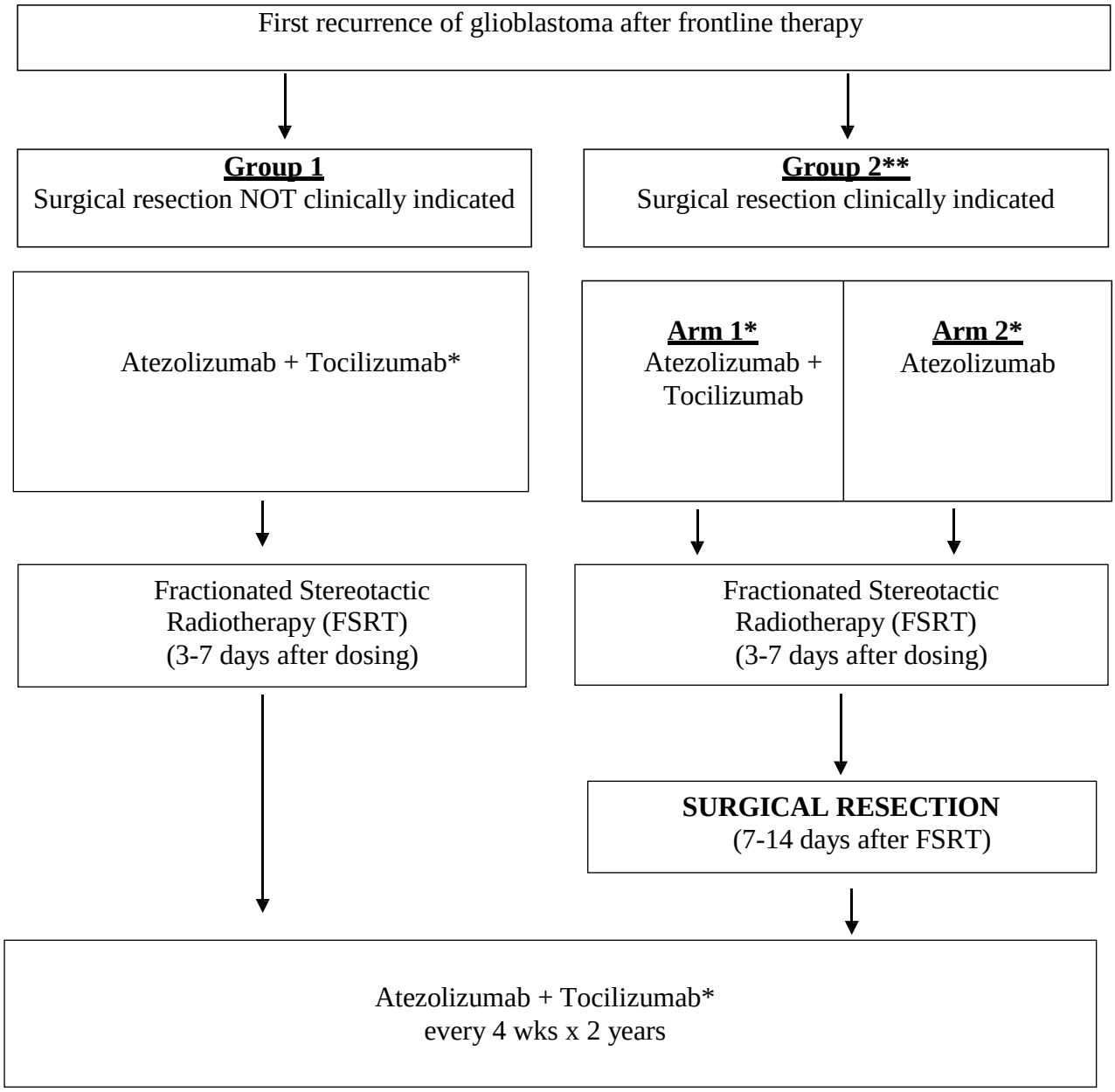
NRG-BN010
PHASE II SCHEMA
OPENED TO ACCRUAL WITH PROTOCOL AMENDMENT 3



*See Section 5.1 for systemic treatment details.
**Randomize 1:1

3. ELIGIBILITY AND INELIGIBILITY CRITERIA

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

Inclusion of Women and Minorities
NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see
http://grants.nih.gov/grants/funding/phs398/phs398.pdf

3.1 Eligibility Criteria (14-NOV-2022)

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

3.1.1 Histopathologically proven diagnosis of glioblastoma, OR molecular diagnosis of glioblastoma per c-IMPACT-NOW criteria ("diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV"; this requires presence of amplification of *EGFR*, whole chromosome 7 gain AND whole chromosome 10 loss, or *TERT* promoter mutation)

3.1.2 Tumor that is in first recurrence following prior first-line radiation therapy (prior dose ≥40Gy).
Note: Prior temozolomide, prior tumor-treating fields, and/or Gliadel wafers (if placed at initial tumor resection) are allowed, but none of these are required.

3.1.3 Unequivocal radiographic evidence of tumor progression by contrast-enhanced magnetic resonance imaging (MRI) scan within 21 days prior to registration

3.1.4 Per radiation oncologist review of MRI within 21 days prior to registration, must have focus of progressive, contrast-enhancing tumor that is amenable to FSRT, defined as the following:

- At least 1cm x 1cm contrast-enhancing tumor that is no greater than 4cm in largest dimension
- FSRT target is at least 0.5 cm from the optic chiasm and brainstem
- Note, multifocal disease (i.e., other sites of tumor beyond the tumor being targeted for FSRT) is allowed if the above criteria are met for the tumor that is the proposed target for FSRT

3.1.5 Surgical cohort only (Phase II only):

- Must be a candidate for repeat surgery (significant debulking or gross total resection of the contrast enhancing area) as determined by the neurosurgeon or multidisciplinary team.

3.1.6 Tumor O-6-methylguanine-deoxyribonucleic acid (DNA) methyltransferase (MGMT) methylation status must be available from any prior GBM tumor specimen; results of routinely used methods for MGMT methylation testing (e.g. mutagenically separated polymerase chain reaction [MSPCR] or quantitative polymerase chain reaction [PCR]) are acceptable)

3.1.7 The following intervals from previous treatments to registration are required to be eligible:

- If prior radiation was <60 Gy, an interval of at least 12 weeks (84 days) must have elapsed since the completion of radiation therapy
- If prior radiation was ≥60 Gy, an interval of least 6 months (182 days) must have elapsed since the completion of radiation therapy, unless the target lesion for FSRT is outside of the 80% isodose line of the original radiation plan
- At least 21 days from temozolomide
- At least 28 days from any investigational (not Food and Drug Administration [FDA]-approved for glioblastoma) agents, or within a time interval less than at least 5 half-lives of the investigational agent whichever is shorter (Note: anti-PD-1, anti-PD-L1, or anti-CTLA-4 therapeutic antibody or pathway-targeting agents are not allowed).

3.1.8 Age ≥ 18 years.

3.1.9 Karnofsky performance status ≥70 within 14 days prior to registration.

3.1.10 History/physical examination within 14 days prior to registration.

3.1.11 Patients must have normal organ and marrow function within 14 days prior to registration as defined below:

– leukocytes	≥2,500/mm^3
– absolute neutrophil count	≥1,500/ mm^3
– absolute lymphocyte count.	≥800/ mm^3
– platelets	≥100,000/ mm^3
– hemoglobin	≥8 g/dL
– total bilirubin	≤1.5 × institutional upper limit of normal (ULN) (however, patients with known Gilbert disease who have serum bilirubin level ≤3 × ULN may be enrolled)
– AST(SGOT)	≤2.5 × ULN
– ALT(SGPT)	≤2.5 × ULN
– alkaline phosphatase	≤2.5 × ULN
– creatinine clearance	≥30 mL/min/1.73 m^2 by Cockcroft-Gault:

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

3.1.12 Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of receipt of study treatment, and for 60 days (males) or 90 days (females) from the last dose of tocilizumab and for 5 months (150 days) after the last dose of atezolizumab. Administration of atezolizumab or tocilizumab may have an adverse effect on pregnancy and poses a risk to the human fetus, including embryo-lethality. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

3.1.13 Women of childbearing potential must have a negative serum or urine pregnancy test within 14 days prior to registration.

3.1.14 Patients positive for human immunodeficiency virus (HIV) are allowed on study (note: HIV testing is not required), but HIV-positive patients must have:

- An undetectable viral load within 6 months of registration.
- A stable regimen of highly active anti-retroviral therapy (HAART)
- No requirement for concurrent antibiotics or antifungal agents for the prevention of opportunistic infections

3.1.15 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).

3.1.16 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.

3.1.17 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry.

3.1.18 Availability of prior radiotherapy treatment plan details in DICOM format.

3.2 Ineligibility Criteria

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

3.2.1 Known somatic tumor mutation in *IDH1* or *IDH2* gene. If not previously completed, sequencing of the *IDH1* and *IDH2* genes is not required to determine trial eligibility.

3.2.2 Known germline DNA repair defect (mismatch repair deficiency, *POLE* mutation, e.g.). If not previously completed, germline sequencing is not required to determine trial eligibility.

3.2.3 Diffuse leptomeningeal disease.

3.2.4 Known contrast-enhancing tumor in brainstem or spinal cord. If not previously completed, spinal imaging is not required to determine trial eligibility.

3.2.5 Patients with clinically significant mass effect or midline shift (e.g., 1-2 cm of midline shift)

3.2.6 Prior bevacizumab therapy.

3.2.7 Patients with a prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of the investigational regimen are excluded from this trial. Otherwise, patients with prior or concurrent malignancy are eligible.

3.2.8 Patients with prior allogeneic bone marrow transplantation or prior solid organ transplantation.

3.2.9 Prior treatment with anti-PD-1, anti-PD-L1, or anti-CTLA-4 therapeutic antibody or pathway-targeting agents.

3.2.10 Treatment with systemic immunostimulatory agents (including, but not limited to, interferon [IFN]-α or interleukin [IL]-2) within 4 weeks prior to registration.

3.2.11 Treatment with systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to registration.

3.2.12 Systemic corticosteroids used to treat brain edema and/or related symptoms at a dose of >2mg of dexamethasone (or equivalent) daily within 5 days prior to registration. Patients receiving systemic corticosteroids for other indications are excluded.

3.2.13 Patients with increased risk for gastrointestinal perforations including history of diverticulitis.

3.2.14 Known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies.

3.2.15 History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.

3.2.16 Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis; cirrhosis; fatty liver; and inherited liver disease.

3.2.17 History or risk of autoimmune disease, including, but not limited to, systemic lupus erythematosus, rheumatoid arthritis, psoriatic arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis.
Note: patients with the below conditions are eligible:

- Autoimmune hypothyroidism on a stable dose of thyroid replacement hormone are eligible.
- Controlled Type 1 diabetes mellitus on a stable insulin regimen are eligible.
- Eczema, psoriasis, lichen simplex chronicus or vitiligo with dermatologic manifestations only are permitted provided that they meet the following conditions:
    - Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations
    - Rash must cover less than 10% of body surface area (BSA)
    - Disease is well controlled at baseline and only requiring low potency topical steroids (*e.g.*, hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%)
    - No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors; high potency or oral steroids)

3.2.18 History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), or organizing pneumonia (*i.e.*, bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.).
Note: History of radiation pneumonitis in a prior radiation field (fibrosis) is permitted.

3.2.19 Patients with active tuberculosis (TB) are excluded.

3.2.20 Severe infections within 3 weeks prior to registration including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia.

3.2.21 Signs or symptoms of infection within 1 week prior to registration.

3.2.22 Received oral or intravenous (IV) antibiotics within 2 weeks prior to registration.
Note: Patients receiving prophylactic antibiotics (*e.g.*, for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.

3.2.23 Major surgical procedure within 21 days prior to registration or anticipation of need for a major surgical procedure during the course of study treatment.

3.2.24 Administration of a live, attenuated vaccine within 4 weeks before registration or anticipation that such a live, attenuated vaccine will be required during receipt of study treatment and up to 5 months after the last dose of study drug

3.2.25 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.26 Women who are pregnant or nursing (and unwilling to discontinue) are excluded from this study. Atezolizumab and tocilizumab are agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with atezolizumab and tocilizumab breastfeeding should be discontinued if the mother is treated with atezolizumab and tocilizumab.