Informed Consent Form

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AF42 Informed Consent Form for Human Research at The Second Affiliated Hospital of Zhejiang University School of Medicine

Dear patient:

We invite you to participate in a clinical study entitled “Intensified Adjuvant Therapy for High-Risk Newly Diagnosed Glioblastoma With Subtotal Resection or Short-Term Progression: A Prospective, Single-Arm Phase II Clinical Study.” Before you decide whether to participate in this study, please carefully read the following content. It can help you understand the study, why the study is being conducted, the study procedures and duration, and the possible benefits, risks, and inconveniences of participation.

The following is an introduction to this study:

I. Study Background and Study Purpose

1. Epidemiological Background of Glioblastoma

Brain glioma refers to tumors originating from glial cells and is the most common primary intracranial tumor [1]. The 2021 WHO Classification of Tumors of the Central Nervous System classifies brain gliomas into grades 1-4; grades 1 and 2 are low-grade gliomas, and grades 3 and 4 are high-grade gliomas. The incidence of brain glioma in China is 5-8 per 100,000, and its 5-year mortality rate among systemic tumors is second only to pancreatic cancer and lung cancer. Brain glioma is characterized by high disability and high recurrence rates, seriously threatening patients' lives, impairing quality of life, and imposing heavy psychological and economic burdens on patients, families, and society.

Glioblastoma (GBM) is a WHO grade 4 high-grade glioma and is the most common primary malignant tumor of the adult central nervous system, accounting for approximately 57% of all brain gliomas and 48% of all primary malignant tumors of the central nervous system [2]. GMB is the most aggressive malignant brain tumor and has an extremely poor prognosis, with a 1-year survival rate of approximately 40.6% and a 5-year survival rate of only 5.6% [3].

2. Standard Treatment for Newly Diagnosed Glioblastoma

The treatment of newly diagnosed GBM is based primarily on surgical tumor resection, combined with radiotherapy, chemotherapy, and other comprehensive treatments. Maximal safe tumor resection combined with postoperative involved-field radiotherapy and concurrent and adjuvant temozolomide (TMZ) chemotherapy (the Stupp regimen) is the standard first-line treatment for newly diagnosed GBM [4]. In patients with newly diagnosed GBM treated with the Stupp regimen, the median overall survival (OS) is 14.6 months, the 2-year OS rate is 26.5%, and the 2-year PFS rate is 10.7%. Different from the Stupp regimen, in which oral TMZ begins on the first day of radiotherapy, the Department of Neurosurgery at Huashan Hospital in Shanghai conducted a multicenter clinical study of early postoperative TMZ chemotherapy (2 weeks after surgery), followed by concurrent chemoradiotherapy (the START regimen). The results showed that the median OS in the START regimen group reached 17.6 months, significantly superior to the Stupp regimen [5]. According to the 2024 NCCN, SNO-EANO, and the Chinese Guidelines for the Diagnosis and Treatment of Brain Glioma (2022 edition), surgery, postoperative radiotherapy, and TMZ chemotherapy are currently the standard treatment for newly diagnosed GBM. However, even with standard surgery and chemoradiotherapy, the median OS of GBM patients is approximately 15-18 months, and the 5-year OS rate still remains below 10%. Once GBM recurs, the median OS is estimated to be only 24-44 weeks. Therefore, exploring how to improve treatment efficacy and prognosis is of great significance for patients with GBM.

3. Treatment Advances in Newly Diagnosed Glioblastoma

In recent years, to further improve the prognosis of GBM patients, multiple clinical studies have continuously explored optimal comprehensive treatment strategies for newly diagnosed GBM, including prolonging the duration of adjuvant TMZ chemotherapy, combining other chemotherapeutic drugs, combining anti-angiogenic agents, combining immunotherapy, and tumor-treating fields. Concurrent chemoradiotherapy followed by 6 cycles of adjuvant TMZ

chemotherapy is the standard treatment for GBM patients. A randomized phase II GEINO14-01 clinical trial explored whether extending adjuvant TMZ cycles could improve prognosis. A total of 159 patients were analyzed; the control group received the standard Stupp regimen, and the experimental group received more than 6 cycles of TMZ chemotherapy. The results showed no significant differences in 6-month PFS or OS between the two groups [6].

Several clinical studies have explored the efficacy of combination therapy based on the Stupp regimen. The AVAglio clinical study showed that bevacizumab combined with radiotherapy and TMZ prolonged the median PFS of newly diagnosed GBM patients by 4.4 months, but did not improve OS [7]. A randomized, open-label phase III CeTeG/NOA-09 clinical trial initiated by the Neuro-Oncology Working Group of the German Cancer Society analyzed the value of lomustine combined with TMZ in GBM patients. The results showed that the combination achieved an overall OS of 48.1 months in GBM patients with MGMT promoter methylation, compared with 31.4 months with TMZ alone [8]. On the basis of the Stupp regimen, adding tumor-treating fields (TTF) during adjuvant TMZ prolonged the median OS of patients with newly diagnosed GBM by 4.9 months and increased the 5-year survival rate to 13% [9]. Based on the significant efficacy of combined anti-CTLA-4 and anti-PD-1 immunotherapy in preclinical GBM models, a phase I clinical study, NRG-BN002, evaluated the safety of immune checkpoint inhibitors alone or in combination in newly diagnosed GBM. Combined anti-CTLA-4 and anti-PD-1 immunotherapy had good tolerability and safety, with median OS and PFS of 20.7 months and 16.1 months, respectively [10], superior to the standard Stupp regimen. These findings support subsequent phase II/III clinical trials of combined immunotherapy in newly diagnosed GBM patients. The above clinical data suggest that adjuvant TMZ combined with other treatment modalities can improve patient prognosis to a certain extent.

In addition, because radiotherapy is an independent factor affecting survival in GBM patients, exploring whether increasing radiotherapy intensity can further improve prognosis has long been an important area of clinical research. In multiple exploratory studies based on metabolic imaging-guided focal high-dose irradiation, a meta-analysis including 22 prospective clinical studies showed that dose escalation to 62.5 Gy to 80 Gy, compared with the standard dose of 60 Gy, did not significantly improve prognosis [11]. This may be related to failure to distinguish gross total resection from subtotal resection or short-term recurrence, and to increased radiotherapy-related adverse reactions because the high-dose region included both residual lesions and the entire tumor bed. A small-sample retrospective analysis of 22 high-risk GBM cases at our center showed that a radiotherapy regimen delivering a high dose of 66 Gy to residual or recurrent lesions, standard doses of 60 Gy to high-risk regions, and 54 Gy to low-risk regions increased mPFS from 5.15 months to 12.3 months (unpublished data). Therefore, delivering small-field high-dose irradiation only to residual or recurrent lesions while delivering current standard-dose radiotherapy to the tumor bed and surrounding high-recurrence-risk areas may further improve survival benefit in GBM patients while controlling radiotherapy-related adverse reactions.

4. Patients With Subtotal Resection or Short-Term Recurrent/Progressive GBM Have a Worse Prognosis

The extent of surgical resection is an independent prognostic factor in GBM patients [12]. A retrospective analysis of 500 patients with newly diagnosed GBM evaluated the effect of extent of surgical resection on prognosis. The results showed that patients with 100%, 90%, 80%, and 78% resection had OS of 16 months, 13.8 months, 12.8 months, and 12.5 months, respectively [13]. This study suggests that patients with subtotal resection or short-term postoperative recurrence/progression require stronger postoperative adjuvant treatment strategies to further improve survival. However, at present, the postoperative adjuvant treatment regimen for GBM patients with subtotal resection or short-term recurrence/progression before postoperative radiotherapy is the same as that for patients with gross total resection. No clinical study has been conducted specifically in the population of patients with subtotal resection or short-term postoperative recurrence/progression to evaluate intensified postoperative adjuvant treatment. Therefore, the benefit of intensified adjuvant therapy in patients with subtotal resection or short-term postoperative recurrence/progression requires further exploration in prospective clinical studies.

In summary, among patients with newly diagnosed GBM with subtotal resection or short-term recurrent/progressive disease, investigating the benefits of intensified adjuvant therapy based on the Stupp regimen in terms of PFS rate, OS

rate, quality of life, and other outcomes will help further optimize comprehensive treatment strategies for GBM patients. Here, we conduct a prospective, single-arm phase II clinical study to explore the efficacy and safety of an intensified treatment regimen consisting of focal high-dose radiotherapy to residual or recurrent lesions and TMZ combined with immunotherapy and anti-angiogenic therapy during the adjuvant phase, thereby providing evidence for optimal comprehensive treatment choices for more patients with GBM.

II. Specific Procedures and Process

This study is a prospective, open-label phase II clinical study for high-risk newly diagnosed GBM patients with subtotal resection or short-term recurrence/progression before radiotherapy. On the basis of the standard Stupp regimen, the radiotherapy dose will be increased during the postoperative concurrent chemoradiotherapy phase, and immunotherapy plus anti-angiogenic drugs will be combined during the adjuvant phase as intensified therapy. Participants will undergo screening evaluation according to the inclusion and exclusion criteria of the protocol, within 28 days before randomization. Patients who agree to participate in this study will sign the informed consent form (ICF) before undergoing any screening procedures. After completion of all screening activities, eligible enrolled patients may begin study treatment. According to the sample size estimate, a total of 60 participants are planned to be enrolled. For postoperative residual lesions or short-term postoperative recurrent/progressive lesions, focal high-dose irradiation of PGTV 66 Gy/30F will be delivered; the high-risk area around the tumor bed will receive PTV1 60 Gy/30F, and the low-risk area will receive PTV2 54 Gy/30F. Immunotherapy combined with anti-angiogenic drug therapy will begin on day 1 of adjuvant treatment, with intravenous PD-1 monoclonal antibody 200 mg and bevacizumab 10 mg/kg, with 21 days as one cycle, and an expected total of 18 cycles. Complete blood count, liver and kidney function, myocardial enzymes, thyroid function, and electrocardiogram will be reviewed weekly, and cranial MR will be reviewed every 4 weeks to evaluate efficacy and toxicities, with follow-up observation. The study period begins on 2025-12-01 and ends on 2027-12-31, to explore the efficacy of intensified adjuvant therapy for high-risk newly diagnosed glioblastoma with subtotal resection or short-term progression.

III. What You Need to Do If You Participate in the Study

You will undergo screening evaluation according to the inclusion and exclusion criteria of this protocol. If you agree to participate, you will sign the informed consent form (ICF). After all screening activities are completed, if you are eligible for enrollment, you may begin study treatment according to the assigned regimen after randomization. Complete blood count, liver and kidney function, myocardial enzymes, thyroid function, and electrocardiogram will be reviewed weekly, and cranial MR will be reviewed every 4 weeks to evaluate efficacy and toxicities.

You may voluntarily withdraw from the study at any time, or you may be required to withdraw from the study by the investigator or sponsor for safety or behavioral reasons, or because you are unable to comply with the study visit schedule or procedures required by the protocol.

IV. Possible Benefits of Participating in This Study

1. Personal benefits: For glioblastoma, the current standard treatment is the Stupp regimen. However, the postoperative adjuvant treatment for newly diagnosed GBM patients with subtotal resection or short-term recurrence/progression before postoperative radiotherapy is currently the same as that for patients with gross total resection, and there is no postoperative intensified adjuvant therapy specifically for patients with subtotal resection or short-term postoperative recurrence/progression. The main purpose of this regimen is to improve recurrence-free survival and further improve quality of life for subjects; at the same time, the entire treatment process allows close follow-up and attention from investigators. However, you may also receive no benefit.

2. Social benefits: To explore whether intensified treatment for newly diagnosed GBM patients with subtotal resection or short-term postoperative recurrence/progression can provide further survival benefit, promote the further

development of clinical research, facilitate the development of more effective drugs, modify standard treatment regimens, and promote public health.

V. Possible Adverse Reactions, Risks, and Risk Prevention Measures Associated With Participation in This Study

Common adverse reactions of immunotherapy: pneumonitis, diarrhea, colitis, hepatitis, nephritis, gastritis, etc.; endocrine disorders such as hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency, hyperglycemia, or type 1 diabetes mellitus; skin-related adverse reactions, including Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN); thrombocytopenia; and other immune-related adverse reactions such as pancreatitis/myocarditis/encephalitis.

Common adverse reactions of anti-angiogenic therapy: hypertension, proteinuria, bleeding, thrombosis, arterial thromboembolism, etc.

Common adverse reactions of high-dose radiotherapy: cerebral edema, radiation necrosis, memory decline, cognitive decline, etc.

To prevent risks, investigators will closely observe and follow up throughout the treatment period and manage issues in a timely manner. If a study-related serious adverse event occurs, we will promptly contact your agent, and the hospital will seek compensation for you in accordance with relevant laws and regulations.

VI. Description of Costs

Current routine treatment does not require the study drugs. The experimental group implements a buy-one-get-one-free program (provided first, then purchased). Radiotherapy costs will not increase. The price of sintilimab is RMB 1,080 per vial; each cycle requires RMB 2,160, and each patient requires 18 cycles, totaling 2160 x 18 = RMB 38,880. The buy-one-get-one-free program (provided first, then purchased) can reduce the patient's economic burden by 50%, saving a total of RMB 19,440. Bevacizumab anti-angiogenic therapy is a standard treatment for recurrent glioblastoma. The price is RMB 1,126 per vial; each cycle requires RMB 4,504, and each patient requires 18 cycles, totaling 4504 x 18 = RMB 81,072. It can be covered by medical insurance.

VII. Compensation for Participation, Including Compensation for Injury

Transportation expenses: RMB 100 per visit.

There is no special reduction or exemption for imaging examinations in the experimental group and control group.

If injury is caused by the study, we will provide active treatment, and the relevant costs will be fully waived.

VIII. Alternative Options

If subjects do not participate in this study or withdraw from the study, they may continue to receive routine standard diagnosis and treatment, or may participate in other studies.

IX. Confidentiality of Your Personal Information

Your medical records (including study medical records and physical/chemical examination reports) will be stored in the hospital as required. Except for investigators, ethics committee, monitors, auditors, drug regulatory authorities, and other relevant personnel who will be allowed to access your medical records, other persons unrelated to the study have no right to access your medical records without permission. Public reports of the results of this study will not disclose

your personal identity. We will make every effort, within the permitted scope, to protect the privacy of your personal medical information.

X. Termination of Participation in the Study

Participation in this study is entirely voluntary. You may refuse to participate in this study or withdraw from the study at any time without giving a reason. This will not affect your relationship with your doctor, your medical care, or cause any other loss of benefits. In addition, your participation in this study may be terminated for the following reasons:

1. You fail to follow the study doctor's medical instructions.

2. You develop a serious condition that may require treatment.

3. The study doctor believes that terminating the study is in the best interests of your health and welfare.

XI. Ethics Committee

This study has been reported to the Human Research Ethics Committee of The Second Affiliated Hospital of Zhejiang University School of Medicine, has undergone comprehensive review by the committee, including assessment of risks to subjects, and has been approved. During the study, for matters related to ethics and rights, please contact the Human Research Ethics Committee of The Second Affiliated Hospital of Zhejiang University School of Medicine. Telephone: daytime 0571-87783759; nighttime (general duty): 13757118366; email address: HREC2013@126.com

I confirm that I have read and understood the informed consent form for this study, voluntarily accept the treatment methods in this study, and agree that my medical data may be used for publication of this study.

Subject signature: _____ Contact information: _____ Date: _____

Agent signature: _____ Relationship to subject: _____ Contact information: _____ Date: _____

(If needed)

Witness (if needed): _____ Contact information: _____ Date: _____

I confirm that I have explained the details of this study to the patient, including his/her rights and possible benefits and risks, and have provided him/her with a signed copy of the informed consent form.

Investigator signature: _____

Contact information: _____ (mobile phone) Date: _____