NRG-BN011
SCHEMA

STEP 1 REGISTRATION
Central Pathology Review for confirmation of glioblastoma (GBM) histology and of methylated MGMT promotor status
NOTE: Tumor tissue must be received and central review confirmation completed before STEP 2 registration can occur.*

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STEP 2 REGISTRATION

STRATIFY
- Recursive partitioning analysis (RPA) (III vs IV vs V)
- Intent to use tumor treating fields (Optune) (yes vs no)

RANDOMIZE (1:1)

Arm 1	**Arm 2**
Radiation Therapy with Concomitant and Adjuvant Temozolomide	Radiation Therapy with Concomitant and Adjuvant Lomustine and Temozolomide

See Section 5.1 for agent treatment details and Section 5.2 for radiation therapy details.

*****Patients with unmethylated MGMT may be considered for enrollment on NRG-BN007. Please see Section 10.2 for additional information.

3. ELIGIBILITY AND INELIGIBILITY CRITERIA

Notes: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility see protocol cover page. For radiation therapy-related eligibility questions, please contact RTQA (see protocol cover page).

3.1 Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

Prior to Step 1 Registration

3.1.1 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).

3.1.2 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 and 10). Note that tissue for central pathology review and central MGMT assessment must be received by the NYU Center for Biospecimen Research and Development (CBRD) 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 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. Note: In the event of an additional tumor resection(s), tissue must be received within 23 days of the most recent resection and the latest resection must have been performed within 30 days after the initial resection. Surgical resection is required; stereotactic biopsy alone is not allowed because it will not provide sufficient tissue for MGMT analysis.

3.1.3 Contrast-enhanced brain MRI within 4 days 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.

3.1.4 Willing to use highly effective method of contraception for participants of childbearing potential (participants who may become pregnant or who may impregnate a partner) during therapy and for 6 months after completing treatment; this inclusion is necessary because the treatment in this study may be significantly teratogenic.(see Section 9 for definition of highly effective contraception).

3.1.5 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry and, for patients treated in the U.S., authorization permitting release of personal health information.

Prior to Step 2 Registration

3.1.6 Histopathologically proven diagnosis of glioblastoma (or gliosarcoma as a subtype of glioblastoma) confirmed by central pathology review (See Section 10 for details);

3.1.7 MGMT promoter with 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 unmethylated MGMT promoter are excluded. **Patients with unmethylated MGMT may be considered for enrollment on NRG-BN007. Please see Section 10 for additional information.**

3.1.8 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.)

3.1.9 History/physical examination within 28 days prior to Step 2 registration;

3.1.10 Karnofsky Performance Status (KPS) ≥ 70 within 28 days prior to Step 2 registration;

3.1.11 Neurologic Function assessment within 28 days prior to Step 2 registration;

3.1.12 Age 18-70 years;

3.1.13 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 ≥2,000/mm^3
- absolute neutrophil count ≥1,500/mm^3
- platelets ≥100,000/mm^3
- total bilirubin ≤1.5× institutional/lab upper limit of normal (ULN)
- AST(SGOT) ≤2.5 × ULN
- ALT(SGPT) ≤2.5 × ULN
- serum creatinine ≤1.5× ULN

OR

- creatinine clearance (CrCl) ≥50 mL/min (if using the Cockcroft-Gault formula below):

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg / dL)}} \quad \{\times 0.85 \text{ for female patients}\}$$

3.1.14 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.
Note: Known positive test for hepatitis B virus surface antigen (HBV sAg) indicating acute or chronic infection would make the patient ineligible unless the viral load becomes undetectable on suppressive therapy. Patients who are immune to hepatitis B (anti-Hepatitis B surface antibody positive) are eligible (e.g. patients immunized against hepatitis B).

3.1.15 For 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.
Note: Known positive test for hepatitis C virus ribonucleic acid (HCV RNA) indicating acute or chronic infection would make the patient ineligible unless the viral load becomes undetectable on suppressive therapy.

3.1.16 Known human immunodeficiency virus (HIV) infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months prior to step 2 registration are eligible for this trial. Testing is not required for entry into protocol.

3.1.17 Negative serum or urine pregnancy test (in persons of childbearing potential) within 7 days prior to Step 2 registration.

- Childbearing potential is defined as any person who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal.

Prior to Step 2 Registration

3.2 Ineligibility Criteria

Patients with any of the following conditions are NOT eligible for this study.

3.2.1 Prior therapy for tumor except for 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, vaccine or other immunotherapy, brachytherapy, or convection enhanced delivery;

- **Note**: 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

3.2.2 Current or planned treatment with any other investigational agents for the study cancer

3.2.3 Definitive clinical or radiologic evidence of metastatic disease outside the brain

3.2.4 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

3.2.5 Prior radiotherapy to the head or neck that would result in overlap of radiation therapy fields

3.2.6 Pregnancy and individuals unwilling to discontinue nursing due to the potential teratogenic effects and potential risk for adverse events in nursing infants.

3.2.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to temozolomide or lomustine.

3.2.8 History of pulmonary fibrosis.

3.2.9 Uncontrolled intercurrent illness including, but not limited to:

- Ongoing or active infection requiring IV antibiotics, IV antiviral, or IV antifungal treatment,
- 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 within 6 months prior to Step 2 registration,
- Uncontrolled cardiac arrhythmia,
- Psychiatric illness/social situations that would limit compliance with study requirements.