

CCF IRB CC877 ABTC 0901

Full Title

An Open Label, Phase 2 Study Evaluating the Safety and Efficacy of IMC-3G3 or IMC-1121B in Patients with Recurrent Glioblastoma Multiforme

Principal Investigator

David Peereboom, MD

Contact Information

Cathy Smolenski, RN, BSN
Research Nurse
216.445.1067

Objectives

Primary Objective:

To assess disease progression-free survival (PFS) rate at 6 months in patients with recurrent glioblastoma multiforme treated with IMC-1121B or IMC-3G3.

Secondary Objectives:

- 1) To evaluate acute and late toxicities associated with the regimens.
- 2) To assess tumor objective response rate (ORR).
- 3) To estimate overall survival (OS).
- 4) To describe the pharmacokinetic (PK) and pharmacodynamic profiles and immunogenicity of IMC-3G3 and of IMC-1121B.
- 5) To explore ancillary imaging with DCE-MRI (including volumetric analysis, vessel size, vascular permeability, fluid attenuation inversion recovery, apparent diffusion coefficient and diffusion tensor imaging) on 8 patients in each study group at specified time points.
- 6) To describe blood and/or tumor tissue expression (when available) of PDGFR α , PDGF, VEGFR, and VEGF.

Eligibility

Inclusion

1. Patients must be at least 18 years of age.
2. Patients must have histologically confirmed supratentorial glioblastoma multiforme (GBM) which is progressive or recurrent after radiation therapy and chemotherapy (temozolomide). Patients with previously low grade glioma who progressed after radiotherapy and chemotherapy and are biopsied and found to have a GBM are eligible.
3. Patients must have measurable contrast enhancing progressive or recurrent GBM by MRI (within 14 days before starting treatment).
4. Patients must have recovered from toxicity of prior therapy. An interval of at least 3 months must have elapsed since the completion of the most recent course of radiation therapy, while at least 3 weeks must have elapsed since the completion of a non-nitrosourea containing chemotherapy regimen, and at least 6 weeks since the completion of a nitrosourea containing chemotherapy regimen. NOTE: For non-cytotoxic, FDA-approved agents (i.e. celecoxib, thalidomide, etc.) therapy may be started 2 weeks after discontinuing such an agent provided the patient has fully recovered from all toxicity associated with the agent. For investigational, non-cytotoxic agents a minimum of 3 weeks must have elapsed before the patient will be eligible for this study.
5. Patients must have a Karnofsky performance status \geq 60% (i.e. the patient must be able to care for himself/herself with occasional help from others).
6. Patients must have adequate hematologic, renal and liver function as defined by the following laboratory criteria: absolute neutrophil count \geq 1500/mm³; platelets \geq 100,000/mm³; hemoglobin \geq 9 g/dL; creatinine \leq 1.5mg/dL OR a

creatinine clearance (measured or calculated) > 60 mL/min; total bilirubin ≤ 1.5mg/dl; transaminases ≤3 times above the upper limits of the institutional norm.

7. Patient's urinary protein is ≤ 2+ on dipstick or routine urinalysis (UA). If urine dipstick or routine analysis indicates >2+ proteinuria, then a 24-hour urine must be collected and must demonstrate ≤ 1000 mg of protein in 24 hours to allow participation in the study.

8. Patient must have adequate coagulation function (an international normalized ratio (INR) ≤1.5 and partial thromboplastin time (PTT) ≤ 5 seconds above the ULN.

9. Patients must be able to provide written informed consent.

10. Women of childbearing potential must have a negative serum pregnancy test. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation, and for at least 8 weeks following the last dose of study drug.

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

12. The patient has a life expectancy of ≥ 3 months.

13. Patients must have tumor tissue form completed and signed by a pathologist. See Section 9.5.1 for details.

1. 14. Patients consent to and are able to undergo MRI serial imaging.

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. (Examples of medical illnesses include [but are not limited to] the following: uncontrolled hypertension, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situation that would limit compliance with study requirements.)

2. Patients who are pregnant or lactating.
3. Patients who have been previously treated with other agents that directly inhibit PDGFR, PDGF, VEGF, or VEGFRs.
4. Patients receiving concurrent therapy for their tumor (i.e. chemotherapeutics or investigational agents). Concurrent steroid use is allowed.
5. Patients with a concurrent malignancy are ineligible unless they are patients with curatively treated carcinoma-in-situ or basal cell carcinoma of the skin. Patients with a prior malignancy are ineligible unless they have been free of disease for \geq five years.
6. Patients who have had a major bleeding episode \leq 3 months prior to the start of treatment.
7. Patients who have had a myocardial infarction, unstable angina pectoris, cerebrovascular accident or transient ischemic attack \leq 6 months prior to start of treatment.
8. Patients with a serious or non-healing wound, ulcer, or bone fracture.
9. Patients with uncontrolled or poorly controlled hypertension, despite standard medical management.
10. Patients with known allergy to any of the treatment components.
11. Patients with known human immunodeficiency virus or acquired immunodeficiency syndrome-related illness.

12. Patients who have undergone major surgery (including a procedure like brain biopsy) within 28 days prior to the start of treatment, or subcutaneous venous access device placement within 7 days prior to study enrollment.

13. Patients who are concurrently receiving therapeutic anticoagulation, chronic daily treatment with aspirin (> 325 mg/day) or other known inhibitors of platelet function.

14. Patients with uncontrolled thrombotic or hemorrhagic disorders.

15. Patients with an elective or planned surgery to be performed during the course of the trial.

16. Patients who have experienced any Grade 3-4 gastrointestinal bleeding within 3 months prior to first dose of study medication, or gross hemoptysis ($\geq \frac{1}{2}$ teaspoon) within 2 months prior to first dose of study medication.

NOTE: There is no limit to the number of prior GBM treatments for patients enrolling on this study.