Enhanced Adjuvant Therapy for Newly Diagnosed Glioblastoma With Partial Surgical Resection or Short-term Progression: a Bayesian Adaptive Randomized Phase II Study

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Informed Consent Form

Dear patient:

We invite you to participate in a clinical study on "Enhanced Adjuvant Therapy for Newly Diagnosed Glioblastoma with Surgical Partial Resection or Short Term Progression: Bayesian Adaptive Randomized Phase II Study". Before deciding whether to participate in this study, please carefully read the following content, which can help you understand the study and why it was conducted, the procedure and duration of the study, and the potential benefits, risks, and inconveniences that may arise from participating in the study.

The following is an introduction to this study:

1、 Research background and purpose

1.1 Epidemiological background of glioblastoma

Brain glioma refers to a tumor originating from brain glial cells and is the most common primary intracranial tumor. The 2021 edition of the WHO Central Nervous System Tumor Classification categorizes gliomas into grades 1-4, with grades 1 and 2 being low-grade gliomas and grades 3 and 4 being high-grade gliomas. The incidence rate of brain glioma in China is 5-8/100000, and the 5-year mortality rate is only second to pancreatic cancer and lung cancer in general tumors. Gliomas have high disability and recurrence rates, posing a serious threat to patients' lives, affecting their quality of life, and imposing heavy psychological and economic burdens on individuals, families, and even society.

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

1.2 Standard treatment for newly diagnosed glioblastoma

The treatment for newly diagnosed GBM mainly involves surgical resection of the tumor, combined with comprehensive treatment methods such as radiotherapy and chemotherapy. The combination of tumor resection within the maximum safe range, postoperative radiation therapy involving the field, and concurrent and adjuvant Temozolomide (TMZ) chemotherapy (Stupp regimen) is the standard first-line treatment for newly diagnosed GBM [4]. The median overall survival (OS) of newly diagnosed GBM patients treated with Stupp regimen was 14.6 months, with a 2-year OS rate of 26.5% and a 2-year PFS rate of 10.7%. Unlike the Stupp regimen, which started oral administration of TMZ on the first day of radiotherapy, the neurosurgery department of Huashan Hospital in Shanghai conducted a multicenter clinical study (START regimen) using TMZ chemotherapy in the early postoperative period (2 weeks after surgery) of GBM, followed by synchronous radiotherapy and chemotherapy. The results showed that the median OS of the START regimen group could reach 17.6 months, significantly better than the Stupp regimen [5]. According to the 2024 NCCN, SNO-EANO, and the Chinese Guidelines for the Diagnosis and Treatment of Gliomas (2022 edition), surgery, postoperative radiotherapy, and TMZ chemotherapy are currently the standard treatment options for newly diagnosed GBM. However, even with standard treatments such as surgery and chemotherapy, the median OS of GBM patients is about 15-18 months, and the 5-year OS rate is still less than 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 GBM patients.

1.3 Progress in the treatment of newly diagnosed glioblastoma

In recent years, in order to further improve the prognosis of GBM patients, multiple clinical studies have been conducted to determine the optimal comprehensive treatment plan for newly diagnosed GBM

Continuous exploration, including extending the duration of TMZ adjuvant chemotherapy, combining other chemotherapy drugs, combining anti vascular drugs, combining immunotherapy, and electric field therapy. Simultaneous chemoradiotherapy combined with TMZ adjuvant chemotherapy for 6 cycles is the standard treatment regimen for GBM patients. A phase II randomized GEINO14-01 clinical study explored whether prolonging the TMZ adjuvant therapy cycle could improve patient prognosis. A total of 159 patients were analyzed in the study, with the control group receiving the standard Stupp regimen and the experimental group receiving more than 6 cycles of TMZ chemotherapy. The results showed no significant difference in 6-month PFS and OS between the two groups [6].

Several clinical studies have explored the efficacy of combination therapy based on the Stupp regimen. AVAglio clinical studies have shown that the combination of bevacizumab, radiotherapy, and TMZ treatment prolongs median PFS by 4.4 months in newly diagnosed GBM patients, but does 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 Society of Oncology analyzed the application value of the combination of lomustine and TMZ in the treatment of GBM patients. The results showed that the combination of the two could achieve a total OS of 48.1 months for GBM patients with MGMT gene promoter methylation, while using TMZ alone was only 31.4 months [8]. On the basis of the Stupp protocol, electric field therapy (TTF) was added during the adjuvant TMZ period, which extended the median OS of newly diagnosed GBM patients by 4.9 months and increased the 5-year survival rate to 13% [9]. Based on preclinical studies showing significant efficacy of anti-CTLA-4 and anti-PD-1 combination immunotherapy in a GBM model, a phase I clinical study NRG-BN002 evaluated the safety of immune checkpoint inhibitors alone or in combination for newly diagnosed GBM. The combination immunotherapy of anti-CTLA-4 and anti-PD-1 has good tolerability and safety, with median OS and PFS of 20.7 months and 16.1 months, respectively [10], and is more effective than the standard Stupp regimen. This research result supports the subsequent phase II/III clinical trials of combined immunotherapy for newly diagnosed GBM patients. The above clinical research data suggests that the combination of TMZ and other treatment methods can improve patient prognosis to a certain extent.

In addition, considering that radiotherapy is an independent factor affecting the survival of GBM patients, exploring whether increasing the intensity of radiotherapy can further improve the prognosis of GBM patients has always been an important area of clinical research. Multiple exploratory studies have been conducted based on metabolic imaging to investigate whether local high-dose radiation therapy can improve patient prognosis. A meta-analysis of 22 prospective clinical studies showed that increasing the radiation dose to between 62.5Gy and 80Gy did not significantly improve patient prognosis compared to the standard dose of 60Gy [11], which may be related to the failure to distinguish between patients undergoing complete resection, partial resection, or short-term recurrence, as well as an increase in radiation side effects in high-dose areas including the entire tumor bed. Therefore, administering low-dose radiation to residual or recurrent lesions alone, and administering current standard dose radiation therapy to tumor beds and high-risk areas for recurrence, may further improve the survival benefits of GBM patients while controlling adverse reactions to radiation therapy.

1.4 Partial surgical resection or short-term recurrence leads to poorer prognosis in GBM patients

The degree of surgical resection is an independent factor in predicting the prognosis of GBM patients [12]. A retrospective analysis of the impact of surgical resection degree on prognosis in 500 newly diagnosed GBM patients showed that the OS of patients with 100% resection, 90% resection, 80% resection, and 78% resection were 16 months, 13.8 months, 12.8 months, and 12.5 months, respectively [13]. This study suggests that patients undergoing partial surgical resection or short-term postoperative recurrence and progression require stronger

postoperative adjuvant therapy to further improve survival. However, currently there are no clinical studies on postoperative adjuvant therapy for patients with GBM who have undergone partial surgical resection or short-term recurrence and progression before postoperative radiotherapy, which are consistent with those who have undergone total surgical resection. Therefore, strengthening adjuvant therapy in the surgical part

Further prospective clinical studies are needed to explore the benefits in patients with resection or short-term recurrence and progression after surgery.

In summary, in newly diagnosed GBM patients undergoing partial surgical resection or short-term recurrence progression, studying the benefits of intensified adjuvant therapy on PFS rate, OS rate, quality of life, and other aspects based on the Stupp regimen can help further optimize the comprehensive treatment plan for GBM patients. Here, we conduct a prospective randomized controlled clinical study to provide a basis for selecting the optimal comprehensive treatment for more GBM patients.

2、Specific procedures and processes

This study is a prospective Bayesian adaptive randomized phase II clinical trial of enhanced adjuvant therapy for newly diagnosed glioblastoma with partial surgical resection or short-term progression. The Stupp regimen is the standard treatment regimen (control group), while the experimental group receives enhanced treatment by combining different drugs or increasing the radiation dose based on the Stupp standard treatment regimen. Participants will undergo screening and evaluation according to the inclusion and exclusion criteria of the protocol, within 28 days prior to randomization. Patients who agree to participate in this study will sign an informed consent form (ICF) prior to the screening process. After completing all screening activities, those who meet the criteria can start receiving study treatment. Based on sample size estimation, a total of 210 patients are planned to be enrolled. Among the first 28 patients, an average of 7 patients will be allocated to each group for initial randomization to ensure the balance of each group in the early stages of the trial. Starting from the 29th patient, the 12-month PFS rate will be re estimated for every 15 patients enrolled, and the subsequent randomization probability will be calculated based on the observed data. On the first day of self adjuvant therapy, the PD-1/VEGF bispecific group received intravenous administration of PD-1/VEGF bispecific antibody 20mg/kg treatment, with 21 days per cycle, is expected to be administered for a total of 8 cycles. The PD-1/CTLA-4 dual antibody group received intravenous infusion of 6mg/kg PD-1/CTLA-4 dual antibody once on the first day of self adjuvant therapy, with 14 days per cycle. It is expected to be administered for a total of 12 cycles. The dose adjusted Stupp regimen group (mStupp) administered PGTV locally to residual or short-term recurrent lesions after surgery 66Gy/30Gy high-dose irradiation, PTV1 60Gy/30F in high-risk areas around the tumor bed, and 54Gy/30F radiotherapy in low-risk areas. Each group will have weekly blood routine, liver and kidney function, myocardial enzyme spectrum, thyroid function, electrocardiogram, and head MR every 4 weeks to evaluate the efficacy and toxic side effects. Follow up observation will be conducted. The study will start on January 1, 2025 and end on

December 31, 2027, to explore the efficacy of enhanced adjuvant therapy for newly diagnosed glioblastoma with partial surgical resection or short-term progression.

3、What do you need to do if you want to participate in the research

You will be screened and evaluated according to the inclusion criteria of the program. If you agree to participate, you will sign an informed consent form (ICF). After completing all screening activities, if you meet the criteria for enrollment, you can start receiving study treatment according to the established randomization protocol. Weekly review of blood routine, liver and kidney function, myocardial enzyme spectrum, thyroid function, electrocardiogram, and every 4 weeks review of head MR to evaluate efficacy and toxic side effects.

You may withdraw from the study at any time at your own discretion, or be requested to do so by the investigator or sponsor due to safety or behavioral reasons, or inability to comply with the study visit time or steps required by the protocol.

4、The benefits that participating in this study may bring to you

(1) Personal benefits: For glioblastoma, the current standard treatment regimen is the Stupp regimen. However, the current adjuvant treatment regimen for newly diagnosed GBM patients with partial surgical resection or short-term recurrence and progression before postoperative radiotherapy is the same as that for patients with complete surgical resection. There is no postoperative adjuvant intensive treatment regimen for patients with partial surgical resection or short-term recurrence and progression after surgery. The main purpose of this study is to improve the recurrence free survival rate and further enhance the quality of life of the subjects; At the same time, the entire treatment process can receive close follow-up and attention from researchers. But it is also possible that they will not benefit.

(2) Social benefits: Exploring whether intensified treatment for newly diagnosed GBM patients with partial surgical resection or short-term recurrence and progression after surgery can have further survival benefits, promote further development of clinical research, facilitate the development of more effective drugs, change treatment standards, and promote public health.

5、Possible adverse reactions, risks, and risk prevention measures associated with participating in this study

Common adverse reactions of immunotherapy include pneumonia, diarrhea, colitis, hepatitis, nephritis, gastritis, etc; Endocrine diseases such as hypothyroidism, hyperparathyroidism, hypophysitis, adrenal insufficiency, hyperglycemia or type 1 diabetes; Skin related adverse reactions, including Stevens Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN); Thrombocytopenia; Other immune related adverse reactions such as pancreatitis/myocarditis/encephalitis.

Common adverse reactions of anti vascular drug therapy include hypertension, proteinuria, bleeding, thrombosis, arterial thromboembolism, etc.

Common adverse reactions of high-dose radiotherapy include cerebral edema, radiation necrosis, memory loss, cognitive impairment, etc.

To prevent the occurrence of risks, researchers will closely observe and follow up throughout the entire treatment period for timely treatment. If any serious adverse events related to the research occur, we will promptly contact your representative, and the hospital will seek compensation for you in accordance with relevant laws and regulations.

6、Explanation of Cost Situation

At present, the conventional standard treatment does not require the use of the dual antibody drugs in this study, and the mStupp regimen does not increase the cost of radiotherapy. The price of PD-1/VEGF dual antibody is 2299 yuan per tube, and each cycle requires 22990 yuan. Each patient needs 8 cycles of treatment, totaling 22990x8=183920 yuan; The price of PD-1/CTLA-4 dual antibody is 6166 yuan per tube, and each cycle requires 18498 yuan. Each patient needs 12 cycles of treatment, totaling 18498x12=221976 yuan. The experimental group will receive free medication without any additional financial burden on patients.

7、Compensation for participation in research, including compensation for damages

Blood collection compensation: 100 yuan/time

Transportation fee: 100 yuan/time

There is no special exemption for imaging examinations between the experimental group and the control group.

If the research causes damage, we will provide active treatment and all related costs will be waived.

8、Alternative solutions

If the subjects do not participate in this study or withdraw from the study, they can continue with the standard treatment plan or participate in other studies.

9、Confidentiality of Your Personal Information

Your medical records (including research medical records and physical and chemical examination reports, etc.) will be kept in the hospital according to regulations. Except for researchers, ethics committees, monitoring, inspection, and drug administration departments who will be allowed to access your medical records, other personnel unrelated to the research have no right to access your medical records without permission. The public report of the results of this study will not disclose your personal identity. We will make every effort to protect the privacy of your personal medical information within the permitted scope.

10、Terminate participation in the study

Whether or not to participate in this study depends entirely on your voluntary decision. You may refuse to participate in this study, or withdraw from the study without reason at any time during the study

process, without affecting your relationship with the doctor or causing any loss to your medical or other interests. In addition, your participation in this study may be terminated due to the following reasons:

1. You did not follow the doctor's advice.

2. You have experienced a serious condition that may require treatment.

3. The research doctor believes that terminating the study is most beneficial for your health and well-being.

11、Ethics Committee

This study has been reported to the Human Research Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine. After comprehensive review and risk assessment of the subjects by the committee, it has been approved. During the research process, 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 at 0571-87783759 during the day; Evening (General Duty): 13757118366; e-mail address: HREC2013@126.com

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

Subject Signature:

Contact Information:

Date:

Signature of representative:

Contact information and date of subject relationship (if required)

Witness (if needed):

Contact Information: Date:

I confirm that I have explained the details of this study to the patient, including their rights and potential benefits and risks, and provided them with a signed copy of the informed consent form.

Signature of Researcher:

Contact information: (mobile phone) Date: