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Full Title
A Phase II and Pharmacodynamic Trial of RO4929097 for Patients with Recurrent/Progressive Glioblastoma

Principal Investigator
David Peereboom, MD

Contact Information
Cathy Brewer, RN
Research Nurse
216.444.7937

Objectives

1. Primary Objective:
    - 6-month progression-free survival (PFS6)
2. Secondary Objectives:
    - Radiographic response rate
    - Toxicities associated with this regimen
    - Overall survival
3. Group B Primary Objective
    - Efficiency of neurosphere generation after pretreatment with RO4929097
4. Secondary Laboratory Objectives
    - Expression levels of Notch pathway components and downstream targets
    - Tumor propagation. An extension of lifespan by 50% in tumor bearing mice (mice bearing fresh tumor tissue)
5. Secondary Clinical Objectives
    - Patient event-free survival in correlation with expression levels of Notch pathway components and downstream targets
    - 6-month progression-free survival (PFS6)
    - Toxicities associated with this regimen
    - Overall survival

Eligibility
Inclusion

1. Patients must have histologically proven glioblastoma which is progressive or recurrent following radiation therapy + - chemotherapy.

2. Patients must have measurable contrast-enhancing progressive or recurrent glioblastoma by MRI imaging within two weeks of starting treatment. Patient must be able to tolerate MRIs.
3. Group B patients only: Patients must be eligible for surgical resection according to the following criteria:
    - Expectation that the surgeon can resect ≥ 50% of the Gd-enhancing tumor with low risk of inducing neurological injury
    - Absence of hematologic, cardiac or other medical contraindications to surgery
    - Surgery must take place Monday-Thursday with the exception of patients being treated at Cleveland Clinic/University Hospitals: these patients may undergo surgery Monday - Friday
    - Patients must have a tumor size ≥ 2.5 cm in diameter in two perpendicular planes in order to enable correlative studies
    - Paraffin embedded tissue must be available from initial surgical resection at diagnosis (prior to any treatment).
4. Patients must be 18 years of age or older.
5. Patients may have an unlimited number of prior therapy regimens but no prior γ- secretase inhibitors.
6. Patients must have recovered from severe toxicity of prior therapy. The following intervals from previous treatments are required to be eligible:
    - 3 months from the completion of radiation
    - 6 weeks from a nitrosourea chemotherapy
    - 3 weeks from a non-nitrosourea chemotherapy
    - 4 weeks from any investigational (not FDA-approved) agents
    - 2 weeks from administration of a non-cytotoxic, FDA-approved agent (e.g., small molecule targeted therapy, thalidomide, bevacizumab, etc.)
7. Patients may not be on an enzyme-inducing anti-epileptic drug (EIAED). If previously on an EIAED, patient must be off for at least 14 days prior to the first dose of RO4929097.
8. Patients must have a Karnofsky Performance Status ≥ 60% (i.e. the patient must be able to care for himself/herself with occasional help from others).
9. Patients must have organ and marrow function as defined below:
    - Hemoglobin ≥ 9 g/dL
    - Leukocytes ≥ 3,000/mcL
    - Absolute neutrophil count ≥ 1,500/mcL
    - Platelets ≥ 100,000/mcL
    - Total bilirubin ≤ institutional upper limit of normal
    - AST(SGOT)/ALT(SGPT) ≤ 4.0 X institutional upper limit of normal Creatinine within institutional upper limit of normal OR
    - Creatinine clearance ≥ 60 mL/min/1.73 m2 for patients with creatinine levels above institutional normal
10. Patients must be able to provide written informed consent.

11. Women of childbearing potential and men must use two forms of contraception (i.e., barrier contraception and one other method of contraception) starting prior to study entry, for the duration of study participation, and for at least 12 months posttreatment. For appropriate methods of contraception considered acceptable, see Appendix I. Should a woman become pregnant or suspect she is pregnant while she or her partner are participating in this study and for 12 months after study participation, the patient should inform the treating physician immediately. Pregnancy Testing: Women of childbearing potential are required to have a negative serum pregnancy test (with a sensitivity of at least 25 mIU/mL) within 10-14 days prior to treatment start and be required to agree to have the test repeated within 24 hours prior to the first dose of RO4929097 (serum or urine). A pregnancy test (serum or urine) will also be administered every 4 weeks (within 24 hours prior to starting every cycle) if their menstrual cycles are regular or every 2 weeks if their cycles are irregular while on study. A positive urine test must be confirmed by a serum pregnancy test. Prior to dispensing RO4929097, the investigator must confirm and document the patient's use of two contraceptive methods, dates of negative pregnancy test, and confirm the patient's understanding of the potential of RO4929097 to cause serious or life-threatening birth defects.
12. Female patients of childbearing potential are defined as follows:
    - Patients with regular menses
    - Patients, after menarche with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding
    - Women who have had tubal ligation

    Female patients may be considered to NOT be of childbearing potential for the following reasons:

    - The patient has undergone total abdominal hysterectomy with bilateral salpingooophorectomy or bilateral oophorectomy
    - The patient is medically confirmed to be menopausal (no menstrual period) for 24 consecutive months
13. Patients may not be breast-feeding.
14. Patients must have no concurrent malignancy except curatively treated basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix, breast, or bladder. Patients with prior malignancies must be disease-free for ≥ five years.

1. Patients must have a Mini Mental State Exam score of ≥ 15.

Exclusions

1. Patients with serious concurrent infection or medical illness, which would jeopardize the ability of the patient to receive the treatment outlined in this protocol with reasonable safety, are ineligible.
2. Patients with prior treatment with γ-secretase inhibitors are ineligible.
3. Patients may not be receiving any other investigational agents.
4. Patients with a history of allergic reactions attributed to compounds of similar chemical or biologic composition to RO4929097 or other agents used in the study are ineligible.
5. Patients with malabsorption syndrome or other condition that would interfere with intestinal absorption are ineligible. Patients must be able to swallow capsules.
6. Patients with the following cardiovascular abnormalities are ineligible: baseline QTcF > 450 msec (male) or QTcF > 470 msec (female).
7. Patients who are serologically positive for Hepatitis B or C, or who have cirrhosis are ineligible.
8. Patients with a history of uncontrolled hypocalcemia, hypomagnesemia, hyponatremia or hypokalemia defined as less than the lower limit of normal for the institution, despite adequate electrolyte supplementation are excluded from this study.
9. Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia other than chronic, stable atrial fibrillation, or psychiatric illness/social situations that would limit compliance with study requirements, are ineligible.
10. Pregnant women or those who are breastfeeding are ineligible.
11. HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with RO4929097.

Patients who have not recovered to < CTCAE grade 2 toxicities related to prior therapy are not eligible to participate in this study.