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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Study Protocol

1， Research Background

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[1]。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[2]。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, which was 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 continuously exploring the optimal comprehensive treatment plan for newly diagnosed GBM, including extending the time 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 TMZ chemotherapy for more than 6 cycles. The results showed no significant difference in PFS and OS between the two groups at 6 months[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 overall survival[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 assisted 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]， The therapeutic effect is superior to 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 based on metabolic imaging guidance on 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]， It may be related to the failure to distinguish between complete resection and partial resection or short-term recurrence patients, as well as the increased side effects of radiotherapy 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 Patients with partial surgical resection or short-term recurrence and progression of GBM have a worse prognosis

The degree of surgical resection is an independent factor for 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, further prospective clinical studies are needed to explore the benefits of intensified adjuvant therapy in patients undergoing partial surgical resection or short-term postoperative recurrence and progression.

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 Bayesian adaptive randomized controlled

clinical study. Unlike traditional randomization methods, Bayesian adaptive randomization can continuously update probability estimates during the trial to better utilize trial data and dynamically adjust randomization ratios or intervention strategies based on trial results, providing a basis for the optimal comprehensive treatment selection for more GBM patients.

1.5 References

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2， Research objective

This study is a prospective, randomized, controlled, open label, single center phase II study aimed at newly diagnosed GBM patients with short-term recurrence and progression before partial surgical resection or radiotherapy. The aim is to evaluate the effectiveness and safety of intensified adjuvant therapy based on the Stupp standard treatment regimen.

2.1 Main research objectives

Evaluate the effect of intensified adjuvant therapy on the 3-month, 6-month, and 12-month PFS rates in newly diagnosed GBM patients undergoing partial surgical resection or short-term recurrence progression (using RANO 2.0 criteria).

2.2 Secondary research objectives

2.2.1 Evaluate the impact of intensified adjuvant therapy on 1-year and 2-year overall survival rates and quality of life in patients with newly diagnosed glioblastoma who undergo partial surgical resection or short-term recurrence progression.

2.2.2 Evaluate the safety and incidence of radiation necrosis in newly diagnosed glioblastoma patients undergoing enhanced adjuvant therapy with surgical partial resection or short-term recurrence progression.

3， Research design and methodology:

3.1 Research overall design

This study is a prospective, randomized, controlled, open label, single center phase II study that uses Bayesian adaptive randomization to assess the efficacy and safety of intensified adjuvant therapy in newly diagnosed GBM patients undergoing partial surgical resection or short-term recurrence progression, based on the Stupp standard treatment regimen. Newly diagnosed GBM patients who undergo partial surgical resection or short-term recurrence progression (2-6 weeks after surgery before radiotherapy), after signing informed consent forms, will be screened to meet inclusion and exclusion criteria. In the first stage of Bayesian adaptive randomization, qualified subjects will be stratified and randomized in a 1:1:1:1 ratio to Stupp group, Stupp+PD-1/VEGF bispecific group, Stupp+PD-1/CTLA-4 bispecific group, and modified Stupp group with adjusted radiotherapy dose. In the second stage of Bayesian adaptive randomization, probability estimates are continuously updated based on the efficacy evaluation results of each group in the first stage, and the proportion of individuals randomized to each treatment group is dynamically

adjusted according to the trial results. A new round of randomization is conducted for each group of 16 individuals. The four treatment plans are as follows:

Stupp group: Synchronized TMZ radiotherapy and chemotherapy will begin 2-6 weeks after surgery, and 6 cycles of adjuvant TMZ chemotherapy will begin 28 days after completing the synchronized radiotherapy and chemotherapy. Radiotherapy regimen: PTV1 60Gy/30F in high-risk areas around the tumor bed, 54Gy/30F in low-risk areas. TMZ synchronous chemotherapy regimen: 75mg/m2 po qd. TMZ adjuvant chemotherapy regimen: The first cycle is 150mg/m2 po qd on d1-5,28 days; Cycle 2-6: Cycle 1: 200mg/m2 po qd for d1-5,28 days.

Stupp+PD-1/VEGF dual antibody group: Starting 2-6 weeks after surgery, synchronous TMZ radiotherapy and chemotherapy will be performed. After completing synchronous radiotherapy and chemotherapy for 28 days, TMZ combined with PD-1/VEGF dual antibody will be used as adjuvant therapy. PD-1/VEGF dual antibody 20mg/kg intravenous infusion once, with a cycle of 21 days.

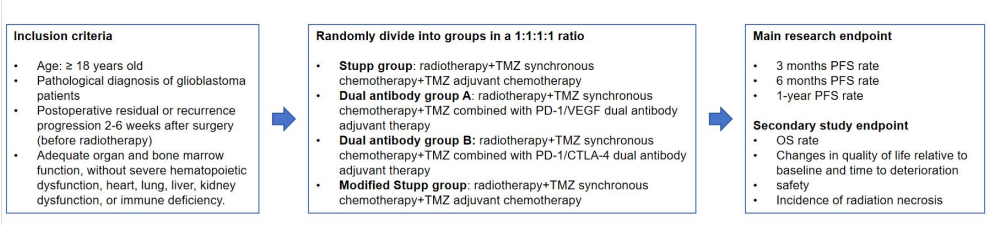
Stupp+PD-1/CTLA-4 dual antibody group: Starting 2-6 weeks after surgery, synchronous TMZ radiotherapy and chemotherapy will be performed. After completing synchronous radiotherapy and chemotherapy for 28 days, TMZ combined with PD-1/CTLA-4 dual antibody will be used as adjuvant therapy. PD-1/CTLA-4 dual antibody 6mg/kg intravenous infusion once, with a cycle of 14 days.

Modified Stupp group: Starting 2-6 weeks after surgery, synchronous TMZ radiotherapy and chemotherapy will be performed. For partially resected lesions or short-term recurrence and progression lesions after surgery, high-dose PGTV 66Gy/30Gy will be given locally. PTV1 in high-risk areas around the tumor bed will be 60Gy/30F, and in low-risk areas will be 54Gy/30F. After completing synchronous radiotherapy and chemotherapy for 28 days, 6 cycles of adjuvant TMZ chemotherapy will be started.

This study is divided into three stages: screening period, treatment period, and follow-up period. The screening period is 2-6 weeks after surgery. Treatment period: Subjects who meet the inclusion criteria but do not meet the exclusion criteria will receive postoperative intensive adjuvant therapy after signing the informed consent form. Follow up period: After stopping the study treatment, the subjects enter the follow-up period. Follow up period: Head MRI examination and evaluation will be conducted at baseline, postoperative, before radiotherapy, and after radiotherapy. MRI enhanced scans will be performed every month during the follow-up period to observe PFS until the end of the follow-up period. For subjects who have not withdrawn their informed consent form, survival information (i.e. date and cause of death, subsequent tumor treatment, etc.) will be collected every month through telephone and/or clinical visits.

This study is expected to have an enrollment period of 24 months and a follow-up period of 24 months.

3.2 Research and Design Flowchart



3.3 Study population

3.3.1 Inclusion Criteria

Patients eligible for this study must meet all of the following criteria:

1) Voluntary participation in clinical research: fully understand and be informed of this study, and sign a written informed consent form; Willing to follow and capable

Complete all experimental procedures.

2) Age: ≥ 18 years old, both male and female are acceptable.

3) Pathologically diagnosed GBM patients

4) Partial surgical resection or recurrence and progression 2-6 weeks after surgery (before radiotherapy)

5) Adequate organ and bone marrow function, without severe hematopoietic dysfunction, heart, lung, liver, kidney dysfunction, or immune deficiency:

a) Blood routine: Absolute neutrophil count (ANC) ≥ 1.5 * 109/L (1500/mm3), platelets ≥ 75 * 109/L, hemoglobin ≥ 9 g/dL (if bone marrow is involved, platelets ≥ 50 * 109/L, ANC ≥ 1.0 * 109/L, hemoglobin ≥ 8 g/dL).

b) Liver function: Serum bilirubin ≤ 1.5 times the upper limit of normal value, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 1.5 times the upper limit of normal value (AST is allowed if there is liver involvement, ALT ≤ 5 times the upper limit of normal value).

c) Renal function: Serum creatinine ≤ 1.5 times the upper limit of normal value.

d) Coagulation function: INR ≤ 1.5 times the upper limit of normal value; PT and APTT are ≤ 1.5 times the upper limit of normal values (unless the subject is receiving anticoagulant treatment and PT and APTT are within the expected range of anticoagulant treatment at the time of screening).

6) Left ventricular ejection fraction (LVEF) ≥ 50% in cardiac function examination.

7) The serum pregnancy test is negative, and effective contraceptive measures have been taken from the signing of the informed consent form until 6 months after the last chemotherapy.

8) Thyroid stimulating hormone (TSH), free thyroxine (FT4), or free triiodothyronine (FT3) are all within the normal range of ± 10%.

9) Ophthalmic examination: including dilated pupil fundus examination, slit lamp examination, and fundus color photography.

3.3.2 Exclusion criteria

Subjects who meet any of the following criteria are not eligible for this study:

1) Currently participating in other clinical studies, or less than 4 weeks after the end of treatment in the previous clinical study.

2) In the past 3 years, there has been a history of malignant tumors other than GBM, or other primary malignant tumors that have not been cured.

3) Previous history of brain radiation therapy.

4) Pregnant or lactating women.

5) After evaluation, there are patients with contraindications to radiotherapy.

6) Serious active comorbidities that may affect the treatment of this study.

7) Active infections that require systematic anti infective treatment, including but not limited to bacterial, fungal, or viral infections.

8) Patients with heart failure, unstable angina, severe uncontrolled ventricular arrhythmias, acute ischemia or myocardial infarction as determined by the New York Heart Association (NYHA) functional classification within the first 6 months of screening.

9) QTcF interval>480milliseconds, unless secondary to bundle branch block.

10) Suffering from uncontrollable comorbidities, including but not limited to uncontrolled hypertension, active peptic ulcers, or bleeding disorders.

11) Individuals with a history of mental illness in the past; Individuals without legal capacity or with limited legal capacity.

12)Medical history or disease evidence that may interfere with the trial results, hinder the subjects' full participation in the study, abnormal treatment or laboratory test values, or other situations that the researchers consider unsuitable for inclusion.

3.3.3 Discontinue research treatment

Subjects may discontinue treatment at any time for any reason, or at the discretion of the investigator in the event of any adverse event. In addition, if the subject is not suitable for treatment, violates the study protocol, or for management and/or other safety reasons, the researcher may discontinue the subject's treatment.

For any of the following reasons, subjects must discontinue treatment but may continue to be monitored during the study:

- The subject or the subject's legal representative requests to stop treatment.
- Adverse events that require discontinuation of treatment as specified in the protocol have occurred.
- Concurrent diseases that hinder further treatment occur.
- The researchers decided to withdraw the subjects from the study.
- The serum pregnancy test result of the subject is positive.
- Poor compliance of the subjects, failure to receive treatment on time, ineffective communication and coordination by the researchers, or possible significant deviations in the trial results that cannot be remedied.

- Researchers believe that based on the disease or personal condition of the subjects, continuing to provide study treatment would put them at unnecessary risk.
- Complete the treatment specified in the plan.

3.3.4 Follow up on withdrawn cases

If the subject or the subject's legal representative withdraws the informed consent form for participation in the study, the subject must withdraw from the study. If the subject withdraws from the study, they will no longer receive treatment or at planned visits. Subject to the subject's consent, participants can undergo survival follow-up after withdrawing from the study. If the subject is lost to follow-up, they must withdraw from the study.
Any patient who withdraws from this study for reasons other than progression should continue to undergo imaging evaluation for a predetermined period of time to collect information about disease progression, until imaging disease progression occurs, new anti-tumor treatment begins, informed consent is withdrawn, death occurs, or the study ends (whichever occurs first). After recording disease progression, researchers need to call patients, their families, or their current treating physicians at least once a month to collect long-term follow-up information on survival.

4， Sample size calculation

（1）Sample size estimation

The aim of this study is to evaluate the progression free survival (PFS) at 12 months in the experimental group receiving intensified adjuvant therapy in addition to the standard treatment Stupp regimen. Based on retrospective research and preliminary data from our center, it is estimated that the PFS of the Stupp group will be 40% and the experimental group will be 70%. To ensure the reliability of the research results, we set the alpha error to 0.05 and the beta error to 0.20 to ensure that the experiment has sufficient statistical power to detect differences between the two groups. Based on these parameters, it is calculated that each group requires 50 patients, for a total of 200 patients. Considering a 5% dropout rate, we plan to recruit 210 patients to ensure sufficient sample size for the final analysis.

（2）New Randomize Method

This project intends to use Bayesian adaptive randomization method to dynamically adjust the probability of patients being assigned to each treatment group. The specific implementation is as follows:
Initial randomization: Among the first 28 patients, an average of 7 were allocated to each group to ensure balance between the two groups during the initial stages of the trial.

Bayesian response randomization: Starting from the 29th patient, the 12-month PFS rate will be re estimated for every 16 patients enrolled, and subsequent randomization probabilities will be calculated based on observed data. This process will use Bayesian statistical principles

to dynamically adjust the probability of patient randomization by updating prior knowledge and new data, in order to improve trial efficiency. Randomization software: We will use professional randomization software, such as SAS or randomization packages in R language, to ensure the fairness and reproducibility of the randomization process.

5， Data management and confidentiality

5.1 Case report form

The main purpose is to obtain the necessary information for the research plan in a complete, accurate, clear, and timely manner. The data in the medical record report form should be consistent with the original file. The filling out of the medical record report form must be complete and clear (using a black or blue ballpoint pen, in compliance with legal document requirements). The medical record report form is a regulatory document that must be suitable for submission to hospital authorities.

All revisions and corrections must be made and confirmed by the researcher, specifying the date of revision/correction. Errors must be clearly retained and cannot be covered with corrected data (such as using correction fluid). The researcher must indicate the reasons for revising important data. The missing data/notes in the medical record should be replaced by underline in the blank input of the medical record report form to avoid unnecessary follow-up investigations.

5.2 Research documents and preservation

Researchers should have a document outlining the research objectives. This file should include all necessary documents for conducting the research. After the research is completed, these documents should be archived according to relevant regulations of the hospital and the country.

5.3 Regulations on data management and data traceability

The designed CRF is in triplicate (carbonless), and the second copy of the CRF is submitted to the data management personnel participating in this clinical trial to establish a unified database. After completing at least 5 CRFs, the trial will be promptly submitted to the data administrator through clinical monitoring to establish the corresponding database. All data will be entered in duplicate using computer software to develop a data entry program.

During this period, the questionnaire will be forwarded to the researchers for data review through clinical monitors, and the researchers should answer and return it as soon as possible. The locked data file cannot be changed again. The database will be handed over to statistical analysts for statistical analysis according to the requirements of the statistical plan. Submit the statistical analysis report to the main researcher of this experiment to write the research report.

Provide training to researchers on relevant regulations and SOPs, and ensure that all researchers strictly comply with them to record truthfully, timely, accurately, and completely, prevent omissions and arbitrary modifications, and avoid forging or fabricating data; Inspectors strengthen the verification of various records. The follow-up medical records of the subjects should be kept together with the CRF as the original data. Each center's laboratory department provides participation in the quality control of the Ministry of Health's clinical laboratory center

The certificate of conformity shall be stored in the computer connected to the inspection equipment for at least three years for future reference.

5.4 data privacy

All records related to the identity of the subjects shall be kept confidential and shall not be disclosed to the public beyond the scope permitted by relevant laws and/or regulations.

6， informed consent

Explanation on Informed Consent

1) Patient obtaining informed consent: The research team will provide detailed research information to potential participants, including research objectives, procedures, potential risks, and benefits. The informed consent process will be conducted in a private and quiet environment to ensure that patients are not under any pressure. Researchers will answer all questions from patients and ensure that they fully understand the research content. The informed consent form will be signed by the patient themselves after fully understanding the research content. If the patient is unable to sign it in person, the legal guardian will sign it on their behalf.

2) Measures for obtaining informed consent from vulnerable groups:

For patients without legal capacity, such as hospitalized patients with serious illnesses and patients with mental illnesses, an informed consent form will be signed by their legal guardians.

For illiterate individuals, verbal consent will be used and a witness will be present to sign and certify.

Special attention will be paid to the autonomy of prisoners, individuals with cognitive impairments, and other disadvantaged groups, ensuring that they are not subjected to any form of coercion or inducement.

For students, staff of our institution, etc., we will ensure that their participation in the research is voluntary and that they will not receive any additional benefits from participating in

the research. For patients with mental/cognitive disorders, a psychiatrist will assess whether they have self-awareness and determine the method of obtaining informed consent based on this assessment.

The process of signing/obtaining informed consent forms

Provision of informed consent form: The research team will provide potential participants with a written informed consent form, which will detail all relevant information about the study.

Explanation of informed consent: Researchers will explain each item in the informed consent form to participants to ensure their full understanding.

Question and Answer: Researchers will give participants the opportunity to ask questions and answer all questions during the explanation process.

Sign informed consent form: After participants fully understand the research content and agree to participate, they will be invited to sign and date the informed consent form.

The person in charge of obtaining informed consent: The acquisition of informed consent forms will be the responsibility of a trained research coordinator or principal investigator (PI).

Time and location: Informed consent will be given at a designated location in the hospital prior to participants being enrolled in the study.

Handling of special circumstances: For participants who are unable to personally sign the informed consent form, appropriate measures will be taken, such as video calls or recorded phone calls, to ensure that they can provide informed consent.

Throughout the entire research process, we will respect the rights of each participant and ensure that they are free to raise questions, opinions, or choose to withdraw from the study at any time. We will regularly review the informed consent process to ensure that it always complies with ethical standards and legal regulations.

7， Adverse Event Reporting

7.1 Definition

AE refers to any adverse medical event that occurs from the signing of the informed consent form by clinical trial subjects until 90 days after the last use of the study treatment, regardless of whether there is a causal relationship with the trial treatment, and is determined as an adverse event.

7.2 Content

1) The aggravation of pre-existing medical conditions/diseases (including symptoms, signs, and laboratory abnormalities) prior to entering clinical trials;

2) Any newly occurring adverse medical events (including symptoms, signs, newly diagnosed diseases);

3) Abnormal laboratory test values or results with clinical significance.

Researchers should record in detail any adverse events (AEs) that occur in the subjects, including the name of the AE and a description of all related symptoms, the time of occurrence, severity, correlation with the investigational drug, duration, measures taken, and final results and outcomes.

7.3 Adverse Event Record

Researchers should carefully observe any adverse reactions that occur in subjects during the clinical study period, require subjects to truthfully report changes in their condition after treatment, avoid inducing questions, and record in detail in the case form CRF, including the time of occurrence, symptoms, signs, degree, duration, laboratory test indicators, treatment methods, process, results, etc. of adverse reactions, and record in detail the situation of concomitant medication.

7.4 Criteria for determining the severity of adverse events

Refer to the grading standards for drug adverse events in NCI-CTCAE 5.0 version.

7.5 Criteria for determining the relationship between adverse events and investigational drugs

AE includes all unexpected clinical manifestations, as long as these events occur after signing the informed consent form, regardless of whether they are related to the experimental treatment, they should be reported as AE. During the treatment period, any discomfort or abnormal changes in objective laboratory test indicators reported by the subject should be recorded truthfully, and the severity, duration, treatment measures, and outcome of the AE should be indicated. The research physician should also comprehensively determine the relationship between the AE and the investigational drug, and evaluate the possible association between the AE and the investigational treatment according to the five level classification system of "definitely related, possibly related, possibly unrelated, definitely unrelated, and unable to determine" Definitely related "," possibly related ", and" unable to determine "are all listed as adverse drug reactions, and the determination criteria are shown in the following table:

Table 1 Criteria for Judging the Relationship between AE and Experimental Treatment

Grading criteria

Definitely related: the occurrence of the event conforms to a reasonable chronological order after treatment, and the event conforms to the known reaction type of the suspected drug;

Alternatively, if the condition improves after discontinuing the medication and the event occurs again after repeated administration.

Possible correlation: The occurrence of events follows a reasonable chronological order after treatment, and the events do not conform to the known reaction type of the suspected drug; The patient's clinical condition or other treatment methods may also cause this event.

Possible unrelated: The occurrence of the event does not conform to a reasonable chronological order after treatment, the event does not conform to the known response type of the suspected drug, and the patient's clinical status or other treatment methods may have caused the event.

Definitely unrelated: The occurrence of the event does not conform to a reasonable chronological order after treatment, the event does not conform to the known response type of the suspected drug, the patient's clinical status or other treatment methods may cause the event, the event disappears after disease improvement or discontinuation of other treatment methods, and the event occurs when other treatment methods are repeatedly used.

Unable to assess: There is no clear relationship between the occurrence of the event and the time sequence after treatment, and it is similar to the known reaction types of the drug. Other drugs used at the same time may also cause corresponding events.

7.6 Serious Adverse Events and Recording and Reporting

1）Definition of SAE

SAE refers to medical events that occur during clinical trials that require hospitalization or prolonged hospitalization, disability, affect work ability, endanger life or death, or cause congenital malformations.

Including the following unexpected medical events: events leading to death; Life threatening events (defined as the risk of immediate death for the subject at the time of the event); Events that require hospitalization or prolonged hospitalization; Events that can lead to permanent or severe disability/functional impairment/affect work ability; Congenital abnormalities or birth defects; Other important medical events (defined as events that endanger the subjects or require intervention to prevent any of the above situations from occurring).

2）Disease progression

Disease progression is defined as the deterioration of the subject's condition caused by the primary tumor targeted by the research treatment. Including advances in imaging and clinical symptoms and signs. The emergence of new metastases relative to the primary tumor, or the progression of

existing metastases, are considered as disease progression. Events that pose a threat to life due to symptoms and signs of disease progression, require hospitalization or prolonged hospitalization, or result in permanent or severe disability/functional impairment/impact on work ability, congenital abnormalities, or birth defects, are not included in accelerated reporting as SAEs. Deaths caused by symptoms and signs of disease progression are reported as SAEs at an accelerated rate.

3）Perform other anti-tumor treatments

The AE records start from the signing of the informed consent form and continue until 90 days after the last use of the study drug. Within 90 days after the last administration, if the subject begins to use other tumor drugs and experiences serious adverse events, a report is required.

4）Hospitalization

Adverse events leading to hospitalization or prolonged hospital stay in clinical studies should be considered as SAEs. Any first-time hospitalization by a medical institution meets this standard. Hospitalization does not include the following situations: rehabilitation institutions; Sanatorium; Routine emergency room admission; Same day surgery (such as outpatient/same day/non bedridden surgery); Hospitalization or prolonged hospital stay that is not related to the worsening of AE is not itself an SAE. For example, being admitted to the hospital due to an existing illness, without any new adverse events or worsening of the existing illness (such as in order to check for laboratory abnormalities that have persisted since before the experiment); Hospitalization due to management reasons (such as annual routine physical examinations); Hospitalization as specified in the trial protocol during clinical trials (such as operating according to the requirements of the trial protocol); Elective hospitalization unrelated to the worsening of adverse events (such as elective surgery); The scheduled treatment or surgical procedure should be recorded in the entire trial protocol and/or individual baseline data of the subjects.

Diagnostic or therapeutic invasive procedures (such as surgery) and non-invasive procedures should not be reported as adverse events (AEs). However, if the disease condition that led to this procedure meets the definition of AE, it should be reported. For example, acute appendicitis that occurred during the AE reporting period should be reported as an AE, and appendectomy performed as a result should be recorded as the treatment method for that AE.

5）SAE's reporting system

The reporting period for SAE should start from the signing of the informed consent form by the subjects and continue until 90 calendar days (including 90 days) after the last use of the study drug. If a serious adverse event (SAE) occurs, whether it is the first report or follow-up report, the researcher must immediately fill out the "New Drug Clinical Research Serious Adverse Event Report Form", sign and date it, and report it to the relevant provincial, autonomous region, or municipality drug regulatory department, NMPA (via EMS), health administrative department (via fax to the Medical Administration Bureau), notify the applicant (via email), and promptly report to the ethics committee within 24 hours of the researcher's knowledge.

SAE occurring 90 days after the last use of the study drug is generally not reported unless suspected to be related to the study drug. SAE should provide detailed records of symptoms, severity, correlation with the investigational drug, occurrence time, treatment time, measures taken, follow-up time and methods, as well as outcomes. If researchers believe that a certain SAE is not related to the investigational drug but potentially related to the study conditions (such as termination of the original treatment or comorbidities during the trial), this relationship should be detailed in the narrative section of the SAE report form. If the intensity of an ongoing SAE or its relationship with the investigational drug changes, a follow-up report should be submitted immediately.

6）Follow up of SAE

All SAEs should be followed up until disappearance, remission to baseline level or ≤ level 1, and stability.

Researchers should be followed up until the end of AE, stable status, reasonable explanation, loss to follow-up, or death; Follow up information should be provided promptly according to the requirements of the sponsor.

If there are no specific requirements in the protocol, AE/SAE collection and follow-up usually begin after the subjects sign the informed consent form, and each AE/SAE must be followed up during the study period; At the end of the study, the collection and follow-up principles for AE/SAE that occurred after the final treatment of the subjects can refer to the following table:

Classification, collection, recording, and follow-up

All SAEs should be followed up until disappearance, remission to baseline level or ≤ level 1, and stability.

Researchers should be followed up until the end of AE, stable status, reasonable explanation, loss to follow-up, or death; Follow up information should be provided promptly according to the requirements of the sponsor.

If there are no specific requirements in the protocol, AE/SAE collection and follow-up usually begin after the subjects sign the informed consent form, and each AE/SAE must be followed up during the study period; At the end of the study, the collection and follow-up principles for AE/SAE that occurred after the final treatment of the subjects can refer to the following table:

- Various adverse events: Take timely measures to handle them and record them in the case report form.Serious Adverse Events (SAEs): Take timely measures to handle them, record them in the case report form, have the researcher decide to discontinue or reduce the drug, immediately report to the ethics committee, drug clinical trial institution, and sponsor, and report to the national and provincial food and drug regulatory authorities within 24 hours