FAST FACTS

ALLIANCE A072301: PHASE III TRIAL OF RADIOTHERAPY FOLLOWED BY ADJUVANT TEMOZOLOMIDE IN COMBINATION WITH THE IDH INHIBITOR VORASIDENIB VS. PLACEBO IN IDH-MUTATED NEWLY-DIAGNOSED GRADE 3 ASTROCYTOMAS

3.0 PATIENT SELECTION

Pre-Registration Eligibility Criteria (Step 0)

3.2.1 Documentation of Disease:

- Histologic diagnosis of astrocytoma, IDH-mutant (CNS WHO grade 3)
- Available diagnostic slides (H&E and immunohistochemical stains for central review)
- Tissue available for central biomarker testing (CDKN2A/B and1p/19q co-deletion [all patients], and IDH1/IDH2 [if needed]); see Section 6.2 for details.

Registration Eligibility Criteria (Step 1)

3.3.1 Documentation of Disease:

- Centrally-confirmed diagnosis of astrocytoma, IDH-mutant (CNS WHO grade 3)
- Presence of IDH1 p.R132 or IDH2 p.172 mutation, confirmed by central review of immunohistochemical stain or molecular testing results, with central confirmation of equivocal results.
- Absence of CDKN2A /B homozygous deletion by central testing
- Absence of whole arm 1p/19q co-deletion (i.e. intact 1p/19q) by central testing.
- No evidence of spinal or leptomeningeal disease.

3.3.2 Prior Treatment

- No prior chemotherapy, cranial irradiation, IDH-inhibitor therapy, radiotherapy, vaccine therapy, small-molecule therapy, or laser ablation.

3.3.3 Prior diagnostic surgery/resection/biopsy ≤ 8 weeks of registration.

3.3.4 Planned radiotherapy and adjuvant chemotherapy.

3.3.5 Age ≥ 12 years

3.3.6 ECOG Performance Status ≤ 2 (or Karnofsky Performance Status [KPS] ≥ 60%)

3.3.7 Required Initial Laboratory Values:

Absolute Neutrophil Count (ANC)	≥ 1,500/mm^3
Hemoglobin	≥ 9 g/dL
Platelet Count	≥ 100,000/mm^3
Total Bilirubin*	≤ 1.5 x upper limit of normal (ULN)
AST (SGOT)/ALT (SGPT)	≤ 2.5 x ULN
Alkaline Phosphatase	≤ 2.5 x ULN
Creatinine	≤ 2.0 x ULN
OR	
Calc. Creatinine Clearance**	> 40 mL/min

*For patients with Gilbert Syndrome, total bilirubin ≤ 1.0 x ULN

**For patients ≥18 years of age, calculated using the Cockcroft-Gault equation. Fc patients < 18 years of age, calculated using the Bedside Schwartz method.

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

3.3.8 Not pregnant and not nursing, because this study involves agents whose genotoxic, mutagenic, and teratogenic effects on the developing fetus and newborn are unknown.

Therefore, for women of childbearing potential only, a negative pregnancy test done ≤ 14 days prior to registration is required.

3.3.9 Women and men of reproductive potential should agree to abstain from sexual intercourse or use two highly effective methods of birth control, at least one of which must be a barrier method, throughout their participation in this study and for at least 90 days after the last dose of vorasidenib**.** Reproductive status and discussions about birth control measures should be documented in the patient's record. Abstinence is acceptable only as true abstinence when this is in line with the preferred and usual lifestyle of the patient; periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of birth control. Highly effective forms of birth control are defined as hormonal oral contraceptives, injectables, patches, intrauterine devices, intrauterine hormone release systems, bilateral tubal ligation, condoms with spermicide, or male partner sterilization.

Comorbid Conditions

3.3.10 No severe or intercurrent illness, no active infection that requires systemic anti-infective therapy, and no active infection with an unexplained fever >38.5°C within 7 days prior to registration.

3.3.11 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

3.3.12 Patients must be able to tolerate or undergo an MRI.

3.3.13 HIV: Patients with known HIV infection on effective anti-retroviral therapy with undetectable viral load within 6 months prior to registration are eligible for this trial.

3.3.14 Hepatitis B: For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

Hepatitis C: 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.

3.3.15 Cardiac function: No significant active cardiac disease within 6 months prior to registration, including New York Heart Association Functional Classification Class III or IV congestive heart failure, myocardial infarction, unstable angina, and/or stroke. To be eligible for this trial, patients should be class 2B or better.

3.3.17 Gastrointestinal: No known active inflammatory gastrointestinal disease, chronic diarrhea, prior gastric resection or lap band dysphagia, short-gut syndrome, gastroparesis, or other condition causing an inability to swallow oral formulations of agents. Gastroesophageal reflux disease under medical treatment is allowed (assuming no drug interaction potential).

3.3.18 Allergies: No known hypersensitivity to any of the components of vorasidenib ortemozolomide.

3.3.19 No other acute or chronic medical condition or laboratory abnormality that may increase the risk associated with study participation or protocol therapy administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for entry into this study.

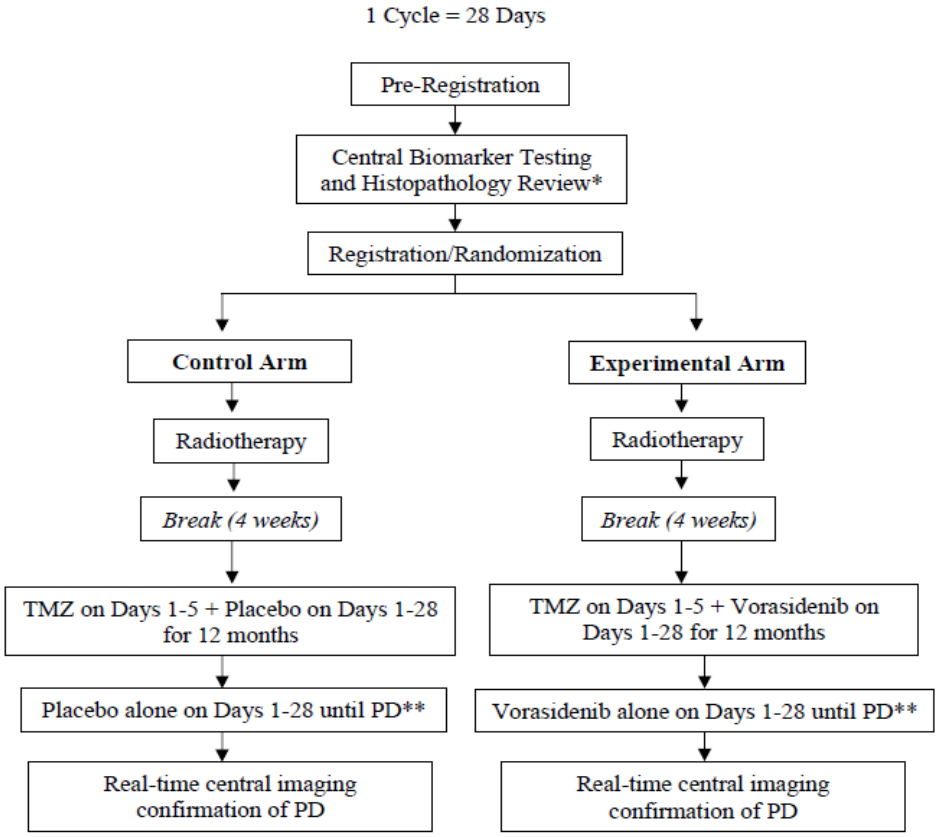
3.3.20 Concomitant Medications

- No concurrent use of other investigational agents.
- No concurrent use of alternating tumor treating field (TTField) therapy. No concurrent use of therapeutic doses of steroids for glioma. Concurrent use of physiologic doses of steroids (defined as equivalent of ≤ 10 mg prednisone daily) for medical conditions unrelated to glioma is allowed. Corticosteroids administered for reasons related to glioma should be used in the smallest dose

possible to control symptoms of cerebral edema and mass effect and discontinued whenever possible.

- No concurrent use of warfarin sodium or any other Coumadin-derivative anticoagulant. Patients must be off Coumadin-derivative anticoagulants for at least 7 days prior to registration. Low molecular weight heparin (LMWH) and factor Xa inhibitors are allowed.
- No concurrent use of strong and moderate CYP1A2 inhibitors, moderate CYP1A2 inducers, or CYP3A substrates where a minimal concentration change can reduce efficacy. Patients should be transferred to other medications prior to registration.

Schema



Abbreviations: TMZ = temozolomide; PD = progressive disease.

*Central testing shows confirmed WHO grade 3 astrocytoma with 1p/19q intact, IDH mutation, absence of CDKN2A/B homozygous codeletion.

**After 12 months of temozolomide + vorasidenib/placebo, treatment with vorasidenib/placebo alone is to continue until disease progression or unacceptable adverse event. Patients will be followed for 10 years or until death, whichever comes first.