FAST FACTS

A071401: PHASE II TRIAL OF SMO/AKT/NF2 INHIBITORS IN PROGRESSIVE MENINGIOMAS WITH SMO/AKT/NF2 MUTATIONS

Eligibility Criteria

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 untreated or uncontrolled fungal, bacterial or viral infections (including HIV), active bleeding diathesis, uncontrolled diabetes mellitus, hypertension, or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Any other concurrent severe and/or uncontrolled medical condition that would, in the treating physician's judgment, cause unacceptable safety risks, contraindicate patient participation in the clinical study, or compromise compliance with the protocol.
- 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.

Reproductive considerations, Capivasertib

In an animal model, capivasertib causes testicular pathology. Capivasertib had an adverse effect on embryonic survival and early postnatal growth when administered to pregnant rats. Use of two forms of highly reliable contraceptives by female patients of child-bearing potential is required throughout the study and for at least 4 weeks after the last dose of study drug. Appropriate methods of birth control include true abstinence, combination hormonal contraceptives, subcutaneous hormonal implant, hormonal patch, hormonal contraceptives (levonorgestre-releasing intrauterine system, medroxyprogesterone acetate depot), (as it is not known if capivasertib has the capacity to affect the metabolism of hormonal contraceptives, hormonal contraception should be combined with a barrier method of contraception), 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). Male patients are required to use barrier methods of contraception. It is not known

whether the preclinical changes seen in the male animal reproductive organs, after treatment with capivasertib will be fully reversible or will permanently affect the ability to produce healthy sperm following treatment. Male patients wishing to father children should be advised to arrange for freezing of sperm samples prior to the start of study treatment. Breastfeeding women are also excluded from study entry.

Reproductive considerations, Abemaciclib:
General Guidance for Women of Child Bearing Potential and/or Use of Contraceptive Methods
Based on findings in animals, abemaciclib can cause fetal harm when administered to a pregnant woman. In animal studies, abemaciclib was teratogenic and caused decreased fetal weight at maternal exposures that were similar to human clinical exposure based on the area under the plasma concentration versus time curve (AUC) at the recommended human dose. Therefore, teratogenicity is considered an important potential risk for abemaciclib. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus. Additionally, there are no available data on effects of breastfeeding. Advise a nursing woman to discontinue breastfeeding during treatment with abemaciclib. The following instructions must be included in investigator-sponsored protocols.

- A female of childbearing potential, must have a negative serum pregnancy test within 7 days of the first dose of abemaciclib and agree to use a highly effective contraception method during the treatment period and for 3 weeks following the last dose of abemaciclib.
- Contraceptive methods may include an intrauterine device [IUD] or barrier method. If condoms are used as a barrier method, a spermicidal agent should be added as a double barrier protection.
- Cases of pregnancy that occur during maternal exposures to abemaciclib should be reported. If a patient or spouse/partner is determined to be pregnant following abemaciclib initiation, she must discontinue treatment immediately. Data on fetal outcome and breastfeeding are to be collected for regulatory reporting and drug safety evaluation.

Drug interactions:
Vismodegib and GSK2256098 are substrates of P-glycoprotein (PgP). The clinical significance of any drug interaction is unknown to date. The risk that capivasertib will cause drug-drug interactions with substrates of P-gp is low.
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.
See also Section 8.1 for other ancillary care and potential interactions for GSK2256098, vismodegib, and capivasertib.

Pre-Registration Eligibility Criteria

1. Tissue available for central pathology review and biomarker testing

   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 MGH/DFCI (a CLIA-certified lab). This review is mandatory prior to registration to confirm eligibility. See Section 6.2 for details on slide/block submission.

Registration Eligibility Criteria

1. Documentation of Disease

a. Histologic Documentation: Histologically proven intracranial meningioma as documented by central pathology review.
b. **Molecular Documentation:** Presence of SMO, PTCH1, NF2, CDKN2A, AKT1, PIK3CA, PTEN mutations, CDKN2A copy number loss, CDK4, CDK6, CCND1, CCND2, CCND3, or CCNE1 copy number gain in tumor sample as documented specifically by the central laboratory, regardless of whether prior genotype testing outside of the central laboratory was performed. See Sections 4.4, 4.5 and Appendix VIII for further details.
c. **Progressive OR residual disease**, as defined by the following:
    a. Residual measurable disease (see also Section 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 25 months. For patients with SMO/PTCH1 mutations enrolling to receive vismodegib, the change can occur between scans separated by up to 25 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.
    b. 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 25 months.
    c. 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. If the progressive meningioma lesion has been radiated, at least 24 weeks must have elapsed from completion of radiation to registration. (See Section 3.3.3). If the progressive lesion is outside of the radiation field, then an interval of at least 2 weeks must have elapsed from completion of radiation to registration.

2. Measurable disease
    a. Measurable disease is defined by a bidimensionally measurable main lesion on MRI or CT images (MRI preferred) with clearly defined margins and a minimum diameter of 10 mm in both dimensions. Multifocal disease is allowed.
    For measurable disease, refer to Section 11.0.
3. Prior Treatment
    a. Prior medical therapy is allowed but not required.
    b. No limit on number of prior therapies.
    c. No chemotherapy, cancer-directed hormonal therapy, or other investigational agents within 28 days prior to registration.
    d. No other concurrent investigational agents or other meningioma-directed therapy (chemotherapy, radiation) while on study. Additionally, no cases of nitrosourea or mitomycin C within 6 weeks prior to registration
    e. For patients treated with external beam radiation, interstitial brachytherapy or radiosurgery, an interval > 4 weeks must have elapsed from completion of radiation treatment to registration. If the progressive lesion is outside of the radiation field, then an interval of at least 2 weeks must have elapsed from completion of radiation to registration. (See 3.3.1).
    f. Steroid dosing stable for at least 4 days.
    g. Recovered to CTCAE grade 1 or less toxicity from other agents with exception of alopecia and fatigue.
    h. No craniotomy within 28 days of registration.
4. Not pregnant and not nursing

a. 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 reference Section 5.0 (Study calendar) for details on pregnancy monitoring during the duration of the trial. Also refer to Section 3.1 for agentspecific reproductive considerations and contraceptive requirements.

5. For patients with NF2/CDKN2A/AKT1/PIK3CA/PTEN mutation, CKDN2A copy number loss, or CDK4/CDK6/CCND1/CCND2/CCND3/CCNE1 copy number gain: Age ≥ 18 years
   For patients with SMO /PTCH1 mutation: Age ≥ 30 years
6. ECOG Performance Status ≤ 2
7. Patient history:
   a. Patients with history of NF may have other stable CNS tumors (schwannoma, acoustic neuroma or ependymoma) if lesions have been stable for 6 months.
   b. No metastatic meningiomas (as defined by extracranial meningiomas outside of CNS) allowed. Spinal meningiomas are allowed.
   c. No history of allergic reactions attributed to compounds of similar or biologic composition to assigned study drug
   d. No Known active hepatitis B or C
   e. No current Child Pugh Class B or C liver disease
   f. No uncontrolled gastric ulcer disease (Grade 3 gastric ulcer disease within 28 days of registration)
   g. No uncontrolled hypertension defined as BP > 140/90
   h. No abdominal fistula, GI perforation, or intra-abdominal abscess within 28 days prior to registration
   i. No major surgery within 28 days prior to registration for any patients with AKT1/PIK3CA/PTEN mutations receiving capivasertib.
   j. For patients going on to receive capivasertib (i.e. enrolled after Update #08) Patients should not have any of the following cardiac criteria:
      1. Any clinically important abnormalities in rhythm, conduction, or morphology of resting EKG (e.g., complete left bundle branch block, third degree heart block).
      2. Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, potential for Torsade de Pointes, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age, or any concomitant medication known to prolong the QT interval
      3. Experience any of the following procedures or conditions in the preceding 6 months: coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, angina pectoris, congestive heart failure NYHA Class ≥ II.
      4. Uncontrolled hypotension (SBP < 90 mmHg and/or DBP < 50 mmHg).
      5. Cardiac ejection fraction outside institutional range of normal or < 50% (whichever is higher) as measured by echocardiogram (or MUGA scan if an echocardiogram can't be performed or is inconclusive). LVEF below lower limit of normal for site.
   k. Patients should not have any of the following criteria
      1. With the exception of alopecia, any unresolved toxicities from prior therapy greater than CTCAE grade 1 at the time of registration
      2. Hemoglobin < 9 g/dL (<5.59 mmol/L). Note: any blood transfusion must be ≥ 14 days prior to the determination of a hemoglobin ≥ 9 g/dL (≥5.59 mmol/L)
      3. Proteinuria 3+ on dipstick analysis or > 500 mg/24 hours

4. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of capivasertib
5. History of hypersensitivity to active or inactive excipients of capivasertib or drugs with a similar chemical structure or class to capivasertib.
6. Current disease or condition known to interfere with absorption, distribution, metabolism, or excretion of drugs.
7. Past medical history of interstitial lung disease, drug-induced interstitial lung disease, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease.
8. Previous allogeneic bone marrow transplant.
9. Known immunodeficiency syndrome.

8. Concomitant medications (Only regarding NF2/CDKN2A/CDK4/CDK6/CCND1/ CCND2/CCND3/CCNE1/AKT1/PIK3CA/PTEN genetic alterations)

   a. 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, as well as for patients with AKT1/PIK3CA/PTEN mutations enrolled to capivasertib. See Section 7.0 for more information
   b. For NF2 patients going on to receive GSK2256098 and for patients with AKT1/PIK3CA/PTEN mutations enrolled to capivasertib: Concomitant treatment with strong CYP3A4 inducers or CYP2D6 substrates is not allowed. Patients must discontinue the drug 14 days prior to registration. See Section 7.0 for more information.
   c. For NF2 patients going on to receive abemaciclib: Avoid concomitant use of CYP3A inducers and strong CYP3A inhibitors. Use caution with coadministered moderate or weak CYP3A inhibitors. See Section 7.0 for more information.

9. Diabetic status
   a. For patients with NF2 or SMO/PTCH1 mutations: No uncontrolled diabetes defined as a known diabetic with HBA1C >7.5 OR fasting glucose > 140 mg/dL.
   b. For patients with AKT1/PIK3CA/PTEN mutations:
      1. Glycosylated hemoglobin (HbA1C) < 8.0% (63.9 mmol/mol)
      2. No Type 1 diabetes mellitus.
      3. No requirement for insulin for routine diabetic management and control
      4. No requirement for more than two oral hypoglycaemic medications for routine diabetic management and control
      5. Patients with a pre-existing diagnosis of Type 2 diabetes mellitus must have fasting glucose < 9.3 mmol/L (167mg/dL). Fasting is defined as no caloric intake for at least 8 hours.
      6. Patients without a pre-existing diagnosis of Type 2 diabetes mellitus must have fasting glucose < 7.0 mmol/L (126 mg/dL). Fasting is defined as no caloric intake for at least 8 hours.

10. Required Initial Laboratory Values:

Absolute Neutrophil Count (ANC)	$\geq 1{,}500/mm^3$
Platelet Count	$\geq 100{,}000/mm^3$
Creatinine OR	≤ 1.5 mg/dL x ULN OR
Calc. Creatinine Clearance	> 50 mL/min
Total Bilirubin	≤ 1.5 x ULN*
AST / ALT	≤ 2.5 x ULN
Sodium, Potassium, & Total Calcium (corrected for serum albumin)	Within normal limits per institutional guidelines
QTcF**	< 450 msec
Resting Heart Rate (determined from EKG)	50-100 BPM ***

* Except in case of Gilbert's disease

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

*** Must be obtained from 12-lead EKG defined by a triplicate EKG for patients assigned to the capivasertib arm. Patients assigned to all other arms will require a single EKG.

11. Comorbid Condition

a. No uncontrolled medical comorbidities per investigator discretion (e.g. interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, history of major surgical resection involving the stomach or small bowel, or pre-existing Crohn's disease or ulcerative colitis or a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea)

Additional Registration Eligibility Criteria for Abemaciclib Arm

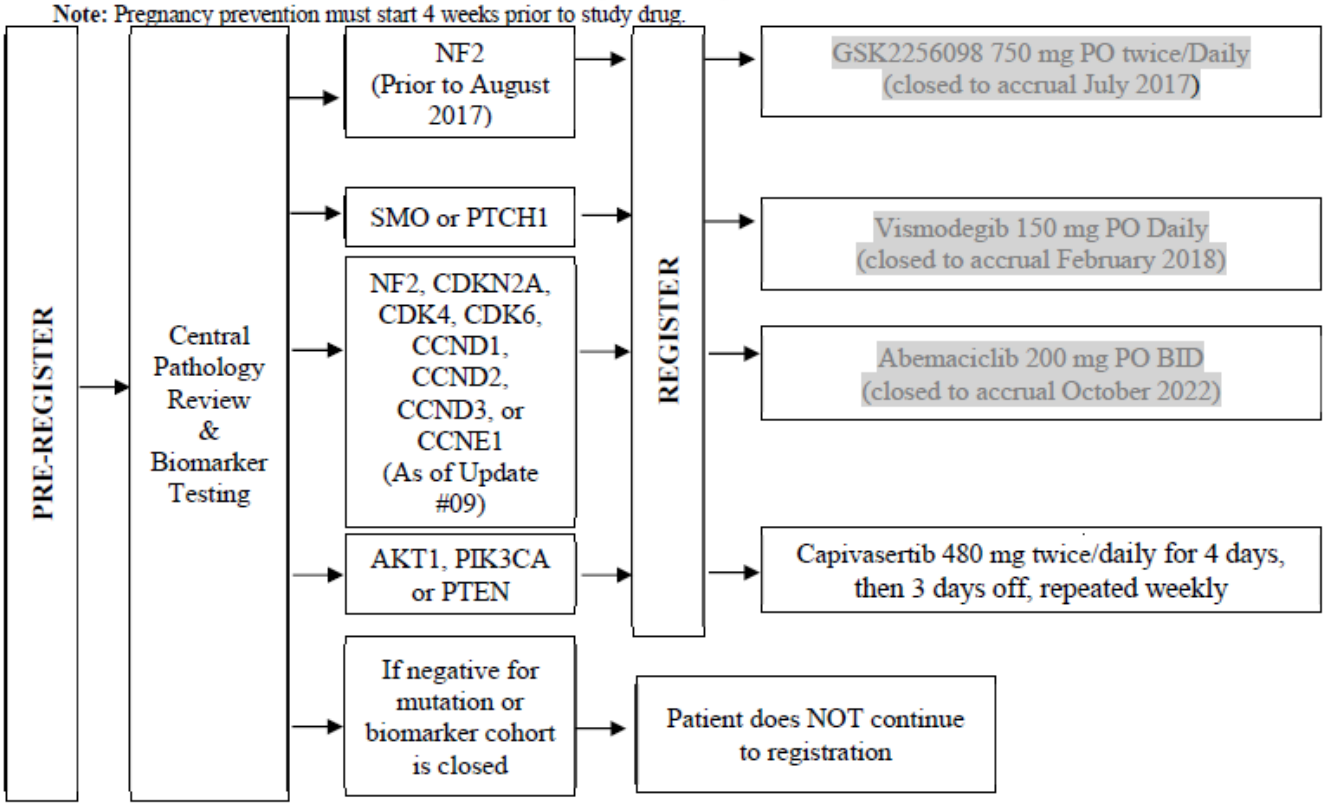
1. Greade 2/3 disease as determined by central pathology review
2. Hemoglobin ≥ 8 g/dL
    1. Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator. Initial treatment must not begin earlier than the day after the erythrocyte transfusion
3. Prior Treatment
    1. Patients who received chemotherapy must have recovered (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≤1) from the acute effects of chemotherapy except for residual alopecia or Grade 2 peripheral neuropathy prior to registration. A washout period of at least 28 days is required between last chemotherapy dose and registration (provided the patient did not receive radiotherapy). Patients who received adjuvant radiotherapy must have completed and fully recovered from the acute effects of radiotherapy. A washout period of at least 28 days is required between end of radiotherapy and registration.

4. No active bacterial infection (requiring intravenous [IV] antibiotics at time of initiating study treatment), fungal infection, or detectable viral infection (such as known human immunodeficiency virus positivity or with known active hepatitis B or C [for example, hepatitis B surface antigen positive]). Screening is not required for enrollment in the absence of symptoms.
5. No personal history of any of the following conditions: syncope of cardiovascular etiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest.

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.

Pre study parameters

- History and physical, weight, height, PS
- Pulse, blood pressure
- Adverse event assessment
- Registration fatigue/uniscale assessment
- CBC
- Basic metabolic panel
- Urine protein
- Serum or urine HCG
- AG and Hepatitis C RNA (physician discretion, not required)
- Fasting cholesterol, triglyerides
- EKG
- MRI/CT brain
- Central review for eligibility