

**NCCTG N057K: Phase I/II Evaluation of Everolimus (RAD001), Radiation and Temozolomide (TMZ)
Followed by Adjuvant Temozolomide and Everolimus in Newly Diagnosed Glioblastoma**

Fast Facts

Provided Drug: Everolimus

Pre-registration – Required Characteristics

1. Central pathology review. This review is mandatory prior to registration to confirm eligibility. It should be initiated as soon after surgery as possible.

Registration – Required Characteristics

1. Histologically confirmed GBM (grade 4 astrocytoma). Gliosarcomas and other grade 4 astrocytoma variants (e.g., giant cell) may be included. Grade 4 oligodendrogliomas or oligoastrocytomas are specifically excluded.
2. ≥ 1 week and ≤ 6 weeks following surgical resection or biopsy.
3. ≥ 18 years of age. Because no dosing or adverse event data are currently available on the use of everolimus in patients < 18 years of age, children are excluded from this study.
4. ECOG Performance Status (PS) of 0, 1 or 2.
5. The following laboratory values obtained ≤ 14 days prior to registration:
 - a. ANC $\geq 1500/\mu\text{L}$
 - b. Hemoglobin ≥ 9.0 g/dL
 - c. PLT $\geq 100,000/\mu\text{L}$
 - d. Total bilirubin ≤ 2.5 x institutional upper limit of normal (ULN)
 - e. Serum total cholesterol < 350 mg/dL
 - f. Serum total triglycerides < 400 mg/dL
 - g. AST(SGOT) ≤ 2.5 x ULN
 - h. Creatinine ≤ 1.5 x ULN
6. Negative serum pregnancy test done ≤ 7 days prior to registration, for women of childbearing potential only.
7. Ability to understand, and willingness to sign, a written informed consent.
8. Willingness to provide mandatory translational research components.
 - a. Mandatory FFPE tumor tissue blocks/slides (Sections 6.34, 17.3).
9. Willingness to abstain from eating grapefruit or drinking grapefruit juice for the duration of the study.
10. Willingness to forego foods high in fat content 2 hours prior to and 2 hours after administration of everolimus therapy.
11. Willingness and ability to comply with antibiotic prophylaxis with either trimethoprim/sulfamethoxazole (daily or 3x per week), oral dapsone (daily) combined with daily levofloxacin, or monthly pentamidine (inhaled or IV) combined with daily levofloxacin.

Registration - Exclusion criteria

1. Prior chemotherapy for any brain tumor. Prior temozolomide or mTOR inhibitor therapies. Any prior cranial radiotherapy.
2. Planned immunization with attenuated live vaccines during study period.
3. Current or prior treatment for this cancer with any other investigational agents.
4. Currently on enzyme inducing anti-convulsants (EIACs) or other strong inducers of CYP3A4. Note: For the purpose of this study, these drugs will be defined as carbamazepine, phenytoin, phenobarbital/primidone, rifabutin, rifampin or St. John's wort.
5. Any of the following because everolimus has potential teratogenic or abortifacient effects based on the potential that mTOR expression is important for normal organ development:
 - a. Pregnant women
 - b. Nursing women
 - c. Men or women of childbearing potential who are unwilling to employ adequate contraception for duration of the study and for 60 days following completion of study therapy.
6. Other active cancers requiring therapy to control disease, or prior cancer diagnoses, which pose a greater than 30% risk of death within the next 2 years.
7. Major surgery (excluding neurosurgical biopsy or resection of brain tumor or treatment of immediate post neurosurgical complication, e.g. intracranial hematoma) or significant traumatic injury occurring ≤ 21 days prior to registration.

8. Gastrointestinal tract disease resulting in an inability to take oral medication or a requirement for IV alimentation, prior surgical procedures affecting absorption, or active uncontrolled peptic ulcer disease.
9. Uncontrolled intercurrent illness including, but not limited to the following:
 - a. ongoing or active infection
 - b. symptomatic congestive heart failure
 - c. unstable angina pectoris
 - d. cardiac arrhythmia
 - e. psychiatric illness/social situations that would limit compliance with study requirements
 - f. severely impaired lung function
 - g. uncontrolled diabetes as defined by fasting serum glucose $>2 \times$ ULN
 - h. any active (acute or chronic) or uncontrolled infection/ disorders.
 - i. liver disease such as cirrhosis, chronic active hepatitis, chronic persistent hepatitis or history of hepatitis B
10. Known to be HIV-positive. Note: The mucosal adverse events of ionizing radiation in HIV-positive patients are significantly greater than in patients without HIV. Therefore, HIV-positive patients will be excluded.
11. Any history of allergy or intolerance to Dacarbazine (DTIC).
12. Patients who require therapeutic dose of warfarin (see Section 9.4). Note: Low molecular weight heparin is allowed. Patients who can be converted to low molecular weight heparin may enroll on the trial once they have discontinued warfarin.
13. Severe allergy to sulfa medications **and** inability to tolerate levofloxacin with dapasone or pentamidine (inhaled or IV).
14. Positive hepatitis B antigen (HBsAg) or hepatitis C serology (HCV) tests.

Pre-Study Parameters

1. Pathology review, radiation and medical oncology consult
 2. History, PE, weight, height, PS, AE assessment
 3. Neuro history and exam
 4. MMSE
 5. Hematology group CBC with differential (WBC, ANC, hemoglobin, PLT, lymphocytes)
 6. Chemistry group (t. bili., alk. phos., glucose, cholesterol, triglycerides, SGOT(AST), creatinine)
 7. Tumor measurement
 8. MRI or CT
 9. Mandatory Research tissue collection
 10. Pregnancy test (if applicable)
 11. Hepatitis B surface antigen (HBsAg) and Hepatitis C screen (HCV)
- See table #4 for details of test schedule

Schema:

