Informed Consent Form.

Project Name: Multicenter, randomized, controlled, open-label Phase II clinical study of Stupp regimen with or without lenvatinib in the treatment of newly diagnosed glioblastoma with methylated MGMT promoter

Version number of the Informed Consent Form: 1.1, dated May 17,2026

Department responsible for the project: Oncology Department

Dear Sir/Madam:

Hello! We invite you to participate in a clinical study: a multicenter, randomized, controlled, open-label Phase II clinical trial evaluating the Stupp regimen with or without lenvatinib for the treatment of newly diagnosed glioblastoma with MGMT promoter methylation positivity. This study is initiated by Dongguan People's Hospital and will run from March 2026 to March 2029, with an expected enrollment of 138 subjects. To safeguard your rights, both the study protocol and informed consent form have been approved by the ethics committee. It is crucial for you to read and understand this informed consent form before agreeing to participate in the study. The document outlines the objectives, procedures, potential benefits, and risks associated with the study, as well as alternative treatment options available and your rights. Please review it carefully, if you have any questions, please consult the study investigator. Your participation in this study is voluntary, and you may withdraw at any stage. If you decide to participate, you will receive a signed copy of the informed consent form. If you choose not to participate, alternative options include receiving post-standardized therapy as recommended by your treating physician.

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I. Research Objectives

Efficacy and safety comparison of lenvatinib combined with the standard Stupp regimen versus the standard Stupp regimen in the treatment of newly diagnosed glioblastoma with MGMT promoter methylation positivity

II. Selection Criteria

1. Selection Criteria:

(1) Initial patients were diagnosed with promoter methylated glioblastoma through postoperative pathology or biopsy, and had not received radiotherapy or chemotherapy.

(2) The time between surgery or biopsy and enrollment should not exceed 21 days.

(3) Age range: 18–75 years;

(4) KPS score ≥ 70;

(5) The functions of major organs meet the following criteria (no use of any blood components or cell growth factors is permitted within 14 days):

a. Neutrophil ANC ≥ 1.5×10 ^{9}/L; platelet count (PLT) ≥ 100×10 ^{9}/L; hemoglobin (HB) ≥ 90 g/L.

b. Total bilirubin ≤ 1.5 × ULN;

c. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels ≤ 3 × upper limit of normal (ULN).

d. Serum creatinine ≤ 1.5 × upper limit of normal (ULN), or creatinine clearance ≥ 50 mL/min (calculated using the Cockcroft-Gault formula);

(6) Life expectancy ≥ 12 weeks;

(7) The dose of glucocorticoids administered within 14 days prior to enrollment was stable or declining.

(8) Fertile males and women of childbearing age are required to use effective contraceptive measures from the date of signing the informed consent form until 6 months after the last administration of the trial drug; women of childbearing age include premenopausal women and those within 2 years post-menopause. Women of childbearing age must have a negative blood pregnancy test result within ≤7 days prior to the first administration of the trial drug.

(9) All participants voluntarily enrolled in this study, signed the informed consent form, demonstrated good compliance, and cooperated with follow-up visits.

2. Exclusion Criteria:

(1) History of allergy to either lenvatinib, temozolomide, or any of their components;

(2) History of other malignant tumors within the past 5 years or concurrent diagnosis thereof, or prior receipt of any antitumor therapy;

(3) Subjects participating in another clinical study are excluded, except for observational studies.

(4) There were significant comorbidities present prior to enrollment that could interfere with temozolomide or lenvatinib therapy.

a. Grade 4 non-hematologic toxicity, excluding alopecia, nausea, and vomiting (CTCAE 5.0)

b. It may interfere with the efficacy of oral medications, including dysphagia, chronic diarrhea, or intestinal obstruction.

(5) Evidence of elevated intracranial pressure (midline shift> 5 mm, clinically significant papilledema, vomiting, nausea, or decreased level of consciousness);

(6) A history of psychiatric medication abuse, alcoholism, or drug use is known;

(7) Women who are pregnant or breastfeeding;

(8) Other conditions deemed by investigators to potentially affect subject safety or trial adherence include, but are not limited to, unstable cardiac disease, kidney disease, poorly controlled diabetes, and mood disorders.

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III. Research Content and Process

This trial is a prospective, multicenter, Phase II randomized controlled clinical study designed to compare the efficacy of lenvatinib combined with temozolomide plus radiotherapy versus temozolomide combined with radiotherapy in treating promoter methylation-positive glioblastoma, using progression-free survival as the primary endpoint while also evaluating efficacy and safety to inform subsequent Phase III studies. The study was divided into a control group receiving temozolomide chemotherapy plus radiotherapy and an experimental group receiving lenvatinib and temozolomide combined with radiotherapy

For the treatment group, 69 subjects were planned to be included in each group, totaling 138 subjects to be enrolled.

Grouping criteria: Patients meeting the aforementioned inclusion/exclusion criteria were randomly assigned in a 1:1 ratio to either the treatment group (lenvatinib-temozolomide group) or the control group (temozolomide group). Stratification factor: Type of surgery (total resection vs. non-total resection). Randomization was performed using a web-based centralized randomization system with block randomization, employing the minimization method based on the semi-randomized variance analysis proposed by Freedman and White. Treatment initiation must commence within 1 week after randomization.

If you agree to participate in this study, each participant will be assigned a unique identifier and a medical record file will be established. During treatment and follow-up periods, researchers will use designated clinical observation forms to collect all data requiring monitoring. We will collect certain biological samples from you, which will be collected by qualified professionals; these samples are intended solely for research purposes.

The treatment regimen for the subjects primarily included the following: (1) Radiotherapy: Adjuvant radiotherapy was initiated 2–6 weeks postoperatively, with a total dose of 60 Gy administered at 2.0 Gy per session for a total of 30 sessions over 6–7 weeks. (2) Chemotherapy: 1) In the temozolomide group, patients received daily oral temozolomide (75 mg/m², once daily) during radiotherapy, followed by 6 cycles of maintenance therapy with temozolomide (150–200 mg/m², taken orally for 5 days followed by a 23-day break, administered every 4 weeks) starting 4 weeks after radiotherapy completion. 2) In the lenvatinib-temozolomide group, patients received daily oral temozolomide (75 mg/m², once daily) and lenvatinib (20 mg, once daily) during radiotherapy, followed by 6 cycles of maintenance therapy with temozolomide (150–200 mg/m², taken orally for 5 days followed by a 23-day break, administered every 4 weeks) starting 4 weeks after radiotherapy completion; lenvatinib was continued orally (20 mg, once daily) until tumor progression or intolerable toxicity occurred.

During the combined chemoradiotherapy phase: For each treatment cycle, record the initiation time, completion time, cycle number, administered drugs and their dosages. Document the patient's general condition, adverse effects of therapy, weekly results of complete blood count (CBC), biochemical tests, and coagulation function assays; also note efficacy evaluations obtained via cranial MRI and other imaging studies after combination therapy. During the maintenance therapy phase: For each treatment cycle, record the initiation time, completion time, cycle number, administered drugs and their dosages. Record the patient's general condition, adverse reactions, CBC results, coagulation parameters, and blood biochemical profiles prior to each treatment cycle.

After chemotherapy completion, subjects were to be followed up at least once every 3 months (±7 days) until death or study completion. Subjects who could not be followed up for more than 6 months for any reason were considered lost to follow-up. Follow-up assessments included physical examinations (primarily neurological examinations), KPS scores, hematological tests, biochemical tests, and cranial MRI scans.

During the study, with your consent, biopsy specimens or 15 uncolored tumor tissue sections/wax blocks suitable for testing were collected. Blood samples were collected at three time points: prior to the first dose administration, after radiotherapy completion (before initiation of maintenance therapy), and upon disease progression (or at study completion) for scientific research purposes (details see Section VI: Acquisition of Biological Samples).

IV. Potential Benefits of Participating in This Study

- During the course of the study, experienced research physicians will actively monitor changes in your condition and provide timely, detailed

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Guidance and Treatment: Your condition may improve with effective treatment.

- The clinical study you participated in may be published as a research paper, providing novel, highly effective, and low-toxicity therapeutic approaches for a broad population of patients receiving first-line treatment for glioblastoma.

V. Potential Risks and Discomforts Associated With Participation in This Study

Temozolomide is a commonly used chemotherapeutic agent for gliomas. Its adverse reactions primarily include: Gastrointestinal reactions: nausea (incidence approximately 53%), vomiting (incidence approximately 42%), constipation (incidence approximately 33%), abdominal pain, diarrhea, and dyspepsia; Hematologic and lymphatic system reactions: neutropenia (incidence approximately 12%), thrombocytopenia (incidence approximately 8%), leukopenia, and lymphopenia; Neurological reactions: headache (incidence approximately 23%), convulsions, dizziness, somnolence, confusion, paresthesia, anxiety, and insomnia; Cutaneous and subcutaneous tissue reactions: alopecia, rash (very common, incidence>1/10), xerosis cutis, pruritus, and erythema; Systemic symptoms: fatigue (very common, incidence>1/10), fever, pain, and dysgeusia; Metabolic and nutritional abnormalities: anorexia (very common, incidence>1/10) and weight loss; Hepatic toxicity: elevated alanine aminotransferase (ALT).

Lenvatinib is a common multi-target tyrosine kinase inhibitor (TKI). Relevant studies have demonstrated its therapeutic value in gliomas. Common adverse effects observed in patients treated with lenvatinib predominantly occur during the early stages of therapy, including: hypertension (highly prevalent in the early treatment phase), which may manifest as varying degrees of elevated blood pressure and, in severe cases, lead to critical complications such as aortic dissection; proteinuria (also highly prevalent in the early treatment phase), characterized by abnormal urinary protein levels during therapy, with severe cases potentially inducing nephrotic syndrome; renal impairment, often resulting from gastrointestinal toxicity-induced dehydration or hypovolemia, leading to renal insufficiency or even renal failure; cardiac abnormalities (heart failure incidence <1%), with risks of heart failure and decreased left ventricular ejection fraction; reversible postencephalitic syndrome (incidence <1%), presenting with neurological symptoms such as headache, drowsiness, confusion, visual disturbances, and epilepsy; hepatotoxicity, frequently causing liver injury, with high-risk patients at risk of hepatic encephalopathy, renal failure, or even fatal liver injury; arterial thromboembolism, potentially triggering cerebrovascular accidents, cerebral ischemia, myocardial infarction, or other thrombotic disorders; hemorrhage, often associated with tumor-related bleeding involving multiple sites (intracranial, hepatic, pulmonary, or airway) with life-threatening risks; and fistula formation or gastrointestinal injuries, which may lead to gastrointestinal perforation, gastrointestinal fistulas, or non-gastrointestinal fistulas involving the trachea, esophagus, skin, or reproductive tract. Abnormal wound healing can delay recovery and increase the risk of poor postoperative healing; prolonged QT interval may lead to an extended QT/QTc ratio on electrocardiogram, with the risk being higher when combined with electrolyte disturbances; diarrhea (highly prevalent and frequently reported during early treatment phases), particularly severe cases, can cause dehydration; thyroid dysfunction, often manifesting as hypothyroidism, may impair normal regulation of thyroid-stimulating hormone. The clinical management principles for these adverse effects are well-established, resulting in relatively low risks. Should any adverse event attributable to participation in this clinical study occur and cause harm, physicians will provide appropriate treatment; medical incidents will be handled according to established medical dispute procedures.

VI. Acquisition of Biological Samples

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Biological tissue samples: With the approval of the ethics committee, all subjects who have signed an informed consent form are required to provide 15 uncolored tumor tissue sections or tissue wax blocks suitable for testing during the screening phase.

Blood biomarkers: At three time points—before the first dose administration, after radiotherapy completion (before initiation of maintenance therapy), and during disease progression (or at study completion)—collect 4 mL of blood samples at each time point and store them in accordance with laboratory specifications.

Using tumor tissue specimens provided during the screening phase, we employed next-generation sequencing (NGS) or immunohistochemistry (IHC) techniques to investigate genetic status—including TERT promoter mutations, 1p/19q deletions, and BRAF V600E—and to assess the correlation between expression levels of lenvatinib-related targets (e.g., VEGFR 1–3, FGFR 1–4, PDGFR α/β) and patients' progression-free survival (PFS) or overall survival (OS).

Using blood samples collected at three time points—before the initial administration, after radiotherapy completion, and during disease progression—to monitor dynamic changes in circulating vascular growth factors (e.g., VEGF, PlGF, sVEGFR2) or circulating tumor DNA (ctDNA) levels.

Investigate whether the early dynamic decline of blood biomarkers (e.g., changes from baseline after radiotherapy completion) can serve as predictive indicators for early efficacy evaluation of the lenvatinib combination regimen, and compare baseline tissue samples with progressive disease blood samples to analyze potential mechanisms of acquired resistance.

The aforementioned blood and tissue specimens will be sent to Nanjing Shihe Gene Biotechnology Co., Ltd. for comprehensive high-throughput genomic sequencing of cancer (covering all exons and selected intronic regions of 463 genes), with the results intended to guide subsequent treatment. All specimens will be handled strictly in accordance with established protocols and immediately destroyed by the testing laboratory upon use.

VII. Confidentiality of the Study

If you decide to participate in this study, your participation and personal data collected during the study will be kept confidential. Your tissue/blood samples will be identified by a study identification number rather than your name, and will be disposed of in accordance with medical regulations upon study completion. Any information that could identify you will not be disclosed to members outside the research team unless with your explicit consent. All study participants and the sponsor are required to maintain confidentiality regarding your identity. Your records will be stored in a locked filing cabinet accessible only to researchers. To ensure compliance with regulations, members of government authorities or ethics committees may access your personal data at the study site when necessary. No personal information about you will be disclosed upon publication of the study results.

VIII. Regarding Research Costs, Compensation, and Damages

- Costs of pharmaceuticals and related diagnostic tests used in the laboratory

The lenvatinib used in the clinical trials conducted by the institute is provided free of charge by our center. In contrast, temozolomide therapy, postoperative radiotherapy, and regular follow-up examinations constitute the standard treatment regimen and monitoring protocol for gliomas; consequently, the associated costs must be borne by the patients themselves and covered by their personal health insurance coverage.

- Compensation for participating in the study

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- Medical and Compensation for Research-Related

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This study has purchased clinical trial liability insurance. In the event of any harm related to this clinical study, you will receive timely and appropriate medical treatment. If harm exceeding the expectations of this clinical study occurs, you will receive prompt and appropriate medical care along with compensation. However, if the harm results from the natural progression of the subject's pre-existing condition or arises from the subject's violation of the trial protocol, such incidents shall not fall within the scope of the investigator's liability.

IX. Alternative Solutions

- Temozolomide + radiotherapy + electric field therapy
- Other treatment options recommended by clinicians.

X. Your Rights and Obligations

You may choose not to participate in this study or notify the investigator at any time to request withdrawal. Your decision will not affect your relationship with healthcare providers, nor will it impact your medical benefits, rights, or medical care; you will not face any unfair treatment or penalties. If you decide to withdraw from the study, please务必 contact your research physician. Should you discontinue treatment or examinations during the study period, the research physician may ask health-related questions and may require additional tests for the purpose of safeguarding your health.

If you require additional treatment, fail to adhere to the study protocol, or if your principal investigator determines that continuing participation in this study does not serve your best interests, the investigator may request your withdrawal from the study. If you experience adverse events or safety concerns during treatment under the clinical trial protocol, the investigator or sponsor may require your withdrawal without prior consent; in such cases, the investigator will discuss the subsequent procedures with you.

You may access information and updates regarding this study at any time. If you have questions related to this study, experience any discomfort or injury during the research process, or have concerns about the rights of participants, please contact Liu Zhigang at 18627585860. For inquiries regarding your rights as a study participant, please contact the Medical Ethics Committee of Dongguan People's Hospital at telephone number (28636365).

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Acknowledgements

The advancement of medical science relies heavily on clinical research. Your participation will contribute significantly to the progress of medical science and to the investigation and exploration of this disease's diagnosis and treatment. As the investigators and sponsors of this study, we will always cherish your contribution and extend our deepest gratitude to you.

Informed Consent Form. Consent Signature Page

Prior to signing this informed consent form, I have read the aforementioned information and understood the purpose of this study as well as the potential benefits and risks associated with participation. I confirm that I have given thorough consideration to the matter and had the opportunity to raise any questions regarding the research protocol and the multicenter, randomized, controlled, open-label Phase II clinical trial evaluating the combination or non-combination use of lenvatinib with or without MGMT promoter methylation therapy in newly diagnosed glioblastoma patients with positive MGMT promoter methylation. All my inquiries have been satisfactorily addressed.

I consent to the research physician collecting and processing my information, including data related to my health. I agree that my information (excluding personal information) will be processed by the sponsor or transferred to companies collaborating with the sponsor. If I decide to withdraw from this study, I consent that any information collected prior to my withdrawal may continue to be processed.

I have the right to receive consulting services at any time and the right to withdraw from this research program at any time without suffering any adverse effects or losing any legitimate rights. I voluntarily sign this informed consent form, participate in this research project, and will fully cooperate with the investigators. I have received a copy of this document.

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Name (standard script)_____ sign one's name：_____

contact number：_____ date：_____year___moon___sun___Time___Section

Legal Representative / Legal Guardian

Name (standard script)_____ sign one's name：_____ Relationship with the subject:_____

contact number：_____ date：_____year___moon___sun___Time___Section

Statement of a Fair Witness

I confirm that the information in the consent form has been accurately explained and understood by the patient and/or the patient's legal representative, and that the consent was voluntarily provided by the patient and/or the patient's legal representative.

Name (standard script)_____ sign one's name：_____

contact number：_____ date：___year___moon___sun___Time___Section

Note: If the patient, legal guardian, or legal representative is unable to read and sign the consent form (e.g., due to severe visual impairment, dyslexia, or illiteracy), at least one impartial witness must be present. The impartial witness must remain present throughout the entire discussion of the informed consent form.

I have accurately informed the subject of the contents of the informed consent form and addressed all questions raised by the subject; the subject has voluntarily participated in this clinical study.

Researcher's Signature:____ contact number：___ date：___year__moon__ sun__Time__Section

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