

FAST FACTS

NRG-BN007 - A RANDOMIZED PHASE II/III OPEN-LABEL STUDY OF IPILIMUMAB AND NIVOLUMAB VERSUS TEMOZOLOMIDE IN PATIENTS WITH NEWLY DIAGNOSED MGMT (TUMOR O-6-METHYLGUANINE DNA METHYLTRANSFERASE) UNMETHYLATED GLIOBLASTOMA

Eligibility Criteria

Prior to Step 1 Registration

1. No known IDH mutation. (If tested before step 1 registration, patients known to have IDH mutation in the tumor on local or other testing are ineligible and should not be registered).
2. Availability of FFPE tumor tissue block and H&E stained slide to be sent for central pathology review for confirmation of histology and MGMT promoter methylation status (See Sections 3.1.1, 3.1.2, and 10). Note that tissue for central pathology review and central MGMT assessment must be received by the NRG Oncology Biospecimen Bank on or before postoperative calendar day 23. If tissue cannot be received by postoperative calendar day 23, then patients may NOT enroll on this trial as central pathology review and stratification will not be complete in time for the patient to start treatment no later than 6 weeks following surgery. Results of central pathology review and central MGMT analysis will generally be conveyed to NRG Oncology within 10 business days of receipt of tissue.
3. Contrast-enhanced brain MRI within 72 hours after surgery.
 - MRI with Axial T2 weighted FLAIR {preferred} or T2 TSE/FSE and 3D contrast-enhanced T1 sequences are required.
 - 3D pre contrast-enhanced T1 sequences are strongly suggested.
4. Women of childbearing potential (WOCBP) and men who are sexually active with WOCBP must be willing to use an adequate method of contraception hormonal or barrier method of birth control; or abstinence during and after treatment (see Section 9.0).
5. The patient or a legally authorized representative must provide study-specific informed consent prior to study entry.

Prior to Step 2 Registration

6. Histopathologically proven diagnosis of glioblastoma (or gliosarcoma as a subtype of glioblastoma) confirmed by central pathology review (See Section 10 for details);
7. MGMT promoter without methylation confirmed by central pathology review (See Section 10 for details). Note: Patients with tissue that is insufficient or inadequate for analysis, fails MGMT testing, or has indeterminate or methylated MGMT promoter are excluded.
8. IDH mutation testing by at least one method (such as immunohistochemistry for IDH1 R132H) must be performed as part of standard of care and no mutation must be found (i.e IDH wildtype). (If a mutation is identified then the patient will be ineligible and must be registered as ineligible at Step 2.)
9. History/physical examination within 28 days prior to Step 2 registration;
10. Karnofsky Performance Status (KPS) ≥ 70 within 28 days prior to Step 2 registration;
11. Neurologic Function assessment within 28 days prior to Step 2 registration;
12. Age ≥ 18 years;

13. Adequate hematologic, renal, and hepatic function within 7 days prior to Step 2 registration defined as follows:
- hemoglobin ≥ 10 g/dl (Note: the use of transfusion or other intervention to achieve Hgb ≥ 10.0 g/dl is acceptable)
 - leukocytes $\geq 2,000/\text{mm}^3$
 - absolute neutrophil count $\geq 1,500/\text{mm}^3$
 - platelets $\geq 100,000/\text{mm}^3$
 - total bilirubin $\leq 1.5 \times$ institutional/lab upper limit of normal (ULN)
 - AST(SGOT) $\leq 2.5 \times$ ULN
 - ALT(SGPT) $\leq 2.5 \times$ ULN
 - serum creatinine $\leq 1.5 \times$ ULN
- OR
- creatinine clearance (CrCl) ≥ 50 mL/min (if using the Cockcroft-Gault formula below):

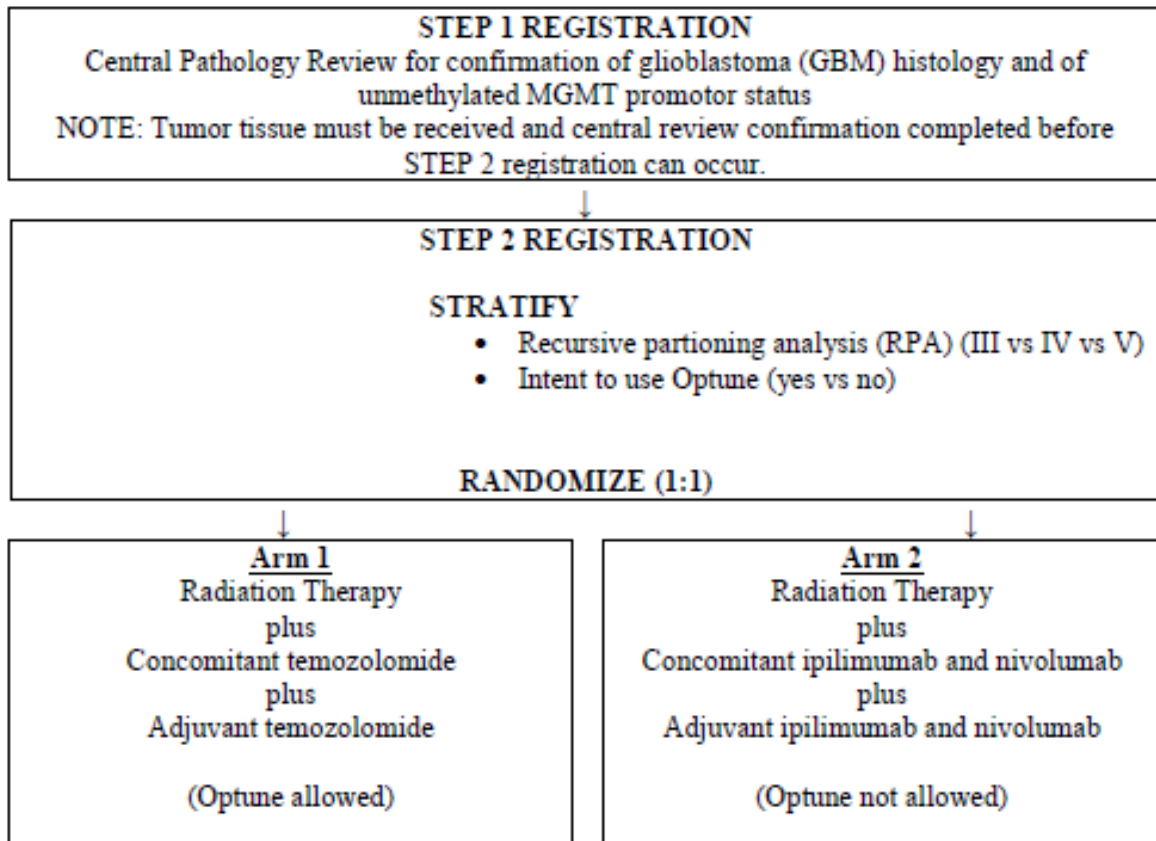
$$\text{CrCl (mL/min)} = [140 - \text{age (years)}] \times \text{weight (kg)}$$
14. For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.
 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured.
 For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.
15. For women of childbearing potential (WOCBP), negative serum or urine pregnancy test within 7 days prior to Step 2 registration. Note that it may need to be repeated if not also within 72 hours prior to treatment start (see section 4)
- Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes.

Ineligibility Criteria

1. Prior therapy for tumor except for biopsy or resection. For example, prior chemotherapy, immunotherapy, or targeted therapy for GBM or lower grade glioma is disallowed (including but not limited to temozolomide, lomustine, bevacizumab, any viral therapy, ipilimumab or other CTLA-4 antibody, PD-1 antibody, CD-137 agonist, CD40 antibody, PDL-1 or 2 antibody, vaccine therapy, polio or similar viral injection as treatment for the tumor, and/or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) as is prior Laser interstitial thermal therapy (LITT), Gliadel wafer, radiotherapy, radiosurgery, gamma knife, cyber knife, vaccine or other immunotherapy, brachytherapy, or convection enhanced delivery;
 - Note that 5-aminolevulinic acid (ALA)-mediated fluorescent guided resection (FGR) photodynamic therapy (PDT) or fluorescein administered prior to/during surgery to aid resection is not exclusionary and is not considered a chemotherapy or intracerebral agent
2. Current or planned treatment with any other investigational agents for the study cancer
3. Definitive clinical or radiologic evidence of metastatic disease outside the brain
4. Prior invasive malignancy (except non-melanomatous skin cancer, cervical cancer in situ and melanoma in situ) unless disease free for a minimum of 2 years
5. Prior radiotherapy to the head or neck that would result in overlap of radiation therapy fields

6. Pregnancy and nursing females due to the potential teratogenic effects and potential risk for adverse events in nursing infants.
7. History of severe hypersensitivity reaction to any monoclonal antibody.
8. History of allergic reactions attributed to compounds of similar chemical or biologic composition to ipilimumab, nivolumab, or temozolomide
9. On any dose of any systemically administered (oral, rectal, intravenous) corticosteroid within 3 days prior to Step 2 registration (see also section 4). Inhaled, topical, and ocular corticosteroids are allowed without limitation but must be recorded. Note that treatment with systemically administered corticosteroid after initiating study treatment is allowed as needed.
10. Patients with known immune impairment who may be unable to respond to anti-CTLA 4 antibody.
11. History of interstitial lung disease including but not limited to sarcoidosis or pneumonitis
12. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, defined as New York Heart Association Functional Classification III/IV (Note: Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification), unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
13. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).
14. Patients with active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids, are excluded. These include but are not limited to: patients with a history of immune-related neurologic disease, CNS or motor neuropathy, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as autoimmune vasculitis [*e.g.*, Wegener's Granulomatosis]), systemic lupus erythematosus (SLE), connective tissue diseases (*e.g.*, systemic progressive sclerosis), scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome, Hashimoto's thyroiditis, autoimmune hepatitis are excluded because of the risk of recurrence or exacerbation of disease.
 - Exceptions: patients with a history of the following conditions are not excluded:
 - o vitiligo
 - o endocrine deficiencies including thyroiditis managed with replacement hormones including physiologic corticosteroids
 - o rheumatoid arthritis and other arthropathies
 - o Sjögren's syndrome and psoriasis controlled with topical medication and patients with positive serology, such as antinuclear antibodies (ANA)
 - anti-thyroid antibodies should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible.
15. Patients who have evidence of active or acute diverticulitis, intra-abdominal abscess, GI obstruction and abdominal carcinomatosis which are known risk factors for bowel perforation are also excluded
16. Current or planned therapy with warfarin

**NRG-BN007
SCHEMA**



See [Section 5.1](#) for agent treatment details and [Section 5.2](#) for radiation therapy details.