SUPPLEMENTARY MATERIAL

Supplementary tables

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Table S1. Inclusion and exclusion criteria

Inclusion criteria
Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study: 1. Diagnosis a. Histologically confirmed diagnosis of World Health Organization Grade IV malignant glioma (glioblastoma or gliosarcoma); b. Documentation of recurrent (or progressive according to RNAO criteria) glioblastoma following prior treatment with surgery (resection or biopsy), radiation therapy and temozolomide chemotherapy; c. A formalin-fixed, paraffin-embedded (FFPE) tumor tissue block or 15 unstained slides (10 minimum) obtained from an archival FFPE tumor tissue block will be required. d. Presence of a measurable tumor lesion that is characterized by gadolinium enhancement on T1-MRI of the brain (with a shortest diameter of >5 mm) and enhanced lesion to normal brain uptake on 18-fluoroethyl-L-tyrosine positron-emission tomography/computed tomography (^{18}F-FET-PET/CT) imaging of the brain; e. If first recurrence of GBM is documented by MRI, an interval of at least 12 weeks after the end of prior radiation therapy is required unless there is either: i) histopathologic confirmation of recurrent tumor, or ii) new enhancement on MRI outside of the radiotherapy treatment field; f. An interval of >28 days and full recovery (ie, no ongoing safety issues) from surgical resection and an interval of >4 weeks after the last administration of any other treatment for glioblastoma. 2. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative, as allowed by local guidance/practice) has been informed of all pertinent aspects of the study. 3. Patients who are willing and able to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures. 4. Age ≥18 years. 5. Estimated life expectancy of at least 3 months. 6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2. 7. No evidence of pre-existing uncontrolled hypertension as documented by 2 baseline blood pressure (BP) readings taken at least 1 hour apart. The baseline systolic BP readings must be ≤140 mm Hg, and the baseline diastolic BP readings must be ≤90 mm Hg. Use of antihypertensive medications to control BP is allowed. 8. Adequate bone marrow function, including: a. Absolute neutrophil count (ANC) ≥1,500/mm3 or ≥1.5 x 109/L; b. Platelets ≥100,000/mm3 or ≥100 x 109/L; c. Hemoglobin ≥9 g/dL (may have been transfused). 9. Adequate renal function, including: a. Estimated creatinine clearance ≥ 30 mL/min as calculated using the Cockcroft-Gault (CG) equation; b. Urinary protein <2+ by urine dipstick. If dipstick is ≥2+, then 24-hour urinary protein <2 g per 24 hours. 10. Adequate liver function, including: 11. Total serum bilirubin ≤1.5 x upper limit of normal (ULN); 12. AST and ALT ≤2.5 x ULN. 13. Serum pregnancy test (for females of childbearing potential) negative at screening. 14. Male patients able to father children and female patients of childbearing potential and at risk for pregnancy must agree to use 2 highly effective methods of contraception throughout the study and for at least 90 days after the last dose of assigned treatment.
Exclusion criteria
Patients with any of the following characteristics/conditions will not be included in the study: 1. Any of the following prior cancer therapies: a. Prior immunotherapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-

cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab), or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways;
b. Prior therapy with axitinib as well as any prior therapies with other VEGF pathway inhibitors (including bevacizumab).

2. Participation in other therapeutic studies within 4 weeks prior to enrollment in the current study.
3. Persisting toxicity related to prior therapy NCI CTCAE v4.03 Grade >1; however, sensory neuropathy Grade ≤2 is acceptable.
4. Current or prior use of immunosuppressive medication within 7 days prior to enrollment, except for steroid treatment needed to palliate glioblastoma associated neurological symptoms and intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection);
5. No treatment with enzyme inducing anti-epileptic drugs (EIAED) during and at least 14 days before the administration of axitinib;
6. Known severe hypersensitivity reactions to monoclonal antibodies (Grade >3), any history of anaphylaxis.
7. Known prior or suspected hypersensitivity to study drugs or any component in their formulations.
8. Diagnosis of any other malignancy within 5 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or of the cervix, or low-grade (Gleason 6 or below) prostate cancer on surveillance with no plans for treatment intervention (eg, surgery, radiation or castration).
9. Active autoimmune disease that might deteriorate when receiving an immunostimulatory agents. Patients with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.
10. Gastrointestinal abnormalities including:
    a. Inability to take oral medication;
    b. Requirement for intravenous alimentation;
    c. Prior surgical procedures affecting absorption including total gastric resection;
    d. Treatment for active peptic ulcer disease in the past 6 months;
    e. Active gastrointestinal bleeding, unrelated to cancer, as evidenced by clinically significant hematemesis, hematochezia or melena in the past 3 months without evidence of resolution documented by endoscopy or colonoscopy;
    f. Malabsorption syndromes.
11. Active infection requiring systemic therapy.
12. Diagnosis of prior immunodeficiency or organ transplant requiring immunosuppressive therapy, or known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.
13. Any test for hepatitis B virus (HBV) or hepatitis C virus (HCV) indicating acute or chronic infection.
14. Vaccination within 4 weeks of the first dose of avelumab and while on trial is prohibited except for administration of inactivated vaccines (for example, inactivated influenza vaccines).
15. Requirement of anticoagulant therapy with oral vitamin K antagonists. Low-dose anticoagulants for maintenance of patency of central venous access device or prevention of deep venous thrombosis is allowed. Therapeutic use of low molecular weight heparin is allowed.
16. Evidence of inadequate wound healing (including dehiscence of the craniotomy scar).
17. Grade ≥3 hemorrhage within 4 weeks of patient enrollment.
18. Any of the following in the previous 12 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, LVEF less than LLN, clinically significant pericardial effusion, cerebrovascular accident, transient ischemic attack.
19. Any of the following in the previous 6 months: deep vein thrombosis or symptomatic pulmonary embolism.
20. Evidence of tumor involvement of the myocardium or pericardium or tumor thrombus extending to the heart.
21. Current use or anticipated need for treatment with drugs or foods that are known strong CYP3A4/5 inhibitors, including their administration within 10 days prior to patient enrollment (eg, grapefruit juice or grapefruit/grapefruit-related citrus fruits [eg, Seville oranges, pomelos], ketoconazole, miconazole, itraconazole, voriconazole, posaconazole, clarithromycin,

telithromycin, indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, fosamprenavir nefazodone, lopinavir, troleandomycin, mibefradil, and conivaptan). The topical use of these medications (if applicable), such as 2% ketoconazole cream, is allowed.

22. Current use or anticipated need for drugs that are known strong CYP3A4/5 inducers, including their administration with 10 days prior to patient enrollment (eg, phenobarbital, rifampin, phenytoin, carbamazepine, rifabutin, rifapentin, clevidipine, St John's wort).
23. Pregnant female patients, breastfeeding female patients.
24. Other severe acute or chronic medical conditions including colitis, inflammatory bowel disease, uncontrolled asthma, and pneumonitis or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or investigational product 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.

Table S2. Assessments for neurocognitive function and Health-Related Quality of Life (HRQoL)

HRQoL*	European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (EORTC QLQ-C30), including the brain module (EORTC QLQ-BN20)
Neurocognitive function*	Computerized cognitive assessment (Cogstate) with a test battery assessing processing speed, verbal memory, verbal learning and working memory
* Assessments were performed at baseline (before the start of the treatment), at week 9 (follow-up 1), and thereafter every 12 weeks, in between neuro-oncological tumour response assessments.	

80 **Table S3.** Descriptive statistics of HRQoL and cognitive function at baseline.

		N	*Mean*	*SD*
Cogstate				
log10ms	Psychomotor function	49	2.63	0.12
log10ms	Attention	49	2.83	0.10
log10ms	Working memory	48	3.04	0.14
# correct responses	Verbal learning	49	16.49	7.25
# correct responses	Memory	49	5.35	3.11
HADS (scores 0 - 21)	Anxiety	47	6.85	4.47
	Depression	49	7.41	4.46
EORTC-C30 (scores 0 - 100)	Global Health	49	51.36	21.74
	Physical functioning	49	59.32	26.40
	Role functioning	49	50.00	33.51
	Emotional functioning	50	68.00	26.96
	Cognitive functioning	50	61.00	30.42
	Social functioning	50	62.00	31.41
	Fatigue	50	54.44	26.30
	Nausea and vomiting	49	7.48	12.76
	Pain	50	17.00	25.08
	Dyspnoea	49	14.29	22.57
	Insomnia	49	27.89	32.17
	Appetite loss	49	15.65	29.74
	Constipation	50	12.00	21.04
	Diarrhoea	49	6.12	17.58
	Financial difficulties	50	21.33	31.41
EORTC-BN20 (scores 0 - 100)	Future uncertainty	49	39.29	27.74
	Visual disorder	49	18.82	21.54
	Motor dysfunction	49	28.57	24.53
	Communication deficit	49	30.84	32.10
	Headaches	49	22.45	30.72
	Seizures	49	5.44	15.73

Drowsiness	49	31.29	29.19
Itchy skin	49	7.48	20.71
Hair loss	49	8.16	21.01
Weakness of legs	49	16.33	26.46
Bladder control	49	9.52	18.00