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 integral biomarker testing.

Registration Eligibility Criteria (See Section 3.3)

- Presence of SMO, PTCH1 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 radiation treatment (XRT, brachytherapy, radiosurgery) to registration
- Steroid dosing stable for at least 4 days
- Recovered to CTCAE grade 1 or less toxicity
- No craniotomy within 28 days of registration
- Not pregnant and not nursing
- Age ≥ 18 years (for patients with NF2 mutation)
- Age ≥ 30 years (for patients with SMO/PTCH1 mutation)
- 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
- No 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 uncontrolled hypertension defined as BP > 140/90
- No abdominal fistula, GI perforation, or intra-abdominal abscess within 28 days prior to registration
- No CYP3A4 inhibitors or inducers for 14 days prior to registration or during study treatment (for NF2 patients). See Section 7.2

Required Initial Laboratory Values

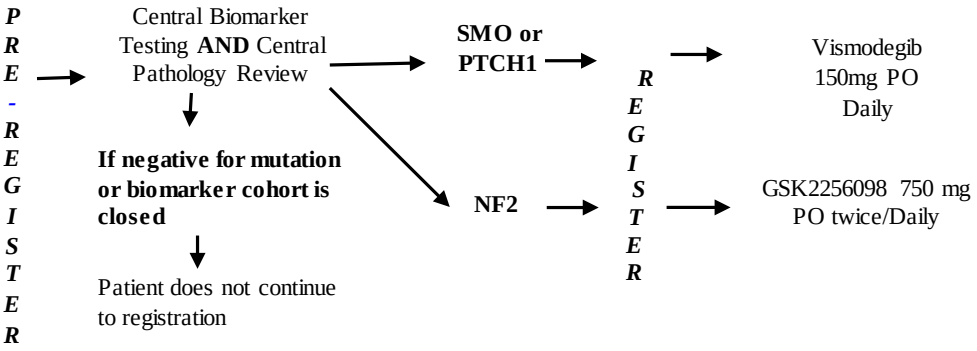
Absolute neutrophil count (ANC)	≥ 1500/mm^3
Platelet Count	≥ 100,000/mm3
Creatinine	≤ 1.5 mg/dl x upper limit of normal (ULN)
OR	
Calc. Creatinine Clearance	> 45 mL/min
UPC	≤ 45mg/mmol*
Total Bilirubin	≤ 1.5 x ULN**
AST / ALT	≤ 2.5 x ULN
Fasting triglyceride	≤ 200mg/dL*
Fasting cholesterol	≤ 240mg/dL*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

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.

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 24 months following treatment (for women) and 2 months (for men).

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 24 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. Women should not breastfeed children for 24 months after the last dose of vismodegib.

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 2 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 2 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 24 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 for central pathology review and biomarker 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, PTCH1 or NF2 mutation in tumor sample as documented by central laboratory. See Sections 4.4, 4.5 and 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 radiation treatment 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/PTCH1 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 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 registration for patients 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