 for reporting requirements.

Due to the teratogenic potential of vismodegib, all patients should not donate blood or blood products during the study and for 7 months after discontinuation of vismodegib

Reproductive considerations, GSK2256098

GSK2256098 has not been tested in pregnant or lactating women.

Women of child-bearing potential and men with female partners of childbearing potential must use two forms of contraception (i.e., barrier contraception and one other method of contraception) at least 4 weeks prior to study entry, for the duration of study participation, and for at least 6 months post-treatment. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom). Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception initiated prior to registration, for the duration of study participation, and 6 months after completion of drug administration.

Drug interactions:

Vismodegib and GSK2256098 are substrates of P-glycoprotein (PgP). The clinical significance of any drug interaction is unknown to date.

Drugs that alter the pH of the upper GI tract (e.g. proton pump inhibitors, H2-receptor antagonists, and antacids) may alter the solubility of vismodegib and reduce its bioavailability. Co-administration with a proton pump inhibitor, H2-receptor antagonist or antacid, systemic exposure of vismodegib may be decreased and the effect on efficacy is unknown to date.

3.2 Pre-Registration Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following pages.

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday four weeks later would be considered Day 28.

___ 3.2.1 Central Pathology Review Submission

This review is mandatory prior to registration to confirm eligibility.

Patients must have local diagnosis of meningioma (any grade) and have FFPE tumor block OR meningioma tissue slides available for submission to central pathology review and SMO and NF2 testing by a CLIA-certified lab. This review is mandatory prior to registration to confirm eligibility. See Section 6.2 for details on slide/block submission.

3.3 Registration Eligibility Criteria

___ 3.3.1 Documentation of Disease

Histologic Documentation: Histologically proven intracranial meningioma as documented by central pathology review.

Molecular Documentation: Presence of SMO or NF2 mutation in tumor sample as documented by central laboratory (*SMO* W535L, *SMO* L412F;; or known missense

COSMIC mutations, nonsense mutations, small indels or copy-number loss in *NF2*). See Appendix VII for further details.

Progressive OR residual disease, as defined by the following:

- **Residual measurable disease (**see also 3.3.2**):** Residual measurable disease immediately after surgery without requirement for progression. For Grade I disease, progression pre-operatively needs to be documented, with an increase in size of the measurable primary lesion on imaging by 25% or more (bidirectional area). The change must occur between scans separated by no more than 12 months. Residual measurable disease will be defined by bidimensionally measurable lesions with clearly defined margins by MRI scans, with a minimum diameter of 10mm in both dimensions. See Section 11.2.
- **Progressive measurable disease (**see also 3.3.2**):** Progression defined as an increase in size of the measurable primary lesion on imaging by 25% or more (bidirectional area). The change must occur between scans separated by no more than 12 months.
- **Post radiation patients**: Patients with measurable and progressive meningioma who have received radiation are potentially eligible, but need to show evidence of progressive disease after completion of radiation. At least 24 weeks must have elapsed from completion of radiation to registration. (See Section 3.3.3).

___ **3.3.2 Measurable disease**

Measurable disease is defined by a bidimensionally measurable main lesion on MRI or CT images (MRI preferred) with clearly defined margins. Multifocal disease is allowed.

For measurable disease, refer to Section 11.0.

___ **3.3.3 Prior Treatment**

- Prior medical therapy is allowed but not required.
- No limit on number of prior therapies.
- No chemotherapy, other investigational agents within 28 days of study treatment.
- No other concurrent investigational agents or other meningioma-directed therapy (chemotherapy, radiation) while on study.
- For patients treated with external beam radiation, interstitial brachytherapy or radiosurgery, an interval > 24 weeks must have elapsed from completion of XRT to registration (See 3.3.1).
- Steroid dosing stable for at least 4 days.
- Recovered to CTCAE grade 1 or less toxicity from other agents with exception of alopecia and fatigue.
- No craniotomy within 28 days of registration.

___ **3.3.4 Not pregnant and not nursing**

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months). Please note the information below is strictly for eligibility purposes, please reference section 5.0 (Study calendar) for details on pregnancy monitoring during the duration of the trial. Also see section 3.1 for further details.

___ **3.3.5 For patients with NF2 mutation:** Age ≥ 18 years

For patients with SMO mutation: Age ≥ 30 years

___ **3.3.6 ECOG Performance Status** ≤ 2

___ **3.3.7 Patient history:**

- Patients with history of NF may have other stable CNS tumors (schwannoma, acoustic neuroma or ependymoma) if lesions have been stable for 6 months.
- No metastatic meningiomas (as defined by extracranial meningiomas) allowed.
- No history of allergic reactions attributed to compounds of similar or biologic composition to assigned study drug.
- No Known active hepatitis B or C
- No current Child Pugh Class B or C liver disease
- No uncontrolled gastric ulcer disease (Grade 3 gastric ulcer disease within 28 days of registration)
- No uncontrolled diabetes defined as a known diabetic with HBA1C >7.5 OR fasting glucose > 140.
- No uncontrolled hypertension defined as BP > 140/90
- No abdominal fistula, GI perforation, or intra-abdominal abscess within 28 days prior to registration

___ **3.3.8 Concomitant Medications**

- Chronic concomitant treatment with strong inhibitors of CYP3A4 inhibitors must discontinue the drug for 14 days prior to registration on the study for patients with with NF2 mutation enrolled to GSK2256098. See Section 7.1 for more information.
- Chronic concomitant treatment with strong CYP3A4 inducers is not allowed. Patients must discontinue the drug 14 days prior to the start of study treatment for patients with with NF2 mutation enrolled to GSK2256098. See Section 7.2 for more information.

___ **3.3.9 Required Initial Laboratory Values:**

Absolute Neutrophil Count (ANC)	≥ 1,500/mm^3
Platelet Count	≥ 100,000/mm^3
Creatinine OR	≤ 1.5 mg/dl x upper limit of normal (ULN)
	OR
Calc. Creatinine Clearance	> 45 mL/min
UPC	≤ 45mg/mmol*
Total Bilirubin	≤ 1.5 x upper limit of normal (ULN)**
AST / ALT	≤ 2.5 x upper limit of normal (ULN)
Fasting triglyceride	≤ 200mg/dL*
Fasting cholesterol	≤ 240mg/dL*
	QTcF*** ≤ 500 msec*

* ONLY APPLICABLE for patients with NF2 mutation (GSK2256098).

** Except in case of Gilbert's disease

*** QT calculated using Fridericia formula: QTc = QT/(RR^0.33), where RR = 60/HR

4.0 PATIENT REGISTRATION

4.1 CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed Statement of Investigator Form (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed Supplemental Investigator Data Form (IDF)
- a completed Financial Disclosure Form (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the CTEP Investigator Registration Help Desk by email at <pmbregpend@ctep.nci.nih.gov>.

4.2 CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

4.3 CTSU Site Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' website by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. However, sites must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB (via IRBManager) to indicate their intention

to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office for compliance in the RSS. The Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in a given study so that the study approval can be applied to those institutions. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

4.3.1 Downloading Site Registration Documents

Site registration forms may be downloaded from the A071401 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password.
- Click on the Protocols tab in the upper left of your screen
- Click on the By Lead Organization folder to expand
- Click on the Alliance link to expand, then select trial protocol # A071401
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

4.3.2 Requirements for A071401 Site Registration

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

4.3.3 Checking Your Site's Registration Status

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password

Click on the Regulatory tab at the top of your screen

Click on the Site Registration tab

Enter your 5-character CTEP Institution Code and click on Go

4.3.4 Submitting Regulatory Requirements

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

4.4 Patient Pre-Registration Requirements

- **Informed consent:** the patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.
- **Cohort Status and Accrual:** Prior to discussing protocol entry with prospective patients, site staff must go to the A071401 study page on the CTSU web site to check cohort status and accrual. Please note that all cohorts are limited to 24 patients. If patient is eligible (from local pathology review), and 20 or more patients have accrued to any cohort, contact the Alliance Registration Office at random01@mayo.edu or 507-284-4130 (during regular business hours 8:00-4:30 CT) to be sure that there is an available spot for the patient. If the Registration Office has confirmed that a spot is available, site staff may then proceed to consent and pre-register the patient.
- **Central pathology review and central molecular laboratory submission:**

  Patients may be pre-registered to this study on the basis of the diagnosis of recurrent or progressive meningioma made at the original institutions. ALL diagnostic H&E's and one tissue block must be submitted. (See Section 6.0).

Submission of these samples for central pathology review and for SMO and NF2 mutations is MANDATORY for all patients pre-registered to this study.

Tissue submission should be accompanied by a completed "Central Pathology and Biomarker Results Form" found on the A071401 study page. **Failure to submit this form with the specimens will delay turnaround time for central review and biomarker testing.** The specimen will be centrally reviewed to confirm study eligibility and cohort assignment. Sites must use this form to confirm eligibility and arm assignment.

4.5 Patient Registration Procedures

Confirmation of eligibility by central review: Sites will be notified via e-mail whether or not the patient is eligible based on the central pathology and central molecular review within 10 business days of delivery of a suitable patient tumor specimen to the MGH Translational Research Laboratory. If a sample has been deemed unsuitable after central pathology review based on differential diagnosis, insufficient tissue amount and/or tumor cellularity, the sample will NOT undergo SMO and NF2 testing and a request for an alternative sample will be made. Upon the completion of testing, the results section of the "Central Pathology and Biomarker Results Form" will be completed by the pathologist and laboratory, scanned and sent via e-mail to the responsible CRA listed on the form. After receiving the results form via e-mail, the institution must forward the form to the Alliance Patient Registration office at random01@mayo.edu in order to register the patient. Once the form is forwarded to the Alliance Patient Registration Office and the Registration Eligibility Criteria have been met, the patient can be registered using the OPEN system (see below). Registration must occur within 14 days of receiving notification of patient molecular eligibility from the central testing laboratory. The same patient ID number obtained at pre-registration from the OPEN system should be used to register the patient. Please contact Alliance Patient Registration office at random01@mayo.edu or 507-284-4130 if registration problems occur.

4.6 Patient Enrollment through OPEN

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. A user manual is available for OPEN users on the CTSU site.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

To receive site reimbursement for specific tests and/or bio-specimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol-specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.7 Registration to Correlative and Companion Studies

4.7.1 Registration to Substudies described in Section 14.0

There are 2 substudies within Alliance A071401. These correlative science studies **must be offered to all patients** enrolled on Alliance A071401 (although patients may opt to not participate). These substudies do not require separate IRB approval. The substudies included within Alliance A071401 is/are:

- Identification of molecular biomarkers of response, Alliance A071401-ST1 (Section 14.1.)
- Imaging biomarkers of response, Alliance A071401-IM1 (Section 14.2)

If a patient answers "yes" to "My samples and related information may kept in a Biobank for use in future health research," they have consented to participate in the substudy described in Section 14.1. The patient should be registered to Alliance A071401-ST1 at the same time they are registered to the treatment trial (A071401). Samples should be submitted per Section 6.2.

4.8 Treatment Assignments and Patient Cohorts

Patients will be assigned to an arm of the trial based on the mutation status. Tumors will be screened for the presence of SMO or NF2 and if present, they will be assigned to the single agent, vismodegib or GSK 2256098 respectively. Within each arm, there will be two cohorts of patients decided by Grade status (grade II and III; grade I). There are accrual goals for each individual cohort within an arm, see Section 13.3 for further accrual information.

If a patient has more than 1 mutation present, they must be enrolled to the least common mutation (NF2 is most common). Upon discontinuation of study agent, the patient will be permitted to enroll to the study with the agent matching the other mutation. The pre-registration step does not need to be repeated but registration step must be repeated to enroll the patient in the new cohort. Please see section 4.5 for details on registration.

Specific Treatment Groups:

Group 1: NF2 mutation, Grade I

Group 2: NF2 mutation, Grade II/III

Group 3: SMO mutation, Grade I

Group 4: SMO mutation, Grade II/III

5.0 STUDY CALENDAR

Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

Pre-Study Testing Intervals

- To be completed ≤ 16 DAYS before registration: All laboratory studies, history and physical.
- To be completed < 28 DAYS before registration: Any scan which is utilized for tumor measurement per protocol.
- To be completed ≤ 42 DAYS before registration: Any baseline exams used for screening, which is not utilized for tumor measurement.

	Prior to Registration*	Day 1 of each cycle (cycle is 28 days)*	Post treatment follow up**	At PD, withdrawal, or removal***
Tests & Observations				
History and physical, weight, PS	X	X	X	
Height	X			
Pulse, Blood Pressure	X	X		
Adverse Event Assessment Ω	X	X	X	
Patient Medication Diary Φ		X	X	
Registration Fatigue/Uniscale Assessment #	X			
EKG (!)	X($)	X($)		
Laboratory Studies				
Complete Blood Count, Differential, Platelets	X	X		
Chemistry (Creatinine, AST, ALT, Alk. Phos., Bili, glucose)	X	X		
Urine Protein	X(!)	X(!)		
Serum or Urine HCG	X(1)	X(1)		
Serologic Hepatitis B Surface Ag and Hepatitis C RNA (physician discretion, not required)	X			
Fasting cholesterol, triglycerides	X(%)	X(%)		
Staging				
Central review for eligibility (pathology and molecular)	X(2)			
MRI/CT Brain (3)	X(4)	A	A	X
Correlative studies: For patients who consent to participate				
Tissue and Blood samples	Archival tissue at baseline for banking and correlative science. Blood samples every 4 cycles, tissue upon recurrence, see Sections 6.2-6.4.			
MR Imaging	DCE MRI imaging should be performed at sites with such capability. DCE MRI will be acquired as part of routine clinical imaging and would not be an extra set of images. See "MRI/CT Brain" under "Staging." See Section 14.2 and Appendix III.			

* Labs completed prior to registration may be used for day 1 of cycle 1 tests if obtained ≤ 16 days prior to treatment. For subsequent cycles, labs, tests and observations may be obtained +/- 3 days from scheduled day of assessment. Radiographic windows are +/- 7 days from scheduled day of assessment.

** Physical examination, adverse event assessment, and medication diary are required 4 weeks (+/- 7 days) after the end of treatment.

*** Patients are followed for survival every 6 months, for a maximum of 5 years from registration. Patients discontinuing for reasons other than progressive disease will have staging scans every 16 weeks (+/- 4 weeks) until they have reached 2 years post-registration or until documented progression. See also Section 12.

Ω Solicited AEs are to be collected starting at baseline. Routine AEs are to be collected starting after registration. See Section 9.3 for expedited reporting of SAEs.

Φ Medication diary should be completed by the patient throughout treatment, and should be collected at day 1 of every cycle starting with day 1 cycle 2. Use the appropriate appendix. See Appendices IV-V.

\# To be completed after pre-registration and ≤ 21 days prior to treatment, see Appendix I.

! Required only for patients with NF2 mutation enrolling/enrolled on GSK2256098

% Required at baseline and every 6 cycles thereafter only for patients with NF2 mutation enrolling/enrolled on GSK2256098.

$ EKG must be performed at 2 time points: within 28 days of registration, and 1 hour after taking the first dose of GSK2256098.

1 For women of childbearing potential (see Sections 3.1 and 3.3.4). Must be done ≤ 7 days prior to registration and ≤ 7 days prior to initiation of vismodegib for patients with *SMO* mutation and ≤ 7 days prior to initiation of GSK 2256098 for patients with NF2 mutation. While on vismodegib, WOCP must continue to receive pregnancy tests on day 1 of every cycle (+/- 3 days).

2 See Sections 4.4 and 6.2 for central review submission.

3 All MRIs must be submitted to the Imaging Core Laboratory within 6 months of acquisition. Images must be submitted from baseline to (and including) progression. For patients who go off study for reasons other than progression (i.e., toxicity) please continue to submit images until progression.

4 Baseline scans can include either: 1) MRI Brain or 2) CT Brain. The CT evaluation option should ONLY be used for patients unable to undergo MR imaging because of non-compatible device. Also see Section 11.0. Supporting documentation is to be submitted, per Section 6.1.1.

A Every 8 weeks (e.g. prior to Cycle 3 Day 1) for 1 year, then every 12 weeks until evidence of progression. Scans may be done within +/- 7 days of a scheduled time point. **Response assessment should include assessment of all sites of disease and use the same imaging method as was used at baseline. All MRIs should follow the consensus MRI protocol outlined in Appendix II even if the site is not acquiring the DCE sequence.**

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data Collection and Submission

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at https://eapps-ctep.nci.nih.gov/iam/index.jsp) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

A Schedule of Forms is available on the Alliance study webpage, within the Case Report Forms section. The Schedule of Forms is also available on the CTSU site within the study-specific Education and Promotion folder, and is named Time & Events.

6.1.1 Supporting documentation

This study requires supporting documentation for diagnosis, response and progression. Supporting documentation will include pathology, radiology, reports and these must be submitted at the following time points:

Baseline: Imaging report, pathology report, operative report, clinic note and Central Pathology and Biomarker Results Form

Response: Imaging report

Progression: Imaging report, and pathology report if applicable

Relapse/recurrence: Pathology report and operative report if applicable

6.2 Specimen collection and submission

<u>For all patients registered to Alliance A071401:</u>

Real time histopathology review will be conducted on the diagnostic tissue (biopsy and/or surgery) to confirm the diagnosis of meningioma (WHO grade I to III). ALL original diagnostic H&E slides and at least 1 FFPE tumor block used to make the diagnosis should be clearly labeled and forwarded **as soon as possible after surgery for pre-registration**. The submission of these samples for histopathology review is required for all patients pre-registered to this study.**

The central review will be performed by Dr. Sandro Santagata at Brigham and Women's Hospital/Dana Farber Cancer Center before being forwarded to Dr. Darrell Borger's laboratory at Massachusetts General for integral molecular testing.

SMO and NF2 mutations will be used as integral biomarkers and key entry criteria for enrollment on this trial. SMO and NF2 mutation status will be determined at Massachusetts General Hospital Translational Research/Biomarker Laboratory directed by Dr. Borger.

Typical turnaround time for central path review is within 3 working days and for SMO and NF2 mutation testing within 10 days of receipt of the slides and tissue.

For patients registered to substudy A071401-ST1:

All participating institutions must ask patients for their consent to participate in the correlative substudies planned for Alliance A071401-ST1, although patient participation is optional. Biomarker studies will be performed. Rationale and methods for the scientific components of these studies are described in Sections 14.2. For patients who consent to participate, tissue and blood will be collected at the following time points listed in the second half of the table below:

	≤ 120 days before registration	**After initial (biopsy/ surgery) and at recurrence***	**Storage/ Shipping conditions**	**Submit to:**
Mandatory for all patients registered to A071401: (parent study)				
ALL diagnostic H&E slides from original diagnosis [1,***]	X		Ambient	Brigham / Dana-Farber Cancer Institute
One paraffin block containing at least 1 cm^2 of viable tumor [1,*,**, ***]	X		Ambient	Brigham / Dana-Farber Cancer Institute
For patients registered to A0711401-ST1, submit the following: Optional				
One diagnostic H&E slide from ***recurrent tumor*** and One paraffin block from **recurrent *tumor*****	N/A	X[(2)]	Ambient	Alliance Biorepository at Mayo Clinic
Whole Blood [3] (EDTA/lavender top)	1 x 10 mL		Cool pack/ship over night	Alliance Biorepository at Mayo Clinic
Whole blood for ctDNA plasma [4] (EDTA/lavender top)	2 x 10ml		Dry Ice/ship over night	Alliance Biorepository at Mayo Clinic

1 Submit as soon as possible after surgery and at pre-registration. Pre-registration requirement, confirmation of diagnosis through central review. For patients with specimens from multiple timepoints, the most recent specimen should be utilized.

2 For future correlative studies as described in Section 14.1.

3 Whole blood to be used for the biomarker analyses described in Section 14.1. **Collect 1 x10 mL during pre-registration which will be used for germline DNA.** See Section 6.4 for instructions.

4 Whole blood to be used for circulating tumor DNA (ctDNA) analyses described in Section 14.1.2**. Collect 2 x 10 mL during pre-registration and every 16 weeks while patient is on study. There are specific instructions for plasma extraction for ctDNA.** See Section 6.4 for details.

* For patients who consent to having their specimens banked (model consent question # 4), residual specimen from central pathology review and integral molecular testing will be sent to the Alliance Biorepository at Mayo Clinic.

****If an institution is unable to provide a tissue block**, cut 15 unstained slides five-micron sections and mount on charged glass slides. Slides need to be cut with a new blade and using a fresh water bath to avoid contamination. **Label the slides with Alliance patient ID number, accession number, and order of sections** *(include thickness of section if applicable)***.** For samples containing less than 1 square cm of tumor tissue, multiple sections should be mounted onto each slide to ensure that the appropriate amount of tumor tissue is available. **Do not bake or place covers slips on the slides.**

***** In patients who have specimens from multiple timepoints, please submit the specimen from the most recent timepoint.**

6.2.1 Specimen submission using the Alliance Biospecimen Management System

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: http://bioms.allianceforclinicaltrialsinoncology.org using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS webpage to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: 1-855-55-BIOMS or Bioms@alliancenctn.org. For assistance in using the application or questions or problems related to specific specimen logging, please contact: 1-855-55-BIOMS or Bioms@alliancenctn.org.

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

All submitted specimens must be labeled with the protocol number (A071401), Alliance patient number, patient's initials and date and type of specimen collected (e.g., serum, whole blood).

A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens.

Instructions for the collection of samples are included below. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

ALL tumor tissue <u>for Central Pathology Review and SMO and NF2 Integral Biomarker Testing:</u>

Shipment on Monday through Thursday by overnight service to assure receipt is encouraged. Do not ship specimens on Fridays or Saturdays.

Sandro Santagata, MD, PhD
C/O Lauren Logan
Center for Molecular Oncologic Pathology
Dana-Farber Cancer Institute
450 Brookline Avenue -JF215A
Boston, MA 02215
Phone: 617-632-5482
Fax: 617-582-8761

Blood submission for patients who agree to participate:

Shipment on Monday through Friday by overnight service to assure receipt is encouraged. Do not ship specimens on Saturdays. Ship samples to the following address:

Alliance BAP Freezer
ST-SL-16
150 Third Street SW
Rochester, MN 55902

For questions about blood submission contact:
Roxann Neumann, RN, BSN, CCRP
Tel: 507-538-0602 Fax: 507-266-0824
neumann.roxann@mayo.edu

Tissue submission for the <u>correlative studies</u> for patients who agree to participate:

Alliance Operations Office
Attn: PC Office (Study A071401)
RO-FF-03-24-CC/NW Clinic
200 First Street Southwest
Rochester, MN 55905

For questions about tissue submission to the biorepository contact:
Helen Tollefson
Tel: 507-266-0724 Fax: 507-266-7240
tollefson.helen@mayo.edu

6.3 Tissue collection and processing for histopathology review

Consistent and accurate histologic grading is important for this study. Submission of **ALL** diagnostic H&E slides and at least 1 paraffin block from the original diagnosis is required for all patients enrolled to this study. At time of recurrence, submission of diagnostic H&E slides and at least 1 paraffin block (or 15 unstained tissue sections cut at 5-micron and mounted on charged glass coverslips if blocks are not available) is required from patients who consent to the optional substudy and experience tumor recurrence.

6.3.1 Central pathology review is required prior to registration.

ALL original diagnostic H&E slides used to make the diagnosis of meningioma should be clearly labeled and forwarded at ambient temperature as soon as possible after surgery for pre-registration. If the original slides cannot be released, recut slides from ALL tumor blocks used to make the diagnosis are acceptable.

6.3.2 The diagnostic slide(s) must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, patient initials, and study patient ID number.

6.3.3 Upon enrollment the residual material will be forwarded for storage to the Alliance Biorepository at Mayo Clinic by the laboratories performing the integral biomarker testing and central pathology review.

6.3.4 Collection of paraffin blocks of archived meningioma tumors

With the patient's consent, and, when available, 1 recurrent FFPE tissue block obtained from tumor specimens may be sent to the Alliance Biorepository at Mayo Clinic.

Please label the tumor specimens with

1). Alliance study number (A071401)

2). Alliance patient ID number

3). Patient's initials

4). Date and time of specimen procurement

The Alliance has instituted special considerations for the small percentage of hospitals whose policy prohibits long-term storage of blocks, and the smaller percentage of hospitals whose policies prohibit release of any block. For those hospitals for which tumor tissue block submission is not feasible, please submit 15 unstained slide from the recurrent tissue block (or as many slides as possible if fewer than 15).

Please contact the Alliance Biorepository at Mayo Clinic if additional assurances with your hospital pathology department are required.

6.4 Blood sample submission

For patients who consent to participate in A071401-ST1, whole blood will be used for the biomarker analyses described in Section 14.1.2.

Whole blood for germline DNA

- Collect one 10 mL of venous blood at pre-registration in lavender top (EDTA anticoagulant) vacutainer tube(s). The tubes should be inverted approximately 8-10 times to mix the EDTA. **Refrigerate (please do not freeze)** sample until shipping. The sample should be placed in a biohazard bag and shipped according to IATA guidelines the same day as the blood is drawn on a **cold pack** (**please do not use dry ice**) by overnight courier service to the Alliance BAP Freezer.

- Whole blood samples should be sent to Alliance biorepository at Mayo. See section 6.2.1 for the address.

Label samples with the following identification:

1) Procurement date
2) Alliance patient number
3) Alliance study number (i.e., A071401-ST1)
4). Patient initials
5) Sample type

Whole blood for circulating tumor DNA (ctDNA) plasma

- Collect 2 x 10 mL whole blood in lavender top (EDTA anticoagulant) vacutainer tube(s). Invert approximately 8-10 times to mix the EDTA
- 1st Centrifugation step: centrifuge the two EDTA tube at 1500g for 15 minutes **at ambient temperature**. After centrifugation, three different fractions are distinguishable: the upper clear plasma layer, the intermediate buffy coat layer containing concentrated leukocytes and the bottom layer of red cells. Draw off the plasma layers from the two centrifuged tubes, minimizing removal of the intermediate buffy coat layers, and transfer the plasma to the 15 mL conical tube.
- 2nd centrifugation step: centrifuge the 15 mL conical tube at 1500g for 15 min **at ambient temperature. After centrifugation,** transfer ~1.5ml of the upper clear plasma layer into each 2ml cryovial tubes (up to 8 vials) *.
- Freeze sample at -80 °C until shipping. The sample should be placed in a biohazard bag and shipped according to IATA guidelines on dry ice within 30 day as the blood is drawn by overnight courier service to the Alliance BAP Freezer. If –80°C is not available, temporary storage on dry ice or at –20°C prior to shipment is acceptable for up to approximately 48 hours.
- Plasma samples in cryovials should be sent to Alliance biorepository at Mayo. See section 6.2.1 for the address.

Label samples with the following identification:

1) Procurement date
2) Alliance patient number
3) Alliance study number (i.e., A071401-ST1)
4) Patient initials
5) Sample type

*Cryovial Choices: Some examples of acceptable 2.0 mL cryovials are: Nalgene (Cat #5012-0020), Fisher (Cat #05-669-57), Corning (Cat #430488), VWR (Cat #16001-102).

6.5 CT and MR Imaging Data Submission

Acquisition of MR imaging in a uniform manner for all patients across the study and for an individual patient on serial imaging is critical information for this trial. We have defined the consensus imaging parameters that are required for imaging on 1.5 T and 3 T MRI scanners and sites should follow these parameters for all patients irrespective of whether or not they enroll in the optional advanced imaging substudy (see Appendix II for required consensus acquisition parameters).

All MRI images will be transmitted electronically from each participating site to the Imaging and Radiation Oncology Core QA center at Ohio State University (IROC Ohio). All study MRIs performed before the approval of Update #5 should be transmitted electronically to IROC.

For patients who consent to participate (model consent question #1), DCE MRI should be performed at sites with such capability. The DCE MRI acquisition protocol is outlined in Appendix III.

For all patients, complete data sets in digital DICOM format and submit to IROC Ohio. Images must be submitted from the following time points: baseline to progression. See Section 5.0. For patients who go off study for reasons other than progression (i.e., toxicity) please continue to collect images until progression. **Institutions are permitted to batch ship images every six months. Sites must turn in images within 180 days of acquisition to be compliant with data submission.** BMP files, JPG files, or hard copies (films) are not acceptable. The raw data of the entire study should be saved until the scan is accepted by the Imaging Core Lab. De-identify the patient data using institutional procedures to remove patient name and medical record number while preserving the Alliance patient ID number and protocol number. The de-identified digital images may be temporarily burned to a CD or transferred to a PC based system.

Data should be transferred **electronically** to the IROC Ohio via TRIAD, Web Transfer or FTP Transfer:

1) TRIAD based data transfer

The standard TRIAD based data transfer approach will be provided separately through IROC efforts per the request by participating sites before their first data submission.

TRIAD is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- Site physics staff who will submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to CTEP Registration Procedures of the protocol for instructions on how to request a CTEP-IAM account.
- To submit images, the site physics user must be on the site's affiliate rosters and be assigned the 'TRIAD site user' role on the CTSU roster. Users should contact the site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role. RAs are able to submit standard of care imaging through the same method.

TRIAD Installations:

When a user applies for a CTEP-IAM account with the proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found by following this link https://triadinstall.acr.org/triadclient/

This process can be done in parallel to obtaining your CTEP-IAM account username and password.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

2) Web Transfer (http://upload.imagingcorelab.com**)**

Any PCs with internet access and web browser (e.g., Internet Explorer, Mozilla Firefox) can be used to web transfer DICOM images and other required files to the Imaging Core Lab. The standard Web Transfer information will be provided separately through the specific trial e-mail, per the request by participating sites before their first data submission.

3) FTP Transfer

Any FTP software can be used to initiate access to the secure FTP Server of the Imaging Core Laboratory. The standard FTP access information will be provided separately through the specific trial e-mail, per the request by participating sites before their first data submission.

Mail/CD Shipment

Only if electronic data transfer approaches cannot be achieved, the de-identified images in digital DICOM format can be burned to a CD and mailed to the Imaging Core Lab. Submit only one patient's images per CD, with the patient's Alliance ID number, study type, date of scans, and name of submitting institution.

Submit these data to:

IROC Ohio
Attn: Alliance Trial A071401
The Ohio State University
Wright Center of Innovation
395 W. 12th Avenue, Suite 414
Columbus, Ohio, 43210
Tel: 614-293-9151
Fax: 614/293-9275

Once the imaging data submission is done, send an e-mail to the Imaging Core Lab at the specific trial email Alliance071401@irocohio.org to inform that the study has been submitted from the institution. Please include the basic information of submitted data sets as follows:

1) Alliance patient ID number
2) Scan time point (i.e., baseline)
3) Date of scans
4) Institution name

IROC Ohio will acknowledge receipt of the imaging data via email confirmation to the institution within 1 business day of receipt, and will notify the institution and Alliance imaging committee of the quality check report within 3 business days.

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 7 days of registration. For questions regarding treatment, please see the study contacts page.

It is acceptable for individual chemotherapy doses to be delivered ≤ a 24-hour (business day) window before and after the protocol-defined date for Day 1 of a new cycle. For example, if the treatment due

date is a Friday, the window for treatment includes the preceding Thursday through the following Monday. In addition, patients are permitted to have a new cycle of chemotherapy delayed up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. Documentation to justify this delay should be provided.

In patients with *SMO*-mutated meningiomas, protocol therapy will consist of vismodegib administered every day. In patients with *NF2*-mutated meningiomas, protocol therapy will consist of GSK2256098 administered twice daily, every day.

Each cycle will consist of 28 days. Treatment will continue until disease progression or unacceptable adverse event.

Arm A (SMO mutation):

Agent	Dose	Route	Frequency
Vismodegib	150 mg	PO	Once daily

Note: If a patient is suspected to be pregnant, GDC-0449 should be IMMEDIATELY discontinued and the study physician contacted. A positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patients is not pregnant, the patient may resume dosing with GDC-0449.

Arm B (NF2 mutation):

Agent	Dose	Route	Frequency
GSK2256098	750 mg	PO	Twice/daily

In patients harboring *SMO*-mutated meningioma, vismodegib will be administered at 150 mg orally daily. If a dose of vismodegib is missed, do not make up that dose; resume dosing with the next scheduled dose. Capsules should not be opened or crushed.

In patients harboring *NF2*-mutated meningioma, GSK2256098 will be administered at 750 mg po twice daily. If a dose of GSK2256098 is missed, do not make up that dose; resume dosing with the next scheduled dose. Capsules should not be opened or crushed.

For all arms, a cycle will be 28 days. Dose modifications will be instituted for toxicity as per Section 8.
Please note all supply of GSK2256098 for this study expires January 2018. Currently, there are no plans for further supply of GSK2256098 to be manufactured, see Section 10.2.

Contrast-enhanced cranial magnetic resonance imaging (MRI) will be performed every 8 weeks. Standard response criteria will be used (Macdonald criteria)[43]. See Section 11. In patients who have stable disease (SD), a partial response (PR) or a complete response (CR), vismodegib or

GSK2256098 will be continued. The therapies will be continued until progressive disease (PD) or study withdrawal due to toxicity or other rationale, at which time patients will be removed from the study. In patients who come off study for reasons other than progression, they will be followed for progression until progression is documented on imaging. All patients who are removed from study treatment, regardless of rationale, will be followed for survival once off study. See Section 5.0 for further details.

7.1 CYP3A4 Inhibitors

Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed on this trial for patients with NF2 mutation enrolled to GSK2256098. The following drugs are EXAMPLES of strong inhibitors of CYP3A4 and are not allowed during treatment with GSK2256098.

- Indinavir
- Clarithromycin
- Ketoconazole

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to inhibit CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA, or your local institution's pharmacist.

A wallet-size card providing information regarding potential drug interactions has been made available in Appendix VIII.

7.2 CYP3A4 Inducers

Chronic concomitant treatment with strong inducers of CYP3A4 is not allowed on this trial for patients with NF2 mutation enrolled to GSK2256098. The following drugs are EXAMPLES of strong inducers of CYP3A4 and are not allowed during treatment with GSK2256098.

- Rifampin
- Carbamazepine

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to induce CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA, or your local institution's pharmacist.

A wallet-size card providing information regarding potential drug interactions has been made available in Appendix VIII.

8.0 DOSE AND TREATMENT MODIFICATIONS

8.1 Ancillary therapy, concomitant medications, and supportive care

8.1.1 Patients should not receive any other agent which would be considered treatment for the primary neoplasm or impact the primary endpoint.

8.1.2 **Patients should receive full supportive care** while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

8.1.3 Treatment with hormones or other chemotherapeutic agents may not be administered except for steroids given for adrenal failure; hormones administered for non-disease-related conditions (e.g., insulin for diabetes); intermittent use of dexamethasone as an antiemetic or if significant symptomatic edema on brain MRI.

8.1.4 Antiemetics may be used at the discretion of the attending physician, with the exception of steroids above.

8.1.5 Diarrhea management is per the discretion of the treating physician. Diarrhea could be managed conservatively with medications such as loperamide.

Patients with severe diarrhea should be assessed for intravenous hydration and correction of electrolyte imbalances.

8.1.6 Palliative radiation therapy may not be administered during study enrollment.

Patients who require radiation therapy during protocol treatment will be removed from protocol therapy due to disease progression.

8.1.7 Rash: Rash prevention measures should be utilized. This includes avoidance of UV exposure with covering of skin and sunscreen, and application of lotion. If rash occurs, consider dermatology consultation to aid management, and topical measures can be utilized.

8.1.8 Surgery: Patients who require surgery during protocol treatment may proceed as such, unless the surgery involves resection of meningioma. Study agent should be held prior to and after surgery, for a maximum of 28 days. If the patient requires an interruption of > 28 days, then they will be removed from protocol therapy.

8.1.9 Hyperlipidemia: Patients taking **GSK2256098** should be treated with appropriate medical therapy for hyperlipidemia and avoiding concomitant medications that interact with study medication.

8.1.10 Hypertension: Patients taking **GSK2256098** should maintain well-controlled blood pressure, especially in the setting of proteinuria.

8.1.11 Alliance Policy Concerning the Use of Growth Factors

The following guidelines are applicable unless otherwise specified in the protocol.

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based, Clinical Practice Guideline. J Clin Oncol 24(19): 3187-3205, 2006.

Epoetin (EPO): Use of epoetin in this protocol is permitted at the discretion of the treating physician. The use of epoetin should follow published guidelines of the American Society of Clinical Oncology 2010 Update of Recommendations on the Use of Epoetin and Darbepoetin in Adult Patients with Cancer. J Clin Oncol 28(33): 4996-5010, 2010.

Due to concerns regarding the inherent toxicity of EPO and the investigational agents employed in the protocol, use of EPO is strongly discouraged.

Filgrastim (G-CSF), tbo-filgrastim and sargramostim (GM-CSF)

1. Filgrastim (G-CSF)/tbo-filgrastim/pegfilgrastim and sargramostim (GM-CSF) treatment for patients on protocols that do not specify their use is discouraged.
2. Filgrastim/tbo-filgrastim/pegfilgrastim and sargramostim may not be used:

a. To avoid dose reductions, delays or to allow for dose escalations specified in the protocol.
b. For the treatment of febrile neutropenia the use of CSFs should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSFs may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSFs in this setting. The use of CSF (filgrastimtbo-filgrastim/pegfilgrastim or sargramostim) must be documented and reported.
c. If filgrastim/tbo-filgrastim/pegfilgrastim or sargramostim are used, they must be obtained from commercial sources.

8.1.12 Hypersensitivity reactions

Treat hypersensitivity reactions to (drug[s]) as per institutional standards.

8.1.13 Reproductive Considerations

See section 3.1 for details on teratogenicity of agents and reproductive considerations while on study agent. Please note that for patients receiving vismodegib they will need to continue pregnancy prevention for 6 months after discontinuation of study drug.

8.1.14 Hepatitis

Liver toxicity is a known side effect of GSK 2256098. Monitor for symptoms of fatigue, nausea, vomiting, right upper quadrant pain, fever, rash, and eosinophilia, especially in the presence of any LFT abnormalities.

If hepatic toxicity develops, it is recommended to repeat liver chemistries within 72 hours, then twice weekly until resolution. In addition, it is recommended that alternate etiologies of liver toxicity be investigated, including viral (hepatitis B&C&E, CMV, EBV), environmental (eg alcohol exposure), and intrinsic liver disease (for which liver imaging should be considered).

8.1.15 QT Prolongation

If a QTcF >500 msec (or >60 msec change in QTcF from baseline) is noted on a scheduled or unscheduled ECG, it is recommended to repeat the EKG to confirm the abnormality. Also, the following is recommended in patients with prolonged QTc:

Electrolytes, particularly potassium and magnesium, should be checked and corrected if abnormal.

Concomitant medications with a potential for QTc interval prolongation should be discontinued if clinically appropriate.

Consider cardiology consultation and continuous monitoring.

8.2 Vismodegib Dose Modifications

- If multiple adverse events are seen, administer dose based on greatest modification required for any single adverse event observed.

- Modifications apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.
- If study agent is held for 4 weeks, study agent will be discontinued.
- Descriptors below utilize CTCAE version 4.0 expedited reporting via CTEP-AERS may be required for some adverse events (See Section 9.0).

8.2.1 Vismodegib dose levels

Vismodegib dose modifications by dose level are not utilized due to the pharmacokinetic characteristics of the drug, see section 1 for further description. Rather disruptions of dose are utilized to manage toxicity. If a treatment interruption occurs, and it is determined that vismodegib will be re-started, the original dose will be maintained (150 mg PO daily).

8.2.2 Musculoskeletal and connective tissue disorder adverse event:

- Grade 3 myalgias, grade ≥ 3 muscle spasms (musculoskeletal disorders **other):** Delay vismodegib until myalgia or muscle spasm improves to ≤ grade 1, then resume vismodegib at same dose.
- **Grade 3 arthralgia**: Delay vismodegib until arthralgia improves to ≤ grade 1, then resume vismodegib at same dose.

8.2.3 Gastrointestinal toxicities:

- Grade ≥ 3 diarrhea: Delay vismodegib until diarrhea improves to ≤ grade 1, then resume vismodegib at same dose.
- Grade ≥ 3 nausea or vomiting: Delay vimodegib until nausea/vomiting improves to ≤ grade 1, then resume vismodegib at same dose

8.2.4 Metabolism and Nutrition disorder:

- **Grade ≥ 3 anorexia:** Delay vismodegib until ≤ grade 2 then resume at same dose.

8.2.5 General disorders:

- **Grade 3 fatigue:** Delay vismodegib until ≤ grade 2 then resume at same dose.

8.2.6 Investigations:

- **Grade 3 weight loss:** Delay vismodegib until ≤ grade 2 then resume at same dose.

8.2.7 Other adverse event:

- For all other grade 3 or 4 nonhematologic events, hold dose until grade ≤ 1, then resume vismodegib at same dose.

8.3 GSK2256098 dose modifications:

- If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.
- GSK2256098 will not be re-escalated once reduced
- If dose reductions beyond dose level -2 is required or GSK2256098 is held for 4 weeks, GSK2256098 will be discontinued.

- If more than one of these toxicities apply, use the most stringent criteria (i.e., the greatest dose reduction.)
- If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered.

CTEP-AERS reporting may be required for some adverse events (See Section 9.0)

8.3.1 Dose Levels

Dose Level	Drug Name	Dose
0*	**GSK2256098**	750 mg po bid
-1	**GSK2256098**	500 mg po bid
-2	**GSK2256098**	500mg po in AM, 250mg po in pm

*Dose level 0 refers to the starting dose.

8.3.2 Gastrointestinal toxicities:

- Grade ≥ 3 diarrhea: Delay GSK2256098 until diarrhea improves to ≤ grade 1, then resume GSK2256098 with one dose level reduced.
- **Grade 3 nausea or vomiting**: Delay GSK2256098 until nausea or vomiting improves to ≤ grade 1, then resume GSK2256098 with one dose level reduced
- **Grade 2 esophageal, gastric, small intestine, or colonic ulcer:** Delay GSK2256098 until grade ≤ 1 then resume at same dose
- **Grade 3 esophageal, gastric, small intestine, or colonic ulcer:** Delay GSK2256098 until grade ≤ 1 then resume at one dose level reduced
- **Grade 4 esophageal, gastric, small intestine, or colonic ulcer:** Discontinue GSK2256098

8.3.3 Hepatic Toxicity:

- **For grade 2 ALT, AST,** delay GSK2256098 until ≤ grade 1, then resume at same dose.
- **For grade 3 or 4 ALT, AST** discontinue GSK2256098.
- **For grade 2 bilirubin,** delay GSK2256098 until grade ≤ 1 then resume at same dose.
- **For grade 3, 4 bilirubin,** discontinue GSK2256098.
- **For combined grade 2 AST/ALT and grade 2 bilirubin, discontinue GSK2256098.**

8.3.4 Metabolism and nutrition:

- **Grade 3, 4 anorexia:** Delay GSK2256098 until ≤ grade 2 then resume at one dose level reduced.

8.3.5 Renal and urinary disorders:

- **Grade 2 proteinuria:** Delay GSK2256098 until ≤ grade 1 then resume at same dose.
- **Grade 3 proteinuria:** Delay GSK2256098 until ≤ grade 1 then resume at one dose level reduced.
- **Grade 2 hematuria:** Delay GSK2256098 until ≤ grade 1 then resume at same dose.
- **Grade 3 hematuria:** Delay GSK2256098 until ≤ grade 1 then resume at one dose level reduced.
- **Grade 4 hematuria:** Discontinue GSK2256098

8.3.6 Dermatologic Toxicity:

- **For grade 2 pruritis,** delay GSK2256098 until grade ≤ 1, then resume at same dose
- **For grade 3 pruritis,** delay GSK2256098 until grade ≤ 1, then resume with one dose level reduced.
- **For grade 2 maculopapular rash,** delay GSK2256098 until grade ≤ 1, then resume at same dose

- **For grade 3 maculopapular rash,** delay GSK2256098 until grade ≤ 1, then resume with one dose level reduced.

8.3.7 Investigations:

- For either grade 3 Electrocardiogram QT corrected interval prolonged OR increase in QTc from baseline of > 60 msec, in patient without underlying bundle branch block, discontinue GSK2256098
- For grade 3 Electrocardiogram QT corrected interval prolonged in patient with underlying bundle branch block and baseline QTc < 450 msec, discontinue GSK2256098
- For patient with underlying bundle branch block and baseline QTc of 450 to 480 msec, discontinue GSK2256098 with QTc ≥ 530 msec
- For grade 4 Electrocardiogram QT corrected interval prolonged, discontinue GSK2256098

8.3.8 Other adverse event:

- For all other grade 3 or 4 nonhematologic events, hold dose until grade ≤ 1, then resume GSK2256098 at same dose.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. The CTCAE is available at ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

9.1 Routine adverse event reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0. For this trial, the Adverse Events: Solicited form is used for routine AE reporting in Rave.

Solicited Adverse Events: The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment.

CTCAE v4.0 Term	CTCAE vX.0 System Organ Class (SOC)
Weight loss	Investigations
Proteinuria	Investigations
Fatigue	General disorders and administration site conditions
Anorexia	Metabolism and nutrition disorders
Diarrhea	Gastrointestinal disorders
Dyspepsia	Gastrointestinal disorders
Arthralgia	Musculoskeletal and connective tissue disorders
Headache	Nervous system disorders
Rash maculopapular	Skin and subcutaneous tissues disorders

9.2 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center.

***Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)**

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible	a	a	a, b	a, b	a, b
Probable	a	a	a, b	a, b	a, b
Definite	a	a	a, b	a, b	a, b

a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.
b) Adverse Events: Late CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

9.3 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Alliance investigators are required to notify the Investigational Drug Branch (IDB), the Alliance Central Protocol Operations Program, the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 will be utilized for AE reporting. The CTCAE is identified and located on the CTEP website

at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE. All reactions determined to be "reportable" in an expedited manner must be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS).

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

9.3.1 Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	ade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exclusion to CTEP-AERS Expedited Reporting Requirements for Phase 1 and Early Phase 2 Trials Utilizing an Agent Under a non-CTEP IND:

- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- Grade 1-3 fatigue and hospitalization resulting from such do not require expedited reporting via CTEP-AERS reporting, but should be reported via routine AE reporting.
- Grade 3 fatigue does not require expedited reporting via CTEP-AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 alopecia and hospitalization resulting from such do not require expedited reporting via CTEP-AERS reporting, but should be reported via routine AE reporting.
- Grade 3 alopecia does not require expedited reporting via CTEP-AERS reporting, but should be reported via routine AE reporting
- Reporting of cases of secondary AML/MDS is to be done using the NCI/CTEP Secondary AML/MDS Report Form. New primary malignancies should be reported using the Notice of New Primary Form.
- All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors. In CTCAE version

4.0, the new malignancies (both second and secondary) may be reported as one of the following: (1) Leukemia secondary to oncology chemotherapy, (2) Myelodysplastic syndrome, (3) Treatment-related secondary malignancy, or (4) Neoplasms benign, malignant and unspecified-other. Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

- CTEP-AERS reports should be submitted electronically.
- When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should be completed and submitted, along with any additional medical information (form is available on the CTEP website at http://ctep.cancer.gov/). The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

Expedited Adverse Event Reporting for Suspected Exposure to Agent that May Cause Serious or Life-threatening Birth Defects for Patients Receiving Vismodegib

- CTEP considers **any possible prenatal exposure to vismodegib**, a reportable expedited adverse event that should be reported to CTEP-AERS as a 24-hour notification followed by a complete report within 5 calendar days.

- Any patient suspected of being pregnant or fathering a child, (i.e. any female patient or female partner of a male patient, respectively), or should any lapse in contraception occur, should stop taking vismodegib until it is confirmed that pregnancy has not occurred.

- Pregnancies that occur up to 12 months after the last dose of vismodegib will be followed until the outcome of the pregnancy is known.

- The adverse event (pregnancy) should be reported as a Grade 4 event using CTCAE 4.0 as follows:
  - Endocrine disorders - Other (Prenatal exposure to a possible teratogen)
  - A completed "Possible Prenatal Exposure to Teratogen Report" Form (Appendix VI; note that "AdEERS" has been replaced by "CTEP-AERS") should be attached to the complete CTEP-AERS Report. This form may also be faxed to CTEP along with any relevant supporting medical information at *301-230-0159* (alternative FAX Number: *301-897-7404*).
  - This form should be submitted for any female patient or any female partner of a male patient who becomes pregnant during therapy or up to 12 months after the last dose of vismodegib.

- Any congenital anomaly/birth defect in a child conceived to a female patient or to a female partner of a male patient exposed to GDC-0449 during treatment or within 12 months after the last dose of vismodegib should be reported as an expedited adverse event to CTEP-AERS as a 24-hour notification followed by a complete report within 5 calendar days.

- Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious. Any abortion occurring during the study or within 12 months after the last dose of

vismodegib to a female patient or to a female partner of a male patient exposed to the agent during treatment or within 12 months after the last dose of vismodegib should be reported as an expedited adverse event to CTEP-AERS as a 24-hour notification followed by a complete report within 5 calendar days.

9.4 Comprehensive Adverse Events and Potential Risks list (CAEPR) for GDC-0449 (Vismodegib, NSC 747691)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1893 patients.* Below is the CAEPR for GDC-0449 (Vismodegib).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, April 1, 2016[1]

Adverse Events with Possible Relationship to GDC-0449 (Vismodegib) (CTCAE 4.0 Term) [n= 1893]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GASTROINTESTINAL DISORDERS			
	Constipation		
	Diarrhea		***Diarrhea (Gr 2)***
	Dyspepsia		
	Nausea		***Nausea (Gr 3)***
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
INVESTIGATIONS			
Weight loss			***Weight loss (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
Musculoskeletal and connective tissue disorder - Other (muscle spasms/twitching)			***Musculoskeletal and connective tissue disorder - Other (muscle spasms/twitching) (Gr 2)***
NERVOUS SYSTEM DISORDERS			
Dysgeusia			***Dysgeusia (Gr 2)***
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Irregular menstruation[2]			***Irregular menstruation[2] (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Alopecia			***Alopecia (Gr 2)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Irregular menstruation was observed in 30% (3 of 10) women of child bearing age and/or in 28% (18 of 64) women who had menses at baseline who were enrolled in studies of advanced BCC.

[3]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on GDC-0449 (Vismodegib) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that GDC-0449 (Vismodegib) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Febrile neutropenia; Thrombotic thrombocytopenic purpura
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac arrest; Heart failure; Myocardial infarction; Pericardial tamponade; Sinus bradycardia
EYE DISORDERS - Keratitis; Retinal vascular disorder
GASTROINTESTINAL DISORDERS - Abdominal distension; Abdominal pain; Ascites; Dry mouth; Dysphagia; Esophageal pain; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (thrush); Gastrointestinal hemorrhage[3]; Gastrointestinal pain; Ileus; Mucositis oral; Pancreatitis; Stomach pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Facial pain; Fever; Injection site reaction; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic failure; Portal hypertension
INFECTIONS AND INFESTATIONS - Infection[4]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Hip fracture
INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; CPK increased; Cholesterol high; Creatinine increased; GGT increased; INR increased; Investigations - Other (brain natriuretic peptide increased); Investigations - Other (elevated LDH); Lipase increased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Flank pain; Generalized muscle weakness; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (muscle tightness/stiffness); Myalgia; Neck pain; Pain in extremity; Trismus
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Leukemia secondary to oncology chemotherapy; Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Dizziness; Dysesthesia; Headache; Intracranial hemorrhage; Movements involuntary; Nervous system disorders - Other (amimia); Olfactory nerve disorder; Paresthesia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Stroke; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Hallucinations; Insomnia; Psychosis
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal hemorrhage
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Erectile dysfunction

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Aspiration; Cough; Dyspnea; Epistaxis; Hiccups; Hypoxia; Pleural effusion; Pneumonitis; Postnasal drip; Pulmonary edema; Respiratory, thoracic and mediastinal disorders - Other (COPD); Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain); Sneezing; Sore throat
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Hyperhidrosis; Nail ridging; Pruritus; Rash acneiform; Rash maculo-papular; Skin and subcutaneous tissue disorders - Other (hair color changes); Skin and subcutaneous tissue disorders - Other (psoriasis); Skin and subcutaneous tissue disorders - Other (skin exfoliation); Skin ulceration; Stevens-Johnson syndrome
VASCULAR DISORDERS - Hypertension; Hypotension; Thromboembolic event; Vasculitis

Note: GDC-0449 (Vismodegib) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.0 DRUG INFORMATION

Investigators ordering and/or dispensing supplied agents at any time for study treatment must be currently registered with PMB, DCTD, NCI. A registered investigator must co-sign for other non-registered personnel prescribing the supplied agents.

10.1 Vismodegib (GDC-0449, Erivedge®, NSC# 747691, IND#126926) IND holder: Alliance

Procurement

Vismodegib is an investigational, oral small molecule inhibitor of SMO that will be provided by Genentech and distributed by Biologics Inc. Use the order form on the A071401 webpage to order vismodegib.

Formulation

Vismodegib is supplied as 150 mg capsules. Each vismodegib capsule contains 150 mg vismodegib and the following inactive ingredients: microcrystalline cellulose PH101, lactose monohydrate, sodium lauryl sulfate, povidone K29/32, sodium starch glycolate, talc, magnesium stearate, and purified water. The capsule shell contains gelatin, titanium dioxide, red iron oxide, and black iron oxide.

Preparation, Storage and Stability

All drug supplies should be stored in a secure location, at room temperature. Do not store above 30ºC. Information on the shelf life of the capsules is provided on the label.

Administration

Vismodegib is taken orally once daily with or without food. If a dose is missed, do not make up that dose; resume dosing with the next scheduled dose.

Drug Accountability

The NCI Investigational Agent Accountability Record Form for Oral Agents should be utilized.

Drug Interactions

Vismodegib is a minor substrate of CYP2C8 and CYP3A4 *in vitro*. CYP inhibition is not predicted to alter vismodegib systemic exposure as similar steady-state plasma vismodegib concentrations were observed in patients in clinical trials concomitantly treated with CYP3A4 inducers (e.g. carbamazepine, modafinil, phenobarbital) and CYP3A4 inhibitors (e.g. erythromycin, fluconazole). Vismodegib is not a potent inhibitor of CYP1A2, CYP2B6, CYP2D6, and CYP3A4/5. In vitro, studies indicate vismodegib is an inhibitor of CYP2C8, CYP2C9, CYP2C19 and BCRP. However, visomodegib was found to have low potential for inhibiting CYP2C8 and CYP2C9 as systemic exposure of rosiglitazone and oral contraceptives were not altered with concomitant vismodegib. Vismodegib does not induce CYP1A2, CYP2B6 or CYP3A4/5 in human hepatocytes.

Vismodegib is a substrate of the efflux transporter P-glycoprotein. Co-administration of vismodegib and drugs that inhibit P-glycoprotein (e.g. clarithromycin, itraconazole,

erythromycin, verapamil, diltiazem) may increase systemic exposure and toxicity of vismodegib.

Solubility is altered and bioavailability is reduced with the coadministration of vismodegib and drugs that alter the pH of the upper GI tract (e.g. proton pump inhibitors, H2-receptor antagonists, and antacids). No formal clinical studies have been conducted to evaluate the effect of gastric pH altering agents on vismodegib. Coadminister drugs that alter the pH of the upper GI tract with caution as systemic exposure of vismodegib may be decreased and the effect on efficacy is unknown.

Pharmacokinetics

Absorption: Bioavailability is 31.8%. Absorption is saturable. Vismodegib may be taken without regard to meals because the systemic exposure of vismodegib at steady state is not affected by food.

Distribution: $V_{d:}$ 16.4 to 26.6L. Plasma protein binding is greater than 99%.

Metabolism: Greater than 98% of the total circulating drug related components are parent drug. Metabolic pathways include oxidation, glucuronidation and pyridine ring cleavage. Two metabolites recovered in the feces are produced *in vitro* by CYP2C9 and CYP3A4/5.

Half-life elimination: 4 days after continuous once daily dosing; 12 days after a single dose

Excretion: Feces (82%); urine (4.4%)

Adverse Events

See CAEPR in section 9.4.

Nursing Guidelines

Patients should be advised to keep their supply of vismodegib in a secure location to prevent accidental or deliberate use by others.

Patients should be thoroughly counseled and informed of the teratogenic potential of vismodegib. See Section 3.1.

Vismodegib has the potential to inhibit drugs that are substrates of the CYP2C8, CYP2C9 and CYP2C19 pathways. Assess patient's current medication list, including over the counter agents.

Patients may experience fatigue while on this agent. Instruct patient in energy conserving lifestyle.

Dysgeusia can be seen and is usually mild.

Alopecia has been seen and may be complete (scalp, eyelashes, eyebrows, etc.). Warn patients of this possibility.

Gastrointestinal side effects, including nausea, vomiting (with resulting dehydration) and dyspepsia have been reported. Treat symptomatically and monitor for effectiveness.

Muscle pain and spasms can occur. Treat symptomatically and monitor for effectiveness.

Patients should be instructed to take their pills at the same time each day with or without food. These must be swallowed whole and cannot be crushed or opened for any reason. Patients should not take missed doses, but just resume with the next scheduled dose.

10.2 GSK2256098 (NSC# 783781, IND #126926)

Procurement

GSK2256098 is an investigational, oral small molecule inhibitor of focal adhesion kinase (FAK) supplied by GlaxoSmithKline and distributed by Biologics. Use the order form on the A071401 webpage to order GSK2256098.

GSK2256098 supply has an expiry of January 2018. Currently, there are no plans for further supply to be manufactured, therefore supply of GSK2256098 for this study will expire January 2018.

Formulation

GSK2256098 is supplied as 250 mg capsules. The capsule filling contains microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The pink opaque hard gelatin capsule (250 mg) is composed of red iron oxide, titanium dioxide and gelatin

Preparation, Storage and Stability

All drug supplied should be stored in a secure location, at room temperature protected from light. GSK2256098 can be stored at up to 30 degrees Celsius (86 degrees Fahrenheit).

Administration

GSK2256098 is taken orally twice daily with or without food. If a dose of GSK2256098 is missed, do not make up that dose; resume dosing with the next scheduled dose. Capsules should not be opened or crushed. Retain GSK2256098 in the bottle provided until use.

Drug Accountability

The NCI Investigational Agent Accountability Record Form for Oral Agents should be utilized.

Upon completion of the trial, all remaining drug at the site must be destroyed as per local institutional policy, and notification of destruction must be sent to pharmaffairs@alliancenctn.org within 90 days of trial completion.

*Drug Interaction*s

No in vivo studies have been performed specifically to evaluate potential interactions with drugs that may be co-administered with GSK2256098.

GSK2256098 is primarily metabolized by CYP3A4 and is a substrate of membrane transporter P-glycoprotein. Strong inhibitors of CYP3A4 may increase exposure of GSK256098. Strong inducers of CYP3A4 may decrease exposure of GSK2256098.

GSK2256098 is an inhibitor of CYP2C8, CYP2C9 and CYP3A4, UGT1A1 and of the membrane transporter protein OATP1B1. GSK2256098 is an inducer of CYP3A4 and CYP2B6. GSK2256098 may also inhibit transport of P-glycoprotein substrates. Caution should be used with concomitant medications that are substrates with narrow therapeutic indices of CYP2C8, CYP2C9, CYP3A4, UGT1A1 and P-glycoprotein.

Pharmacokinetics

Absorption: Rapidly absorbed with a time to maximal concentration of 1 to 3 hours. Following administration of a high-fat meal, the Tmax was delayed and mean Cmax decreased by 55% relative to the fasted state; the change in AUC (15% decrease) was not clinically meaningful. Food decreased the rate, but not the extent of GSK2256098 absorption.

Distribution: Plasma protein binding is 89.2%.

Metabolism: Hepatic via CYP3A4 (98.8%) with a minimal contribution from CYP2C8.

$\mathbf{T}_{1/2}$: Mean half-life was 4.4 hours (at 1000 mg dose level).

Adverse Events

The most frequently reported adverse events associated with continuous oral BID dosing of GSK2256098 were nausea (76%), diarrhea (65%), vomiting (58%), decreased appetite (47%), proteinuria (26%), fatigue (24%), asthenia (23%), hyperbilirubinemia (23%), constipation (21%) and hypercholesterolemia (21%).

Special Warnings and Precautions for Use

Patients receiving GSK2256098 should avoid direct sunlight or UV exposure while receiving study medication. In case of direct exposure, the use of protective clothing, sun glasses and sunscreen is recommended.

Nursing Guidelines

Instruct patients that GSK2256098 may be taken with or without food.

Do not crush or open capsules.

Agent should be taken twice daily. Missed doses should not be made up.

While formal drug to drug studies have not been performed, drugs that are strong inducers of CYP3A4 may decrease the exposure of agent. Assess patient's concomitant medications and instruct patients to report any new medications to the study team.

Gastrointestinal side effects were common, including nausea, diarrhea and vomiting. Treat symptomatically and assess for effectiveness of intervention.

Instruct patients that fatigue and asthenia may occur. Instruct patient in energy conserving lifestyle.

Monitor bilirubin and instruct patients to report any jaundice symptoms to the study team immediately.

Patients should be instructed to avoid direct sunlight or UV exposure. Patients should be instructed on the use of protective clothing, sun glasses and sunscreen.

Monitor bilirubin and instruct patients to report any jaundice symptoms to the study team immediately. Patients should be instructed to avoid direct sunlight or UV exposure. Patients should be instructed on the use of protective clothing, sun glasses and sunscreen.

11.0 MEASUREMENT OF EFFECT

Response and progression will be evaluated in this study using the new international criteria proposed by MacDonald guidelines.[43] Primary endpoint will be based on local radiology review. Central radiology review will be carried out for measurement of secondary endpoint.

11.1 Schedule of Evaluations:

For the purposes of this study, patients should be reevaluated every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 8 weeks following initial documentation of objective response.

Supporting documentation of response should be submitted, per Section 6.1.1.

11.2 Definitions of Measurable and Non-Measurable Disease

11.2.1 Measurable Disease

Bidimensionally measurable lesions with clearly defined margins by MRI scans, with a minimum diameter of 10mm in both dimensions.

For multifocal intracranial disease, no more than 5 target measurable lesions (each >=10mm in diameter in both dimensions) should be selected for measurement. Target lesions should be selected on the basis of their size (lesions with longest diameter), be representative of other lesions and lend themselves to reproducible repeated measurements.

11.2.2 Non-Measurable Disease

Unidimensionally measurable lesions, masses with margins not clearly defined.

11.3 Guidelines for Evaluation of Measurable Disease

11.3.1 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up.

11.3.2 Acceptable Modalities for Measurable Disease:

- **Conventional CT and MRI:** This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

  As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

11.3.3 Measurement at Follow-up Evaluation:

- A subsequent scan must be obtained every 8 weeks following initial documentation of an objective status of either complete response (CR) or partial response (PR).

- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks (see Section 11.4.4).

11.4 Measurement of Treatment/Intervention Effect

11.4.1 Measurable lesions

Bidimensionally enhancing measurable lesions with clearly defined margins by MRI or CT scan. Necrosis or cystic changes (nonenhancing disease) should not be included in the measurement of tumor area.

11.4.2 Non-measurable lesions

Non-measurable sites of disease (Section 11.2.2) should also be recorded at baseline. These lesions should be followed in accord with section 11.4.3.3.

11.4.3 Response Criteria

11.4.3.1 All measurable lesions followed by CT/MRI must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring measurable lesions.

Note: Non-measurable lesions should be evaluated at each assessment, especially in the case of first response or confirmation of response.

11.4.3.2 Evaluation of Measurable Lesions

Current Response Criteria for Malignant Gliomas (Macdonald Criteria)[43]

Response	Criteria
Complete response	Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; no corticosteroids; and stable or improved clinically
Partial response	Requires all of the following: ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no new lesions; stable or reduced corticosteroid dose; and stable or improved clinically
Stable disease	Requires all of the following: does not qualify for complete response, partial response, or progression; and stable clinically
Progression	Defined by any of the following: ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions; any new lesion; or clinical deterioration

- **Complete Response (CR):** All of the following must be true:
  a. Disappearance of all enhancing lesions on consecutive magnetic resonance imaging (MRI) or CT at least 8 weeks apart. No new lesions. No evidence of non-measurable disease. All measurable and nonmeasurable lesions and sites must be assessed using the same techniques at baseline. Patients must be on no steroids. Neurologically/clinically stable or improved
- **Partial Response (PR):**
  a. ≥ 50% decrease under baseline in the sum of products of perpendicular diameters all enhancing measurable lesions. No progression of nonmeasurable disease. No new lesions. All measurable and non-measurable lesions and sites must be assessed using the same techniques as baseline.

Patients must be on stable or decreasing dose of steroids. Neurologically/clinically stable or improved

- **Progression (PD):** At least one of the following must be true:
  a. $\geq$ 25% increase in the sum of products of all enhancing measurable lesions over smallest sum observed (over baseline if no decrease) using the same techniques as baseline, OR clear worsening of any nonmeasurable disease, OR appearance of any new lesion/site, OR clear clinical worsening or failure to return for evaluation due to death or deteriorating condition (unless clearly unrelated to this cancer)
  b. >25% increase in the sum of products of all measurable enhancing lesions but < 50% increase in the sum of products of all measurable enhancing lesions AND no new lesions/sites in scans obtained in the first 16 weeks of therapy AND no clear clinical deterioration: When all of these conditions are met, the patient may continue on drug for 4 weeks. Imaging must be repeated 4 weeks later (+/- 7 days). If imaging at 4 weeks shows continued growth of greater than 25%, then patient has definitive progression.
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD. Stable clinically.

11.4.3.3 Evaluation of Non-Measurable Lesions

- **Complete Response (CR):** All of the following must be true:
  a. Disappearance of all measurable lesions.
- **Non-CR/Non-PD:** Persistence of one or more non-measurable lesions.
- **Progression (PD):** At least one of the following must be true:
  a. Unequivocal progression of existing measurable lesions (NOTE: Unequivocal progression should not normally trump measurable lesion. It must be representative of overall disease status change.)

11.4.4 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on measurable lesions and non-measurable lesions and new disease as defined in the following tables:

For Patients with Measurable Disease

Measurable lesions	Non-measurable lesions	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

* See Section 11.4.3.1
** See Section 11.4.3.2

11.4.5 Symptomatic neurologic deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration.

A patient is classified as having PD due to "symptomatic deterioration" if any of the following occur that are not either related to study treatment or other medical conditions:

- Worsening of neurologic examination.
- Worsening of tumor-related and/or neurologic symptoms.
- Decline in performance status of >1 level on ECOG scale.
- Increased steroid dosage lasting > 14 days
- Increase in seizure frequency or severity lasting > 14 days

11.5 Definitions of analysis variables

Formal definitions of variables used in analyses can be found in the Statistical Considerations section of the protocol.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Treatment

12.1.1 CR, PR, or SD: Patients who are in CR, PR or SD, as assessed by local radiology review, will continue on therapy until progression of disease, excessive toxicity requiring the patient to come off of treatment, or the patient withdraws from treatment. After treatment is discontinued, patients will be followed per the study calendar in section 5.0.

12.1.2 Disease Progression: Remove from protocol therapy any patient with disease progression. Document details, including tumor measurements, on data forms.

After disease progression, patients should be followed for survival per the study calendar (Section 5.0).

12.1.3 Discontinuation of study agent: If the patient discontinues study agent, patients should be followed for disease progression and survival per the study calendar (Section 5.0).

12.2 Definitions and Follow-up Requirements

Definition of ineligible patients: A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible. Patients who are deemed ineligible may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient were to continue protocol treatment. Notification of the local IRB may be necessary per local IRB policies.

Definition of clinical follow-up: The follow-up period where the study participant is no longer receiving treatment, but is still following the study calendar for tests, exams, and correlative endpoints (e.g., specimen collection, quality of life, disease assessments as required by the study).

Definition of survival only follow-up: The follow-up period where the study participant is monitored for long-term endpoints, is no longer receiving study treatment, and is not required to follow the study calendar for tests, exams, and correlative endpoints (e.g. specimen collection, quality of life, disease assessments as required by the study). In this follow-up period, there is a schedule in which case report forms should be submitted, but the physician visits are based on the standard of care.

12.2.1 Follow-up for Ineligible Patients

Study participants who are registered to the trial but deemed ineligible must complete follow-up requirements as specified below.

Baseline, on-study and off-treatment notice data submission required.

12.2.2 Follow-up for Patients Never Receiving Protocol Intervention

Study participants who are registered to the trial but who never go on to receive study intervention must still complete follow-up requirements as specified below.

Baseline, on-study and off-treatment notice data submission required.

12.3 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.

- Follow the patient for protocol endpoints as required by the Study Calendar.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design

Each arm is a prospective, one-stage phase 2 study evaluating the efficacy of SMO or FAK inhibitors in patients with *SMO*-mutated or *NF2*-mutated meningiomas, respectively. There will be a separate phase 2 arm for each of the two tumor mutation groups and each tumor grade cohort. Patients with recurrent or progressive Grade I-III meningiomas will be eligible for this trial. Samples will undergo central pathology review. Patient's tumor samples will be tested for the presence of *SMO* or *NF2* mutations. Patients harboring SMO or NF2 mutations and who meet eligibility criteria will be enrolled. Within each arm, there will be two different patient cohorts based on histology: grade I versus II/III meningiomas. There is no planned interim analysis. The sample size calculation was done with EAST v6.3.

13.2 Statistical Design and Analysis for the Primary Endpoint

The statistical design and primary endpoint is the same for each treatment arm within the trial.

13.2.1 Primary endpoints

The co-primary end points are progression-free survival at 6 months (PFS6) and response rate. PFS6 is defined as not having progressive disease or death within six months of the first day of treatment. A patient will be deemed to have a response if they have a confirmed PR or CR. Contrast-enhanced cranial magnetic resonance imaging (MRI) will be performed every 8 weeks. Standard response criteria will be used (see Section 11.0).

All patients meeting the eligibility criteria that have signed the consent form and have begun treatment will be considered evaluable for the analysis of primary endpoint.

Safety Analysis (SA) population: All patients who received any quantity of study drug. Patients will be grouped according to treatment received.

13.2.2 Statistical Design

The goal will be to enroll 12 patients per cohort within each arm. A total of 48 patients will be enrolled. There will be a separate Phase II arm for each group: patients with SMO mutations and patients with NF2 mutations. The design of each Phase II arm is identical. Each arm will require 24 patients.

Within each mutation defined treatment arm, there will be 12 accrued to a cohort of grade I patients and 12 accrued to a cohort of grade II/III patients, and the statistical design will be identical for the 2 mutation defined treatment arms.

Within each treatment arm, the trial will distinguish between tumor response rates of 20% vs. 2.5%. If at least 3 responses (at least 12.5%) are observed among the 24 evaluable patients, the agent will be considered worthy of further testing in this mutation defined treatment arm, yielding at least 89% power to detect a true response rate of at least 20%, with a significance level of .021 against the null hypothesis of 2.5% response rate.

Within each grade II/III cohort of a treatment arm, the trial will distinguish between 6 month PFS rates of 55% vs. 15%. If at least 5 patients (at least 42%) demonstrate 6 month PFS, among the 12 evaluable patients, the agent will be considered worthy of further testing in this mutation defined grade II/III cohort, yielding at least 89% power to detect a true 6 month PFS rate of at least 55%, with a significance level of .024 against the null hypothesis of 15% 6 month PFS rate.

Within each grade I cohort of a treatment arm, the trial will distinguish between 6 month PFS rates of 65% vs. 25%. If at least 7 patients (at least 58%) demonstrate 6 month PFS, among the 12 evaluable patients, the agent will be considered worthy of further testing in this mutation defined grade I cohort, yielding at least 79% power to detect a true 6 month PFS rate of at least 65%, with a significance level of .014 against the null hypothesis of 25% 6 month PFS rate.

Thus, the trial has 89% power to detect a promising response rate in either mutation defined treatment group, 79% power to detect a promising 6 month PFS rate in either mutation defined grade I cohort, and 89% power to detect a promising 6 month PFS rate in either mutation defined grade II/III cohort, with an over-all type I error bound of 11%, against the over-all null hypothesis that neither agent is active with respect to either response rate or PFS.

13.2.3 Analysis Plan

The final analysis will be done after the last enrolled patient had been followed for 6 months from the start of her/his treatment. There should be 24 evaluable patients in each treatment arm and 12 patients within each cohort in each arm (total of 48 evaluable patients). The decision rules will be evaluated for each treatment arm.

The treatment will be considered active within a mutation defined group if any of the following occurs:

- There are 3 or more responses observed among the 24 evaluable patients in the treatment arm
- Within the grade II/III cohort of a treatment arm, 5 or more evaluable patients are progression-free at 6 months from treatment initiation out of the 12 evaluable patients
- Within the grade I cohort of a treatment arm, 7 or more evaluable patients are progression-free at 6 months from treatment initiation out of the 12 evaluable patients

In addition, point estimates will be generated for response rates within each treatment arm with corresponding 95% binomial confidence intervals. Point estimates and 95% binomial confidence intervals will also be generated for the six month progression-free survival rate within each cohort of each treatment arm. Kaplan-Meier curves will be generated for progression-free survival for each cohort within each treatment arm. There will be no formal comparison of rates among the arms and sub-cohorts of patients.

13.3 Sample size, accrual time and study duration

13.3.1 Sample Size

The study design to be utilized is fully described in Section 13.1. There will be 24 evaluable patients assigned to each treatment group of the study based on their tumor mutations (total of 48 evaluable patients). With each mutation treatment arm group, there will be 12 patients accrued to the grade I cohort and 12 patients accrued to the grade II/III cohort. We anticipate accruing an additional 4 patients in each treatment group to account for ineligibilities or cancellations. Thus the maximum target accrual is 56 ((24+4) x 2) in total. In the event that the additional accrual does not produce the required number of evaluable patients, we retain the option of continuing accrual until that goal is met.

13.3.2 Accrual Rate and Accrual Duration

This phase II study is designed to accrue 24 SMO mutation, and 24 NF2 mutation evaluable patients, over approximately 2-3 years. There is little information available for what the precise accrual rate will be. However our goal is to accrue the 48 evaluable patients (with an anticipated maximum of 56 patients to get 48 evaluable) within 3 years.

13.3.2 Primary Endpoint Completion Date for Clinical Trials.gov Reporting

For purpose of ClinicalTrail.gov reporting, the Primary Endpoint Completion Date (PECD) for this study is the time the last patient registered has been followed for at least six months.

13.4 Supplementary Analysis plans

Overall survival and progression free-survival will be summarized for each cohort within each treatment group with Kaplan-Meier curves and estimates. No formal comparison will be made among the cohorts of the treatment groups.

Adverse events (AEs) will be summarized for each treatment group. They will be summarized as the number and frequency of each event. In addition the AEs will be summarized as the number and frequency of patients who experience any AE, AEs of grade 3+, and AEs of grade 4+. This analysis will be purely descriptive.

The response rate determined by central review will be estimated for each cohort within each treatment group with proportion of patients who achieve CR/PR deemed by central review. The ninety percent two-sided confidence intervals will be calculated according to approach of Duffy and Santner. No formal comparison will be made among the cohorts of the treatment groups.

13.5 Monitoring the Study

13.5.1 Adverse Event Stopping Rule

The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e., an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy the following:

if 5 or more patients in the first 20 treated patients (or 25% of all patients after 20 are accrued) experience a grade 4 or higher non-hematologic adverse event.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

13.5.2 Accrual Monitoring Stopping Rule

The study design assumes that 1-2 patients will accrue per month to each treatment arm, leading to a 2-3 year total accrual period. At 12 months, if the total accrual is below 50% of the expected (fewer than 6 patients) the study team will evaluate with the scientific question will be of interest at the completion of the accrual period. It is deemed that the scientific question is likely not to have relevance at the end of the projected accrual period,

the study may close. Otherwise, the study team will continue to boost the accrual rates. The accrual rate will be checked every subsequent 6 months and the likelihood that the study questions will still be of interest at the end of the trial will be evaluated and based on this, a decision will be made whether or not to continue accrual to the study.

13.6 Study Reporting

13.6.1 This study will be monitored by the study team on a monthly basis upon enrollment of the first patient. Reports containing a summary of adverse events by treatment arm will be reviewed. The study team will also monitor the accrual rate.

13.6.2 This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative protocol and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis, either by FTP burst of data or via the CDS web application. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

Note: This study has been assigned to CDUS-Abbreviated reporting, no adverse events (routine or expedited) is required to be reported via CDUS.

13.6.3 This study will be monitored by the Food and Drug Administration due to the Investigational New Drug (IND) status of the agent. An IND report will be produced and submitted to the Regulatory Affairs Manager within 60 days of the anniversary date that the IND went into effect**.**

13.6.4 Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the "ClinicialTrails.gov" web site. The Primary and Secondary Endpoints (ie, "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov.

13.7 Descriptive Factors

As mentioned above, patients will be assigned to a treatment arm based on the mutation status of their tumor. In addition, they will be assigned to a cohort within each treatment arm based on their tumor grade (grade I versus grade II/III). There are not additional descriptive factors.

13.8 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin. There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

The geographical region served by the Alliance, has a population which includes approximately 18 % minorities. Based on national statistics involving similar meningiomas, we expect about 15 % of patients will be classified as minorities by race and about 60 % of patients will be women. Expected sizes of racial by gender subsets for patients to this study are shown in the following table. Note that these values are for the maximum number of patients (56) that we expect to accrue.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	1	1			2
Asian	1				1
Native Hawaiian or Other Pacific Islander		1			1
Black or African American	1	1			2
White	26	17	4	3	50
More Than One Race					
Total	29	20	4	3	56

Ethnic Categories:	**Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino." **Not Hispanic or Latino**
Racial Categories:	**American Indian or Alaskan Native –** a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment. **Asian –** a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.) **Black or African American –** a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American." **Native Hawaiian or other Pacific Islander –** a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands. **White –** a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

14.0 CORRELATIVE AND COMPANION STUDIES

There are 2 sub-studies within Alliance A071401 (A071401-ST1 and A071401-IM1). The correlative science studies **must be offered** to patients enrolled on A071401. All patients are encouraged to participate.

14.1 Correlative Studies using Biospecimens (Alliance A071401-ST1)

14.1.1 Exploratory Identification of Molecular Biomarkers of Response

14.1.1.1 Background

Understanding the genomic context in which oncogenic mutations occur will be of great importance in this prospective, phase 2 study evaluating the efficacy of SMO and FAK inhibitors in patients with SMO-mutated or NF2 mutated meningiomas. Concurrent mutations in other driver oncogenes or tumor suppressors

will be critical to evaluate as will the complexity of the genome of these tumors. The presence or absence of additional genomic changes may influence the behavior of tumor to the proposed therapies. The proposed correlative analyses will allow us to investigate the full extent of genomic aberrations occurring in the study cohort and may allow for improved treatment implementation.

14.1.1.2 Objectives

To support our work on this clinical trial we are currently characterizing two cohorts of patients using a range of genomic technologies in an effort to have a 'database' that will serve as a point of reference and comparison for our clinical trial samples. On these cohorts we are performing high resolution array comparative genomic hybridization arrays, targeted sequencing of over 500 cancer associated genes and genome wide methylation analyses. One cohort contains over 150 patients that have had meningioma resected during the last two years at Brigham and Women's Hospital, and therefore contains meningioma of various histologic subtypes, grade and mutational status (NF2, SMO, AKT1, TRA7, KLF4). The other cohort will contain over 100 samples from grade I and grade II meningioma that have all recurred. Data from these two well annotated cohorts will provide us with a broad and integrated view of the genomics of meningioma subclassification, grading and prognostics – a view that will serve as a backdrop and a point of reference for comparing genomic aberrations observed in our clinical trial samples.

We propose to perform several genome wide tests on both the primary meningioma resection sample and any samples from recurrent tumor. The goal is to identify genetic biomarkers that will predict response to therapy. If normal patient DNA is available we will perform whole exome sequencing on these samples. If normal patient DNA is unavailable we will perform targeted sequencing that is limited to roughly 500 cancer-associated genes. In addition, if sufficient DNA is available from the samples, we will perform genome wide methylation profiling. Using the cohorts mentioned above, we currently have plans to compare the reliability of making copy number calls from data acquired using methylation profiling arrays (comparing to the same samples that have been analyzed by aCGH). If methylation profiling data is adequate for making copy number calls, we will only analyze these samples with methylation arrays, otherwise we will collect data from those arrays and from high resolution 1x1M Agilent CGH Microarray chips to confidently identify tumor-specific genomic copy number changes. Starting at screening, and then every other cycle thereafter, we will collect blood to evaluate for circulating DNA in plasma and we will perform targeted sequencing to identify oncogenic mutations.

We will examine this data for genetic biomarkers (chromosome losses, methylation site signatures, combinations of point mutations) to help identify possible biomarkers that will identify those that will respond to therapy and those that will have an aggressive course. We will look for common mutations that could predict resistance to the therapies. These studies could provide suggestions as to other therapies that might aid tumors that do not respond to SMO or FAK inhibition.

14.1.1.3 Methods for Exploratory Correlative Studies

Whole Exome Sequencing and Analyses

Whole exome sequencing will be performed following DNA fragmentation and purification and then library preparation with DNA barcoding. Read pairs will be aligned to the hg19 reference sequence and somatic variant calling will be performed

within the Firehose environment and will be annotated to genes and compared to events in the Catalogue of Somatic Mutations in Cancer (COSMIC).

Targeted Sequencing and Analyses

Targeted sequencing of over 500 cancer associated genes will be performed on DNA that has been fragmented and used for library preparation with DNA barcoding. Read pairs will be aligned to the hg19 reference sequence and somatic variant calling will be performed within the Firehose environment and will be annotated to genes and compared to events in the Catalogue of Somatic Mutations in Cancer (COSMIC).

Copy number variation

Array - based comparative genomic hybridization (aCGH) will be performed using the stock 1x1M Agilent SurePrint G3 Human CGH Microarray chip to identify tumor-specific genomic copy number changes. Genomic DNA isolated from the FFPE specimen submitted will be hybridized with genomic DNA isolated from a reference DNA sample representing a pool of karyotypically normal individuals (Promega, Madison, WI). The array platform contains 963,029 probes spaced across the human genome with a 2.1 kb overall median probe spacing and a 1.8 kb probe spacing in RefSeq genes.

Methylation arrays

Genome wide methylation profiling will be performed with Illumina 450K arrays that contain over 450,000 sites targeting all CpG islands and shores, miRNA promoter regions, and disease-associated regions associated with GWAS studies, among other regions. This array represents the most effective and most comprehensive method of direct DNA methylation profiling. This technology uses bisulfite conversion and single base-pair extension to determine a percent methylation at individual CpG sites. It permits for rapid clustering of samples based on the global methylation patterns observed.

Data obtained from Illumina 450K arrays will be averaged (percent methylation) across a given CpG island and clustered using unsupervised hierarchical methods and the most variant probes (~1500). Supervised clustering across subgroups of this disease will also be performed to examine whether subgroup-specific methylation patterns exist.

Integration of data will be performed using the integrated genome viewer from the Broad Institute.

Histopathologic and immunohistochemical analysis

All samples available from this cohort (including primary and recurrent tumors) will be classified by WHO tumor classification criteria for tumor type, subtype and grade and mitoses (highest count per 10 high powered fields) will be evaluated. Histologic features for each of the grading criteria that are used in determining WHO grade will be individually recorded as will the presence of brain invasion. For each sample we will perform a formal count of the Mib1 proliferative index using Aperio digital scanning. We can then analyze the data for histologic correlates of response to therapy.

We will also generate a tissue microarray from all samples with sufficient tissue. The TMA will be used for MIB1 staining, as well as for immunohistochemical staining with markers of PI3K and SMO pathway activation. Our group has demonstrated that

immunohistochemical staining with *GAB1* and *STMN1* in meningiomas correlated with *SMO* and *AKT1* mutation status[14].

14.1.1.4 Statistical Considerations

Exploratory analyses on biomarkers will be conducted. Validation of findings in our clinical trial samples can be conducted as needed on archived tissue from meningiomas that have not recurred in over 5-10 years. Because the skull base programs at BWH and MGH are very robust (roughly 40-50 surgeries of skull based meningioma per year), we have ample local resources to compile adequate comparison groups. Our cohort of 150 cases contains over 50 skull based meningioma and we will shortly have an in-depth view of their genomics.

Data obtained from the Illumina 450K arrays will be averaged (percent methylation) across a given CpG island. The most variant ~1500 probes will be used for clustering by unsupervised hierarchical methods. Supervised clustering across subgroups of these samples will also be performed to explore possibly correlations with clinicopathologic parameters. Similar approaches will be used for analysis of aCGH data.

For histologic and immunohistochemical features, as data permits (mitoses, Mib1 profilerative index, etc.), analyses of biomarkers will be summarized by descriptive statistics, including mean, median and standard deviation. Statistical analysis will use Fisher's exact test (association of dichotomous factors), or t-test (comparison of means). Data analysis will be conducted using Prism GraphPad Software and significance will be defined as $P<0.05$.

Differences in these biomarkers between responders and non-responders will be compared with parametric or nonparametric techniques as permitted by the data. For correlative analyses, Cox proportional hazards model will be used to explore the relationship between these biomarkers measured at baseline and PFS and OS. Logistic regression will be used to explore the relationship between these biomarkers measured at baseline and the binary outcome of alive and progression-free at 6 months (APF6)

14.1.2 Circulating tumor DNA (ct-DNA)

14.1.2.1 Background

There is increasing evidence that tumor DNA representing the mutational status of tumor cells can be obtained through the isolation of circulating DNA from blood specimens of patients with cancer[44, 43.] An assay has been developed to identify the major mutations in the *AKT1* gene on the basis of the analysis of circulating tumor DNA (ctDNA) in plasma. Recent analyses have also suggested the feasibility of next-generation sequencing to look more broadly at cancer-specific mutation in ctDNA.

14.1.2.2 Methods

Blood samples will be collected at various timepoints to evaluate oncogenic mutations at baseline and the emergence of new mutations after treatment. Mutations will be evaluated in relevant genes, including but not limited to *AKT1* and *SMO.*

ctDNA will be extracted from plasma samples collected from patients at diagnosis and will be used for the detection of oncogenic mutations using the qRT PCR assays or other technologies such as next-generation sequencing for meningioma- related

oncogenes and tumor suppressors. The prevalence of the mutations measured at baseline and after treatment may provide information on response or resistance to therapy as well as information regarding potential changes in AKT and SMO mutation status during tumor evolution.

14.1.2.3 Statistical Considerations

Exploratory analyses will be conducted. The rates of the different mutations will be summarized by descriptive statistics, the frequency and relative frequency. The agreement with the identification of a mutation in the ctDNA and in tumor tissue will be evaluated using Kappa statistics. Differences in mutation rates between responders and non-responders will be compared with parametric or nonparametric techniques as permitted by the data. Cox proportional hazards model will be used to explore the relationship between the identified mutations and PFS and OS. Logistic regression will be used to explore the relationship between the identified mutations and tumor response status. Finally, the frequency of mutations over time will also be evaluated in a descriptive manner.

14.2 Imaging Biomarkers of Response (A071401-IM1)

14.2.1 Background

We propose to investigate dynamic contrast enhanced (DCE) MRI as an early biomarker of treatment response. Using DCE MRI, physiological parameters related to the tumor vasculature can be calculated. Of particular interest are the parameters K^{trans} which measures vascular permeability and blood vessel surface area and Ve which measures the volume of extravascular extracellular space (the "leakage" space). Meningiomas are known to have high expression of VEGF so have a rich blood supply and avidly enhance on contrast enhanced MRI.[45] In addition, Ve is elevated in meningiomas.[46] Thus, looking at change in tumor vasculature and interstitial space is an intriguing technique to assess meningioma response to therapy. Given that stable disease, i.e. no significant change in meningioma size, is often the best outcome with meningiomas within the first 6-12months of therapy, having an early physiological biomarker of response to any new therapy would be very useful.

Although little data exists in meningiomas, K^{trans} has shown promise in assessing early response to treatment in glioblastoma.[47] Meningiomas are characterized by high vascular permeability that can be measured by DCE MRI and a decrease in K^{trans} has been associated with response to radiation.[48, 49]DCE may also be helpful in distinguishing atypical from typical meningiomas.[44] Thus, we propose to include DCE MRI to determine if change in K^{trans} or Ve can serve as an early physiological biomarker of response.

14.2.2 Objectives

1. To determine if baseline Ktrans or Ve is associated with response.
2. To determine if change in Ktrans or Ve is associated with response.

14.2.3 Methods

For patient who consent to participate, DCE MRI imaging should be performed at sites with such capability. See Appendix III.

DCE MRI will be acquired as part of routine clinical imaging. First, a T1 map of the tissue of interest is created using multiple flip angles (ex. 2, 5, 10, 15, 30 degrees) with a fast gradient echo technique. Dynamic T1-weighted images are then acquired by sampling the

same slab of tissue at a temporal rate of approx. 5 seconds or less at a flip angle of 10 degrees. After acquiring a sufficient number of time points to establish a reliable baseline, a bolus injection of typically 0.1 mMol/kg of gadopentetate-dimeglumine is administered. We continue to acquire dynamic data for 3-5 minutes post contrast injection for a total scan time of 6-10 minutes. Pharmacokinetic modeling of the data is then used to calculate the DCE-based parameters including K^{trans} and Ve.

MRI imaging will be routed from sites to the IROC and then to the Quantitative Tumor Imaging (QTIM) lab for data analysis. Experts in the lab will extract the physiological parameters from the DCE imaging as well as routine measurements such as meningioma volume, volume of FLAIR hyperintensity, and diffusion imaging parameters (ex. ADC). This lab is run by Dr. Elizabeth Gerstner and has expertise in analyzing sophisticated MRI data. QTIM has been responsible for image analysis for multicenter trials including an Adult Brain Tumor Consortium trial in recurrent glioblastoma and a multicenter schwannoma study. Dr. Gerstner is also PI on an ACRIN study looking at FMISO PET and advanced MRI in newly diagnosed glioblastoma so has experience in collaborating on multicenter trials. Furthermore, QTIM has a long track record studying advanced imaging in glioblastoma.[47, 50,51, 52,53]

14.2.4 Statistical Considerations

Exploratory analyses will be conducted. As data permit, analyses of the MRI parameters will be summarized by descriptive statistics, including mean, median and standard deviation. Differences in these parameters between responders and non-responders will be compared with parametric or nonparametric techniques as permitted by the data. For correlative analyses, Cox proportional hazards model will be used to explore the relationship between parameters measured at baseline and PFS and OS. Logistic regression will be used to explore the relationship between parameters measured at baseline and the binary outcome of alive and progression-free at 6 months (APF6).

Overall, the plan is to determine whether the baseline measurements are prognostic for the entire group. We will determine whether there is an association between the baseline measurements and response adjusting for the patient cohort. A priori we do not think that the association between the baseline measurements and response will depend on the type of mutation and treatment. However, if the association between baseline measurements and response are not found to be statistically significantly associated, we will do subgroup analyses to determine if there might be differences in the association between baseline variables and response among the groups. Specifically, we will do perform the analysis for each group separately. We will also do tests for interaction between the cohort group and the baseline variable, though these will likely not have sufficient power due to the small sample sizes.

The overall plan for determining whether a change in the parameters from baseline is associated with response is to first evaluate the association with the change between baseline and first MRI time point (8 weeks into therapy). An additional analysis will be done that uses all the available MRI assessment time points. To account for multiple MRI time points, we will treat the change in MRI from baseline as a time-dependent variable (which could change at each assessment).

15.0 GENERAL REGULATORY CONSIDERATIONS AND CREDENTIALING

None

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APPENDIX I: REGISTRATION FATIGUE/UNISCALE ASSESSMENTS

Registration Fatigue/Uniscale Assessments

At patient registration, this form is to be administered by a nurse/CRA, completed by the patient, and entered into Medidata Rave at the time of registration.

If needed, this appendix can be adapted to use as a source document. A booklet containing this assessment does not exist – please do not order this booklet.

How would you describe:

your level of fatigue, on the average in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
No Fatigue										Fatigue as bad as it can be

your overall quality of life in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

APPENDIX II: REQUIRED CONSENSUS MRI ACQUISITON PARAMETERS

For sites that do NOT have advanced imaging available: (*FDA/NBTS/NCI Standardized MRI Protocol*). See section 6.5.

The MRI acquisition protocols defined in the following table have been defined by an international consensus panel. These parameters have been reviewed and adopted by the National Cancer Institute (NCI) and the Federal Drug Administration (FDA), and these acquisition parameters are required for all national and FDA drug-registration trials. The specific acquisition parameters, the sequence of imaging acquisition, and the plane of imaging are all **required** as explicitly stated in these protocols.

For any patients enrolled prior to Update #05 (or with images acquired prior to Update #05), MRI parameters should remain consistent with baseline or prior image acquisition protocols.

1.5T Protocol:

	Ax FLAIR	Ax DWI	3D T1 Pre	Contrast Injection [a]	Ax T2	3D T1 Post[b]
Sequence	TSE[c] – (turbo dark fluid)	EPI[f]	MPRAGE[d,e]		TSE[c]	MPRAGE[d,e]
Plane	Axial	Axial	Sagittal/Axial		Axial	Sagittal/Axial
Mode	2D	2D	3D		2D	3D
TR [ms]	>6000	>5000	2100[g]		>3500	2100[g]
TE [ms]	100-140	Min	Min		100-120	Min
TI [ms]	2200		1100[h]			1100[h]
Flip Angle	90/≥160	90/180	10-15		90/180	10-15
Frequency	≥256	128	≥172		≥256	≥172
Phase	≥256	128	≥172		≥256	≥172
NEX	≥1	≥1	≥1		≥1	≥1
Frequency Direction	A/P	R/L	A/P		A/P	A/P
FOV	240mm	240mm	256mm (for ≤1.5mm isotropic)[j]		240mm	256mm (for ≤1.5mm isotropic)[j]
Slice Thickness	≤4mm	≤4mm	≤1.5mm[j]		≤4mm	≤1.5mm[j]
Gap/Spacing	0	0	0		0	0
Diffusion Options[i]		*b* = 0, 500, and 1000 s/mm^2				
Parallel Imaging	Up to 2x	Up to 2x	Up to 2x		Up to 2x	Up to 2x
Scan Time (Approx)	4-5 min	3-5 min	5-8 min		3-5 min	5-8 min

[a] 0.1 mmol/kg or up to 20cc (single, full dose) of MR contrast.
[b] Post-contrast 2D axial T1-weighted images should be collected with identical parameters to pre-contrast 2D axial T1-weighted images
[c] TSE = turbo spin echo (Siemens & Philips) is equivalent to FSE (fast spin echo; GE, Hitachi, Toshiba)
[d] MPRAGE = magnetization prepared rapid gradient-echo (Siemens & Hitachi) is equivalent to the inversion recovery SPGR (IR-SPGR or Fast SPGR with inversion activated; GE), 3D turbo field echo (TFE; Philips), or 3D fast field echo (3D Fast FE; Toshiba).

[e] A 3D acquisition without inversion preparation will result in different contrast compared with MPRAGE or another IR-prepped 3D T1-weighted sequences and therefore should be avoided.
[f] In the event of significant patient motion, a radial acquisition scheme may be used (e.g. BLADE [Siemens], PROPELLER [GE], MultiVane [Philips], RADAR [Hitachi], or JET [Toshiba]); however, this acquisition scheme is can cause significant differences in ADC quantification and therefore should be used only if EPI is not an option.
[g] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TR = 5-15ms for similar contrast.
[h] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TI = 400-450ms for similar contrast.
[i] Older model MR scanners that are not capable of >2 *b*-values should use $b = 0$ and 1000 s/mm^2.
[j] FOV and matrix size should be chosen to keep resolution *less than* 1.5mm isotropic voxel size. Note that all voxel measurements should be equal in x, y, and z dimensions.

Acronyms:
Ax = Axial; ADC = apparent diffusion coefficient. FLAIR = fluid attenuated inversion recovery; DWI = diffusion-weighted imaging; 3D = three dimensional; TSE = turbo spin echo; EPI = echo planar imaging; MPRAGE = magnetization prepared rapid gradient-echo; A/P = anterior to posterior; R/L = right to left; NEX = number of excitations or averages; FOV = field of view

3T Protocol:

	Ax FLAIR	Ax DWI	3D T1 Pre		Ax T2	3D T1 Post[b]
Sequence	TSE[c] – (turbo dark fluid)	EPI[f]	MPRAGE[d,e]		TSE[c]	MPRAGE[d,e]
Plane	Axial	Axial	Axial/Sagittal		Axial	Axial/Sagittal
Mode	2D	2D	3D		2D	3D
TR [ms]	>6000	>5000	2100[g]		>2500	2100[g]
TE [ms]	100-140	Min	Min		80-120	Min
TI [ms]	2500		1100[h]			1100[h]
Flip Angle	90/≥160	90/180	10-15		90/≥160	10-15
Frequency	≥256	128	256	**Contrast Injection [a]**	≥256	256
Phase	≥256	128	256		≥256	256
NEX	≥1	≥1	≥1		≥1	≥1
Frequency Direction	A/P	R/L	A/P		A/P	A/P
FOV	240mm	240mm	256mm (for 1mm isotropic)[i]		240mm	256mm (for 1mm isotropic) [i]
Slice Thickness	3mm	3mm	1mm[i]		3mm	1mm[i]
Gap/Spacing	0	0	0		0	0
Diffusion Options		*b* = 0, 500, and 1000 s/mm^2				
Parallel Imaging	Up to 2x	Up to 2x	Up to 2x		Up to 2x	Up to 2x
Scan Time (Approx)	4-5 min	3-5 min	5-8 min		3-5 min	5-8 min

[a] 0.1 mmol/kg or up to 20cc (single, full dose) of MR contrast.
[b] Post-contrast 3D axial T1-weighted images should be collected with identical parameters to pre-contrast 3D axial T1-weighted images
[c] TSE = turbo spin echo (Siemens & Philips) is equivalent to FSE (fast spin echo; GE, Hitachi, Toshiba)
[d] MPRAGE = magnetization prepared rapid gradient-echo (Siemens & Hitachi) is equivalent to the inversion recovery SPGR (IR-SPGR or Fast SPGR with inversion activated; GE), 3D turbo field echo (TFE; Philips), or 3D fast field echo (3D Fast FE; Toshiba).
[e] A 3D acquisition without inversion preparation will result in different contrast compared with MPRAGE or another IR-prepped 3D T1-weighted sequences and therefore should be avoided.
[f] In the event of significant patient motion, a radial acquisition scheme may be used (e.g. BLADE [Siemens], PROPELLER [GE], MultiVane [Philips], RADAR [Hitachi], or JET [Toshiba]); however, this acquisition scheme is can cause significant differences in ADC quantification and therefore should be used only if EPI is not an option.
[g] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TR = 5-15ms for similar contrast.
[h] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TI = 400-450ms for similar contrast.
[i] FOV and matrix size should be chosen to keep resolution at 1mm isotropic voxel size. Note that all voxel measurements should be equal in x, y, and z dimensions.

Acronyms:
Ax = Axial; ADC = apparent diffusion coefficient. FLAIR = fluid attenuated inversion recovery; DWI = diffusion-weighted imaging; 3D = three dimensional; TSE = turbo spin echo; EPI = echo planar imaging; MPRAGE = magnetization prepared rapid gradient-echo; A/P = anterior to posterior; R/L = right to left; NEX = number of excitations or averages; FOV = field of view

APPENDIX III: 1.5T & 3T ADVANCED MRI PROTOCOL FOR SITES ACQUIRING DCE IMAGING

1.5T ADVANCED MRI PROTOCOL FOR SITES ACQUIRING DCE IMAGING

	Ax FLAIR[j]	**Ax DWI**	**Ax T2[h,i]**	**3D T1 Pre[b]**	**T1 Map**	*Contrast Injection[a]*	**DCE[a]**	**3D T1w Post[b]**
Sequence	TSE[c] (turbo dark fluid)	EPI[g]	TSE[c]	MPRAGE [e,f]	3D-FLASH[d]		3D-FLASH[d]	MPRAGE [e,f]
Plane	Axial	Axial	Axial	Sagittal/ Axial	Axial		Axial	Sagittal/ Axial
Mode	2D	2D	2D	3D	3D		3D	3D
TR [ms]	>6000	>5000	>3500	2100[m]	8.7		8.7	2100[m]
TE [ms]	100-140	Min	80-120	Min	Min		Min	Min
TI [ms]	2200			1100[n]				1100[n]
Flip Angle [Degrees]	90/≥160	90/180	90/≥160	10-15	5/10/15 /30		24	10-15
Frequency	≥256	128	≥256	≥172	128		128	≥172
Phase	≥256	128	≥256	≥172	84		84	≥172
NEX	≥1	≥1	≥1	≥1	Average =4, 1 Rep.		Average=1 (~ 71 Reps; ~6sec/rep; 60 sec baseline)	≥1
Frequency Direction	A/P	R/L	A/P	A/P	R/L		R/L	A/P
FOV	240	240	240	256	256 X 208		256 X 208	256
Slice Thickness	≤4mm[l]	≤4mm[l]	≤4mm[l]	≤1.5mm	4mm		4mm	≤1.5mm
Gap/Spacing	0	0	0	0	0		0	0
Diffusion Options[p]		*b* = 0, 500, 1000 s/mm^2						
Parallel Imaging	Up to 2x	Up to 2x	Up to 2x	Up to 2x	Yes- acceleration factor = 2		Yes- acceleration factor = 2	Up to 2x
Scan Time	4-5 min	3-5	3-5 min	5-8 min	< 30 sec ea		7 min	5-8 min
Slices					28		28	

[a] After 60 seconds of baseline image acquisition, a bolus injection of 0.1 mMol/kg of Gadolinium chelated contrast agent is administered as part of the DCE acquisition. Continue to acquire dynamic data for 6 minutes post contrast injection for a total scan time of 7 minutes. Use of a power injector is desirable at an injection rate of 3.5 mL/sec, followed by 20-mL saline flush of the same rate.
[b] Post-contrast 3D T1-weighted images should be collected with equivalent parameters to pre-contrast 3D T1-weighted images
[c] TSE = turbo spin echo (Siemens & Philips) is equivalent to FSE (fast spin echo; GE, Hitachi, Toshiba)
[d] FLASH = fast low angle shot (FLASH; Siemens) is equivalent to the spoil gradient recalled echo (SPGR; GE) or T1- fast field echo (FFE; Philips), fast field echo (FastFE; Toshiba), or the radiofrequency

spoiled steady state acquisition rewound gradient echo (RSSG; Hitachi). A fast gradient echo sequence without inversion preparation is desired.
[e] MPRAGE = magnetization prepared rapid gradient-echo (Siemens & Hitachi) is equivalent to the inversion recovery SPGR (IR-SPGR or Fast SPGR with inversion activated or BRAVO; GE), 3D turbo field echo (TFE; Philips), or 3D fast field echo (3D Fast FE; Toshiba).
[f] A 3D acquisition without inversion preparation will result in different contrast compared with MPRAGE or another IR-prepped 3D T1-weighted sequences and therefore should be avoided.
[g] In the event of significant patient motion, a radial acquisition scheme may be used (e.g. BLADE [Siemens], PROPELLER [GE], MultiVane [Philips], RADAR [Hitachi], or JET [Toshiba]); however, this acquisition scheme is can cause significant differences in ADC quantification and therefore should be used only if EPI is not an option. Further, this type of acquisition takes considerable more time.
[h] Dual echo PD/T2 TSE is optional for possible quantification of tissue T2.
[i] Additional sequences can be substituted into this time slot, so long as 3D post-contrast T1-weighted images are collected between 4 and 8 min after contrast injection.
[j] 3D FLAIR is an optional alternative to 2D FLAIR, with sequence parameters as follows per EORTC guidelines: 3D TSE/FSE acquisition; TE=90-140ms; TR=6000-10000ms; TI=2000-2500ms (chosen based on vendor recommendations for optimized protocol and field strength); GRAPPA≤2; Fat Saturation; Slice thickness ≤ 1.5mm; Orientation Sagittal or Axial; FOV ≤ 250 mm x 250 mm; Matrix ≥ 244x244.
[k] Choice of TI should be chosen based on the magnetic field strength of the system (e.g. TI ≈ 2000ms for 1.5T and TI ≈ 2500ms for 3T).
[l] In order to ensure comparable SNR older 1.5T MR systems can use contiguous (no interslice gap) images with 5mm slice thickness or increase NEX for slice thickness ≤4mm.
[m] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TR = 5-15ms for similar contrast.
[n] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TI = 400-450ms for similar contrast.
[p] Older model MR scanners that are not capable of >2 *b*-values should use $b = 0$ and 1000 s/mm^2.

Acronyms:
Ax = Axial; ADC = apparent diffusion coefficient. FLAIR = fluid attenuated inversion recovery; DWI = diffusion-weighted imaging; 3D = three dimensional; TSE = turbo spin echo; EPI = echo planar imaging; SS-EPI = single-shot echo planar imaging; GE-EPI = gradient echo echo planar imaging; 2DFL = two-dimensional FLASH (fast low angle shot) gradient recalled echo; MPRAGE = magnetization prepared rapid gradient-echo; A/P = anterior to posterior; R/L = right to left; NEX = number of excitations or averages; FOV = field of view; TE = echo time; TR = repetition time; TI = inversion time; PD = proton density

3T ADVANCED MRI PROTOCOL FOR SITES ACQUIRING DCE IMAGING

	Ax FLAIR[j]	**Ax DWI**	**Ax T2[h,i]**	**3D T1 Pre[b]**	**T1 Map**	*Contrast Injection[a]*	**DCE[a]**	**3D T1 Post[b]**
Sequence	TSE[c] (turbo dark fluid)	EPI[g]	TSE[c]	MPRAGE[e, f]	3D-FLASH[d]		3D-FLASH[d]	MPRAGE[e, f]
Plane	Axial	Axial	Axial	Axial/ Sagittal/	Axial		Axial	Axial/ Sagittal
Mode	2D	2D	2D	3D	3D		3D	3D
TR [ms]	>6000	>5000	>2500	2100[m]	5.6		5..6	2100[m]
TE [ms]	100-140	Min	80-120	Min	Min		Min	Min
TI [ms]	2500			1100[n]				1100[n]
Flip Angle [Degrees]	90/≥160	90/180	90/≥160	10-15	5/10/15 /30		24	10-15
Frequency	≥256	128	≥256	256	128		128	256
Phase	≥256	128	≥256	256	62		62	256
NEX	≥1	≥1	≥1	≥1	Average =4, 1 Rep.		Average=1 (98 Reps; 4.3sec/rep; 60 sec baseline)	≥1
Frequency Direction	A/P	R/L	A/P	A/P	R/L		R/L	A/P
FOV	240	240	240	256 (for 1mm isotropic)	256 X 208		256 X 208	256 (for 1mm isotropic)
Slice Thickness	3mm[l]	3mm[l]	3mm[l]	1mm	3mm		3mm	1mm
Gap/Spacing	0	0	0	0	0		0	0
Diffusion Options		b = 0, 500, 1000 s/mm^2 ≥3 directions						
Parallel Imaging	Up to 2x	Up to 2x	Up to 2x	Up to 2x	Yes-acceleration factor = 2		Yes-acceleration factor = 2	Up to 2x
Scan Time (Approx)	4-5 min	3-5 min	3-5 min	5-8 min	< 30 sec ea		7 min	5-8 min
Slice					36		36	

[a] After 60 seconds of baseline image acquisition, a bolus injection of 0.1 mMol/kg of Gadolinium chelated contrast agent is administered as part of the DCE acquisition. Continue to acquire dynamic data for 6 minutes post contrast injection for a total scan time of 7 minutes. Use of a power injector is desirable at an injection rate of 3.5cc/sec, followed by 20-mL saline flush of the same rate.
[b] Post-contrast 3D T1-weighted images should be collected with equivalent parameters to pre-contrast 3D T1-weighted images
[c] TSE = turbo spin echo (Siemens & Philips) is equivalent to FSE (fast spin echo; GE, Hitachi, Toshiba)
[d] FLASH = fast low angle shot (FLASH; Siemens) is equivalent to the spoil gradient recalled echo (SPGR; GE) or T1- fast field echo (FFE; Philips), fast field echo (FastFE; Toshiba), or the radiofrequency spoiled steady state acquisition rewound gradient echo (RSSG; Hitachi). A fast gradient echo sequence without inversion preparation is desired.
[e] MPRAGE = magnetization prepared rapid gradient-echo (Siemens & Hitachi) is equivalent to the inversion recovery SPGR (IR-SPGR or Fast SPGR with inversion activated or BRAVO; GE), 3D turbo field echo (TFE; Philips), or 3D fast field echo (3D Fast FE; Toshiba).
[f] A 3D acquisition without inversion preparation will result in different contrast compared with MPRAGE or another IR-prepped 3D T1-weighted sequences and therefore should be avoided.
[g] In the event of significant patient motion, a radial acquisition scheme may be used (e.g. BLADE [Siemens], PROPELLER [GE], MultiVane [Philips], RADAR [Hitachi], or JET [Toshiba]); however, this acquisition scheme is can cause significant differences in ADC quantification and therefore should be used only if EPI is not an option. Further, this type of acquisition takes considerable more time.
[h] Dual echo PD/T2 TSE is optional for possible quantification of tissue T2.
[i] Additional sequences can be substituted into this time slot, so long as 3D post-contrast T1-weighted images are collected between 4 and 8 min after contrast injection.
[j] 3D FLAIR is an optional alternative to 2D FLAIR, with sequence parameters as follows per EORTC guidelines: 3D TSE/FSE acquisition; TE=90-140ms; TR=6000-10000ms; TI=2000-2500ms (chosen based on vendor recommendations for optimized protocol and field strength); GRAPPA≤2; Fat Saturation; Slice thickness ≤ 1.5mm; Orientation Sagittal or Axial; FOV ≤ 250 mm x 250 mm; Matrix ≥ 244x244.

[m] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TR = 5-15ms for similar contrast.
[n] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TI = 400-450ms for similar contrast.

Acronyms:
Ax = Axial; ADC = apparent diffusion coefficient. FLAIR = fluid attenuated inversion recovery; DWI = diffusion-weighted imaging; 3D = three dimensional; TSE = turbo spin echo; EPI = echo planar imaging; SS-EPI = single-shot echo planar imaging; GE-EPI = gradient echo echo planar imaging; 2DFL = two-dimensional FLASH (fast low angle shot) gradient recalled echo; MPRAGE = magnetization prepared rapid gradient-echo; A/P = anterior to posterior; R/L = right to left; NEX = number of excitations or averages; FOV = field of view; TE = echo time; TR = repetition time; TI = inversion time; PD = proton density

Sequence and Parameter Justification:

BASIC STANDARD PROTOCOL

1) Pre and Post-Contrast 3D T1-Weighted MPRAGE
    a. Recommended sequence from ADNI
    b. Available from all major MRI vendors
    c. EORTC and ACRIN approved sequence
    d. Allows for volumetric estimations of enhancing tumor volume
    e. Allows for calculation of T1 subtraction map-defined enhancing tumor volume
    f. Allows for longitudinal registration of MR scans in the same patient over time
2) T2-Weighted Turbo Spin Echo (TSE) (Optional: Dual Echo PD/T2 TSE)
    a. Available from all major MRI vendors
    b. EORTC and ACRIN approved sequence
    c. Recommended sequence from ADNI (dual echo)
    d. Dual echo may allow for quantitative estimation of "effective" T2 relaxation rate
    e. $T2^{eff}$ has been shown to be sensitive to various pathologies, including AD, TBI, MCI, stroke, MS, psychiatric diseases, etc.
    f. Allows for current RANO evaluations
    g. Dual echo may allow for objective definition of non-enhancing tumor based on $T2^{eff}$
3) Axial T2-Weighted FLAIR
    a. Allows for increased sensitivity for T2 abnormalities
    b. EORTC and ACRIN approved sequence
    c. Allows for RANO evaluations
4) Axial Diffusion Weighted Imaging (DWI)
    a. EORTC and ACRIN approved sequence
    b. Choice of *b*-values and acquisition parameters are in compliance with the recommendations from the NCI-ISMRM consensus meeting for DWI as a cancer biomarker.

OPTIONAL VARIATIONS TO PROTOCOL

These optional sequences are included as they provide more detail on anatomy (FLAIR) or tissue cellularity (DTI) than the 2D FLAIR and DWI sequences but are not always available on every scanner.

5) 3D FLAIR
    a. EORTC approved (optional) sequence
    b. Allows for 1mm isotropic FLAIR
    c. Experimental & may not be available on all MR systems
6) Diffusion Tensor Imaging (DTI)
    a. Advanced modification to the standard DWI sequence
    b. Allows for measures of "diffusion anisotropy", or fractional anisotropy (FA), which has been shown to correlate with cellularity and response to therapy
    c. Routinely used for pre-surgical planning
    d. Can be used to estimate "fiber tracts" via DT tractography
    e. DTI sequences with a high number of directions are important for accurately estimating low FA, which is of interest for tumors

APPENDIX IV: PATIENT MEDICATION DIARY - VISMODEGIB

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 4 week-period while you take **vismodegib**.
2. You will take your dose of **vismodegib** daily.
3. Record the date, the number of capsules you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time.
4. If a dose is missed, do not make up that dose; resume dosing with the next scheduled dose.
5. Capsules should not be opened or crushed.
6. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: ~~10:30 am~~ SB 9:30 am
7. Please return this form to your physician when you go for your next appointment.

Day	Date	Time of daily dose	# of capsules taken	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				

Patient's Signature	Date

Physician's Office will complete this section:

1. Date patient started protocol treatment
   _____
2. Date patient was removed from study
   _____
3. Total number of capsules taken this month (each size)
   _____
4. Physician/Nurse/Data Manager's Signature
   _____

APPENDIX V: PATIENT MEDICATION DIARY - GSK2256098

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 4 week-period while you take **GSK2256098**.
2. You will take your dose of **GSK2256098** twice daily.
3. Record the date, the number of capsules you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time.
4. If a dose is missed, do not make up that dose; resume dosing with the next scheduled dose.
5. Capsules should not be opened or crushed.
6. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: ~~10:30 am~~ SB 9:30 am
7. Please return this form to your physician when you go for your next appointment.

Monitor bilirubin and instruct patients to report any jaundice symptoms to the study team immediately. Patients should be instructed to avoid direct sunlight or UV exposure. Patients should be instructed on the use of protective clothing, sun glasses and sunscreen

Day	Date	Time of AM dose	# of capsules taken	Time of PM dose	# of capsules taken	Comments
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						

26						
27						
28						
Patient's Signature					Date	

Physician's Office will complete this section:

1. Date patient started protocol treatment
   _____
2. Date patient was removed from study
   _____
3. Total number of capsules taken this month (each size)
   _____
4. Physician/Nurse/Data Manager's Signature

_____

APPENDIX VI: POSSIBLE PRENATAL EXPOSURE TO TERATOGEN REPORT

Attach to AdEERS 7-Day Report

Possible Prenatal Exposure to Teratogen Report
AdEERS Ticket Number:_____

Study #:
SAE FAX NO: (301) 230-0159
Alternate FAX NO: (301) 897-7404

Initial Report Date: ___ - ___ - ___ (DD - MMM - YY)	Follow-up Report Date: ___ - ___ - ___ (DD - MMM - YY)
Principal Investigator:	Reporter:
Reporter Telephone #:	Reporter FAX #:

Investigator Number ☐☐☐☐☐ Subject Number ☐☐☐☐☐

Complete all of the investigator and subject number boxes provided. Use leading zeros, when necessary, to complete all expected boxes.

Example: Investigator #407 would be filled in as: 0 0 4 0 7

Subject Initials ☐☐☐

Record the first letter of the subject's first, middle and last name, in that sequence. If the subject has no middle name, enter a dash.

Example: A - C

Subject's Sex: ☐ Female ☐ Male	Subject's Weight: _____ kg	Subject's Date of Birth: ___ - ___ - ___ (DD - MMM - YYYY)

Subject's Ethnicity (check one only): ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Not Available

Subject's Race (check all that apply): ☐ American Indian or Alaska Native ☐ Asian ☐ Black or African American ☐ Native Hawaiian or Other Pacific Islander ☐ White ☐ Not Available

Study Drug: **GDC-0449**	Study Drug Start Date: ___ - ___ - ___ (DD - MMM - YY) Study Drug Stop Date: ___ - ___ - ___ (DD - MMM - YY) OR ☐ Study Drug Continuing		
Dose:	Route: **ORAL**	Frequency: **QD**	Kit #:

First Day of Last Menstrual Period: ___ - ___ - ___ (DD - MMM - YY) Estimated Date of Delivery: ___ - ___ - ___ (DD - MMM - YY)

Method of Contraception (check all that apply):
☐ Oral Contraceptive Pills ☐ Condoms ☐ Periodic Abstinence ☐ Progestin Injection or Implants ☐ Spermacide
☐ Diaphragm ☐ Intrauterine Device (IUD) ☐ Tubal Ligation ☐ Other, specify:_____

Reproductive History: ☐ Gravida _____ ☐ Para _____

Tests performed during pregnancy: ☐ None ☐ Unknown
☐ CVS Results: ☐ Normal ☐ Abnormal
☐ Amniocentesis Results: ☐ Normal ☐ Abnormal
☐ Ultrasound Results: ☐ Normal ☐ Abnormal

Pregnancy Outcome
Was pregnancy interrupted? ☐ Yes ☐ No
If yes, specify: ☐ Elective Termination ☐ Spontaneous Abortion ☐ Ectopic
Date of Termination: ___ - ___ - ___ (DD - MMM - YY)
If pregnancy was **not** terminated, specify pregnancy outcome (and provide infant outcome information)
☐ Vaginal Birth: ☐ Premature ☐ Term OR ☐ C-Section: ☐ Scheduled ☐ Emergency Date of Delivery: ___ - ___ - ___ (DD - MMM - YY)
Infant outcome information: ☐ Normal ☐ Abnormal

Additional Case Details (if needed):

Note: Report possible teratogen exposure to AdEERS within 24 hours. See Protocol Section 11.3.1 for instructions. Attach this form to the complete 5-day AdEERS report.

APPENDIX VII: CENTRAL LABORATORY GENOTYPE TESTING PROCEDURES

Integral Molecular Testing for *SMO*or *NF2* Mutation

Background

The SNaPshot NGS assay is a fully validated clinical test designed and developed at the MGH Center for Integrated Diagnostics and is performed in a CLIA-certified laboratory. This assay combines anchored-multiplex PCR with next-generation sequencing for detection of single nucleotide variants (SNVs) and insertions/deletions (indels) across a number of known cancer genes using genomic DNA derived from patient specimens. The genes evaluated include *SMO*, and *NF2*. This assay has been clinically-validated, standard operating procedures created, and will be locked down during the duration of the trial.

Methodology

Diagnostic formalin-fixed, paraffin-embedded tumor specimens will be used in testing. DNA will be extracted and processed to produce adapter-ligated DNA libraries to be sequenced in a high-throughput manner. This will include fragmentation of the DNA, repair of the DNA strands to produce blunt ended strands, phosphorylation of the 5' ends of the DNA, attachment of dATPs at the 3' ends, ligation of uniquely indexed adapter sequences to both ends of the DNA followed by two rounds of nested PCR for enrichment and amplication of the gene exons of interest. SPRI bead clean-up steps are incorporated within these procedures. Adapter-ligated DNA libraries will be quantified by qPCR using the Kapa Illumina kit and then be sequenced on an Illumina MiSeq or NextSeq genomic sequencer (both the positive and negative strand). Sequencing data generated will then be processed through the clinically-validated MGH bioinformatics pipeline where the sequencing (FASTQ) data is demultiplexed, aligned to the human reference genome and the resultant binary files (BAM) will be generated. Somatic mutations in the patient samples will be deciphered and annotated using the Mutect and Oncotator bioinformatics tools developed at the BROAD institute. Quality assessment includes the incorporation of molecular barcoding and a minimum sequencing depth threshold. See below for further details.

Target Mutations

Gene mutations in *SMO* leading to the amino acid changes p.Leu412Phe and p.Trp535Leu will be assessed through full sequencing of *SMO* exons 6 and 9, respectively. Other mutations in these tested exons will be compared to the COSMIC database of known somatic mutations and reported if found. All 18 exons of the *NF2* gene will be sequenced in their entirety for SNVs and indels that may inactivate protein function. This platform may also identify *NF2* gene deletion if present in a substantial fraction of cells within the patient specimen and will also be reported if identified. These 2 genes will be evaluated together in a single panel, along with additional genes that are not a focus of this study.

Assay Protocol

1. Qualifying mutations in *SMO* or *NF2* (see #7 below) will be identified using a clinically validated SNaPshot NGS assay performed in a CLIA-certified laboratory at the MGH Translational/Biomarker Laboratory (MGH TRL). These procedures will remain in effect throughout the duration of the study.

2. Testing will be performed on diagnostic, formalin-fixed, paraffin-embedded tumor tissue. Sections of tissue (5 microns) that have been mounted onto plus microscope slides will be submitted to the MGH TRL by Dr. Sandro Santagata, along with a hematoxylin and eosin-stained (HE) slide marking the tumor region of interest. Only samples deemed to be of sufficient amount and tumor cellularity for genotyping will be forwarded to the MGH TRL.

3. Quality assurance measures will require that each trial sample is submitted with two identifiers and that an email is sent to the MGH TRL centralized mailbox (MGHTRLClinicalTrials@partners.org) indicating intent to submit the sample and the relevant identifiers. The MGH TRL program coordinator will verify receipt of the sample, whether the sample was received in acceptable condition and specified amount, and will confirm the identifiers before initiating the testing process.

4. Testing samples received into the MGH TRL will be annotated into a laboratory database and a chain of custody sheet will be initiated to track and record each step of the testing process, the staff member conducting the process, the quantity of sample that was utilized during testing, and the quantity of sample that remained after testing.

5. All sections of tumor tissue received will be macroscopically dissected according to the pathologist's marked HE slide. Nucleic acid will be extracted in accordance with a clinically-validated protocol using Agencourt FormaPure technology on a Biomek NXp robotic workstation. While no sections will be saved, remaining extracted nucleic acid that remains after testing will be stored at -80°C in the laboratory's nucleic acid bank. Double-stranded DNA concentration will be determined using Qubit fluorometric quantitation.

6. The clinically validated MGH clinical SNaPshot NGS assay will be used to determine *SMO* and *NF2* mutational status, with sequencing performed on an Illumina MiSeq or NextSeq genome sequencer. The assay has been clinically validated and standard operating procedures have been documented. The specific genetic alterations being interrogated are detailed in section 14.2.

7. Sequencing data generated will be processed through a validated bioinformatics pipeline developed at MGH where the sequencing (FASTQ) data is demultiplexed, aligned to the human reference genome and the resultant binary files (BAM) generated. Somatic mutations in the patient samples will be deciphered and annotated using the Mutect and Oncotator bioinformatics tools developed at the BROAD institute. Quality assessment includes the incorporation of molecular barcoding and a minimum sequencing depth threshold.

8. A mutation will be called based on allelic frequency and read coverage depth of the variant. A 5% allelic frequency will serve as the threshold for calling a single nucleotide variant or indels in *SMO* or *NF2*. Validation testing has indicated that this can be achieved with >5 unique reads in 100x of coverage.

9. Expected turnaround time for testing and reporting is two weeks from the date of sample receipt into the MGH TRL. Inadequate or poor quality sample that requires repeat testing due to inadequate read depth will delay reporting. Central laboratory confirmation testing may be performed in batch with a longer turnaround time, if required.

APPENDIX VIII: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, GSK 2256098. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

GSK 2256098 interacts with a certain specific enzyme in your liver.

- The enzyme(s) in question is CYP3A4 and GSK 2256098 is broken down by this enzyme and may be affected by other drugs that inhibit or induce this enzyme.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

GSK 2256098 may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

GSK 2256098 must be used very carefully with other medicines that use certain liver enzymes. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors of CYP3A4.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.

STUDY DRUG INFORMATION WALLET CARD	
You are enrolled on a clinical trial using the experimental study drug GSK2256098. This clinical trial is sponsored by the NCI. GSK2256098 may interact with drugs that are processed by your liver.]. Because of this, it is very important to: □ Tell your doctors if you stop taking any medicines or if you start taking any new medicines. □ Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial. □ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	**GSK2256098** interacts with a specific liver enzyme called CYP3A4**,** and must be used very carefully with other medicines that interact with this enzyme. □ Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors or substrates of CYP3A4 □ Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor. □ Your study doctor's name is _____ and can be contacted at _____.